

An investigation into treatment administration and survival for people with small cell lung cancer

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Abstract

Background

Chemotherapy is the backbone of treatment for small cell lung cancer (SCLC) but this may change in the future with the emergence of immunotherapy. Current recommendations state performance status (PS) and comorbidity should be used as measures to decide whether chemotherapy is appropriate but in some circumstances this decision comes down to whether the patient is fit enough to withstand its toxicity. Thoracic radiotherapy and prophylactic cranial irradiation (PCI) are adjuncts to chemotherapy and can cause additional side effects, impacting quality of life. This is an important factor to consider as median survival is short. Furthermore, the efficacy of PCI has been questioned in extensive disease (ED-SCLC). In order to deliver effective treatment it is important that clinicians are aware of the short-term risks and long-term survival gains of these therapies so that a balanced, objective decision can be made before treatment is administered.

This thesis aims to improve the patient selection process by quantifying the factors that determine: receipt of treatment, early mortality and long term survival following chemotherapy. In addition, it sets survival benchmarks following the currently used treatments so that novel therapies can be compared in the future.

Methods

English national lung cancer audit data (NLCA) were linked with chemotherapy (SACT) and radiotherapy (RTDS) data to develop a multivariate logistic regression model in order to quantify the factors associated with receipt of treatment, early mortality and 1-year survival. A subsequent systematic review and meta-analysis of early and late

survival following platinum chemotherapy was conducted. MEDLINE, EMBASE and online libraries from major lung cancer conferences were examined to identify studies from 1946 to 2017. Pooled survival estimates were calculated at 30 and 90 days, 1 year, 2 years and 5 years along with the median survival.

Results

Receipt of treatment

Approximately 60% of people diagnosed with SCLC received chemotherapy in the NLCA data. Receipt of treatment was independently associated with PS, age and the amount of comorbidities ($P < 0.01$ for all factors). There was significant variation in receipt of chemotherapy, radiotherapy and PCI by geographical location ($P < 0.01$ for all treatment modalities). There was no association between receiving chemotherapy and the stage of cancer.

Early survival

The 30-day mortality following chemotherapy for all stages of SCLC was approximately 7.8% in the NLCA data. This was associated with stage (ED-SCLC vs limited stage (LD-SCLC) adjusted OR 1.53 (95%CI 1.02-2.28)) and PS (PS2 vs PS0 adjusted OR 3.76 (95%CI 1.71-8.26)). After case-mix adjustment there was significant variation in 30-day mortality by geographical location ($P = 0.01$). Thirty-day survival was considerably better in the meta-analysis of SCLC studies (all stages 98% (95% CI 98-99%, $I^2 = 66.2\%$, $n = 167$)) and showed minimal variation by study factors. Neutropaenic sepsis and disease progression were the predominant causes of early death following chemotherapy. Overall ninety-day survival was 95% (95% CI 94-96%, $I^2 = 81.7\%$, $n = 166$).

Late survival

When the NLCA data were examined there was a considerable difference in 1-year survival between LD-SCLC and ED-SCLC (approximately 60.6% and 26.2 % respectively). For individuals with LD-SCLC this was associated with PS, chemotherapy, receipt of radiotherapy (total dose $\geq 40\text{Gy}$) and PCI. Whereas in ED-SCLC sex, PS, comorbidity, receipt of radiotherapy (total dose $\geq 30\text{Gy}$) and PCI were associated. The odds of 1-year survival for individuals who received 6 cycles of chemotherapy, instead of 4, were not significantly different (6 cycles vs 4 LD-SCLC adjusted OR 0.97 (95%CI 0.48-1.97) and ED-SCLC adjusted OR 1.34 (95%CI 0.81-2.22)). One-year survival did not vary considerably across England, with the exception of one hospital network. This network had better survival and tended to give more radiotherapy and PCI. The meta-analysis including all stages of SCLC revealed a pooled 1-year survival of 54% (95%CI 51-57%, $I^2=93.3\%$, $n=189$). The reporting of 2 and 5-year survival were almost exclusive to LD-SCLC cohorts (41% (95%CI 38-44%, $I^2=78.9\%$, $n=85$) and 23% (95%CI 20-25%, $I^2=72.3\%$, $n=48$) respectively).

The median survival for individuals who did not receive chemotherapy in the national audit data was 251 days (95% CI 201-284 days) for LD-SCLC and 32 days (95% CI 28-36 days) for ED-SCLC. The meta-analysis of studies that administered chemotherapy revealed a median survival of 18.0 months (95% CI 17.0-19.1 months, $I^2=77.3\%$, $n=110$) for LD-SCLC and 9.6 months (95%CI 8.9-10.3 months, $I^2=95.2\%$, $n=103$) for ED-SCLC. These figures varied substantially by the year of study, cohort ethnicity, PS, receipt of radiotherapy and PCI, with the latter two factors applying to LD-SCLC only.

Conclusions

This research provides robust survival benchmarks for the currently recommended treatments of SCLC. Age, PS and the number of comorbidities influenced whether a person received chemotherapy yet PS and stage were the central factors determining prognosis. These two factors, PS and stage, could be used to estimate the risk of early death following chemotherapy and guide treatment decision-making. In addition to assessing early mortality risk, thoracic radiotherapy and PCI should be encouraged in favour of prolonging chemotherapy beyond 4 cycles as this may yield better 1-year survival. Indeed, reducing the geographical inequalities in access to these treatments may also augment outcomes. Further survival advances can be achieved with the development of novel therapies, however, these will require approval by national commissioning bodies prior to use in clinical practice. The survival benchmarks identified within this thesis can be used in the appraisal process to ensure the survival gains of novel therapies are true and are worth their cost.

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At a glance it does not feel like three years have passed since I started this PhD. However, when I reflect on the changes that have happened in my life over these three years and the things I have learnt from this research the significance of the length of this time hits home. I would therefore firstly like to thank my supervisors for the significant amount of time, effort and knowledge they have invested in me over these three years and I am fully indebted to them for this. Thank you Prof Richard Hubbard, Prof David Baldwin and Prof Tricia McKeever.

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Lastly, I will tip my hat to the bicycle and white water kayak for providing me with a means of escapism.

Ride on!

Publications arising

Abstracts of work within this thesis that have been presented at conferences can be found in Appendix A. Below are articles that have been published in, or submitted to, peer reviewed journals.

In press

G S Jones, T M McKeever, R B Hubbard, A Khakwani, D R Baldwin. Factors influencing treatment selection and 30-day mortality after chemotherapy for small-cell lung cancer: An analysis of national audit data. *European Journal of Cancer*. 2018 November, 103:176-183.

G S Jones, D R Baldwin. Recent advances in the management of lung cancer. *Clinical Medicine*. 2018 April, 18 S41-46.

Under peer review

G S Jones, K Elimian, D R Baldwin, R B Hubbard, T M McKeever A systematic review of survival following anti-cancer treatment for small-cell lung cancer. *European Respiratory Journal*.

G S Jones, A Khakwani, A Pascoe, K Foweraker, T M McKeever, D R Baldwin, R B Hubbard. Quantifying factors associated with 1-year survival for people with small cell lung cancer using national audit, chemotherapy and Radiotherapy data. *Thorax*

List of abbreviations

ASCO- American society of clinical oncology

CAV- Cyclophosphamide, doxorubicin and vincristine

CI- Confidence interval

COPD- Chronic obstructive pulmonary disease

COSD- Cancer outcomes and services dataset

CQUIN- Commissioning for quality and innovation

CT- Computerised tomography

DNA- Deoxyribonucleic acid

EBUS-TBNA- Endobronchial ultrasound-guided transbronchial needle aspiration

ED-SCLC- Extensive disease small cell lung cancer

EGFR- Epidermal growth factor receptor

EORTC- European organisation for research and treatment of cancer

ESMO- European society of medical oncology

FDA- Food and drug administration

Gy- Gray units of radiation

IASLC- International association for the study of lung cancer

ICD 10- International classification of disease version 10

IQR- Interquartile range

IT- Information technology

LCNEC- Large cell neuroendocrine carcinoma

LDH- Lactate dehydrogenase

LD-SCLC- Limited disease small cell lung cancer

M-Metastasis

MDT- Multidisciplinary team

NCRAS- National cancer registration service

NET- Neuroendocrine tumour

NHS- National health service

NICE- Nation institute for health and care excellence

NLCA- National lung cancer audit

N-Node

NSCLC- Non-small cell lung cancer

ONS- Office of national statistics

OPCS- Operation procedure codes

OR- Odds ratio

PCI- Prophylactic cranial irradiation

PD1/ PDL1- Programmed cell death protein 1/programmed death-ligand 1

PHE- Public health England

PS- Performance status

RCT- Randomised controlled trial

RTDS- National radiotherapy dataset

SABR- Stereotactic ablative body radiotherapy

SACT- Systemic anti-cancer therapies

SAP- Serum alkaline phosphatase

SCLC- Small cell lung cancer

SES- Socioeconomic status

SNOMED- Systematised nomenclature of medicine

T- Tumour

UK- United Kingdom

USA- United States

VALSG- Veterans administration lung cancer study group

VATS- Video assisted thoracoscopic Surgery

WHO- World health organisation

Chapter 1 Introduction

This chapter discusses the epidemiology of lung cancer and the history of smoking tobacco. The staging, treatment modalities and structure of lung cancer care in England are explained. Lastly, the objectives and content of this thesis are outlined.

1.1 Incidence of lung cancer

During 2018 there were 2.09 million people diagnosed with lung cancer, making it the most common malignancy worldwide.¹ Annually, lung cancer accounts for 1.69 million deaths, which is nearly 18% of all cancer related deaths.² The highest incidence rates are observed in eastern Asia, Europe and North America whilst the lowest are seen in Africa.³ In the United Kingdom (UK) lung cancer is the third commonest cancer and approximately 46,000 people were diagnosed in 2015.⁴ In 2012 it was estimated to cost the UK economy £2.4billion a year.⁵ The incidence rate of lung cancer increases from 45 years of age and peaks in older populations, primarily the 80-90 year group. However, the overall age standardised incidence has declined over the last 40 years (demonstrated in *Figure 1.1*).⁴ This is a result of a marked decline amongst men and a small increase in women. These age related patterns are a reflection of the higher smoking prevalence during the first half of the 20th century, as tobacco smoking is the single most reversible risk factor for the development of lung cancer.

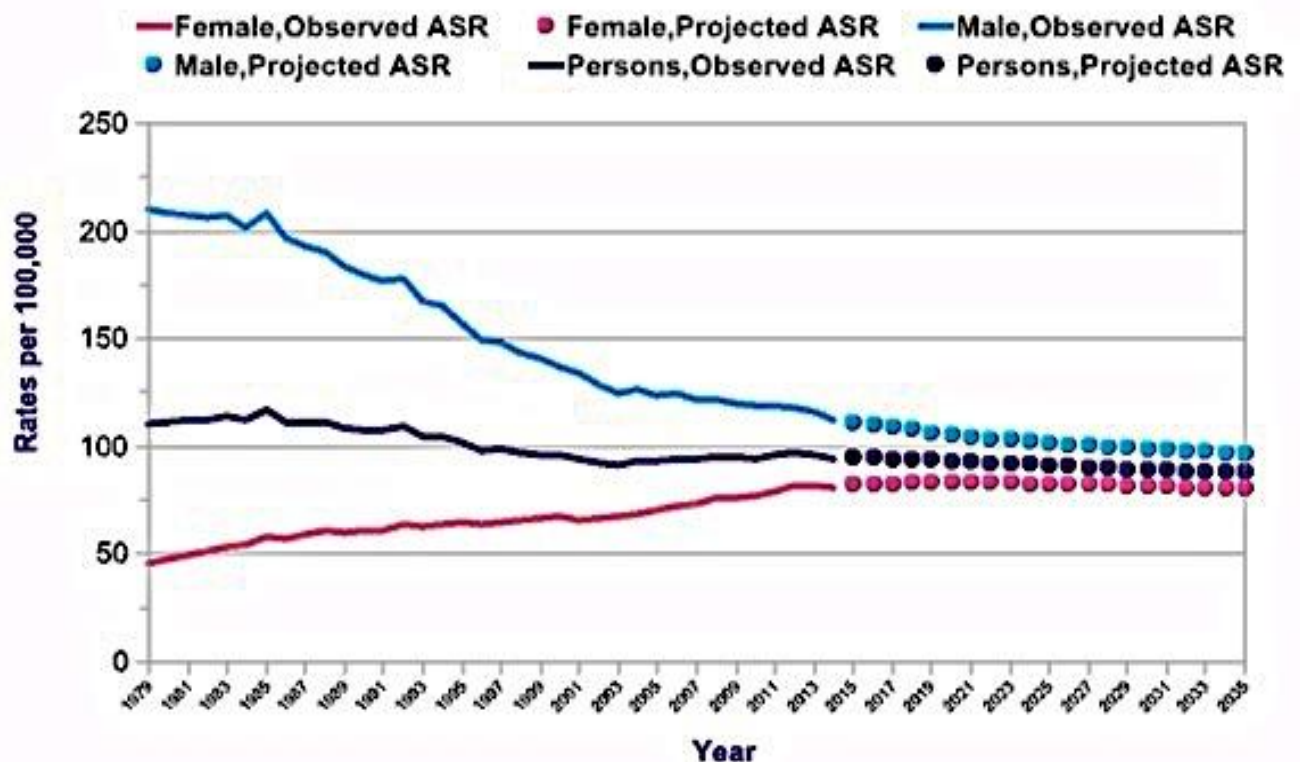


Figure 1-1 Age standardised rate of lung cancer in the UK over time. Reproduced with permission from Cancer research UK.

1.2 Risk factors for lung cancer-Tobacco

1.2.1 History of tobacco

Shortly after Christopher Columbus discovered the Americas in 1492 tobacco was being consumed around the world. Initially used as “snuff” in the 18th century it was later inhaled through smoking cigars. To begin with, cigarettes were produced by the slow process of hand rolling, but this changed. During the industrial revolution, in response to a cash reward offered by the tobacco company Allen and Ginter, James Bonsack created an automated cigarette rolling machine. This could roll 120,000 cigarettes in 10 hours, thereby revolutionising production. This process translated into

cigarettes becoming a more affordable commodity and no longer a luxury item. Since then tobacco companies have developed increasingly sophisticated machinery and techniques to make the cost of producing a cigarette lower. An example of this is reconstituted tobacco, which is a thinly pressed sheet of tobacco dust and stems with extra nicotine added in order to enhance addiction. The incidence of smoking increased at the outbreak of the world wars as tobacco was promoted and rationed to service personnel.⁶ Many of these individuals continued to smoke in the post-war era which led to smoking being accepted as a “social norm”. At this time it seemed common knowledge that smoking was detrimental to health but few of the early studies were accepted and were actively challenged by the tobacco industry.⁷ Eventually attitudes started to change following a series of publications relating to the doctors cohort study by Doll and Hill which found an association between lung cancer and smoking. In this study heavy smokers (≥ 25 g tobacco smoked a day) were twenty times more likely to die from lung cancer than non-smokers.^{8,9}

1.2.2 Tobacco control

The incidence of lung cancer closely reflects the patterns of smoking with an approximate 20-year lag phase.¹⁰ The incidence of lung cancer peaked for men during the 1980s and is now in decline but for women it has slowly risen (as demonstrated in *Figure 1.2*). In the UK during 2017 15.1% of adults smoked, which is considerably less than in 2010 where this was 20.1%.¹¹ These trends in smoking and lung cancer incidence are a result of successive tobacco control measures which were first introduced in the 1980s. The methods deployed have included higher taxation on tobacco products, banning poster and television advertisements, limiting smoking to outdoors in public spaces as well as removing point of sale displays and standardising

packaging. In addition to these measures there has been an increase in the use of electronic cigarettes and these are now the most popular way that smokers attempt to quit, however the health risks of their long term use is currently unknown.¹² Indeed, quitting smoking before middle age can significantly decrease an individual's risk of lung cancer. However, ex-smokers regardless of their quit duration remain at a higher risk than never smokers.¹³

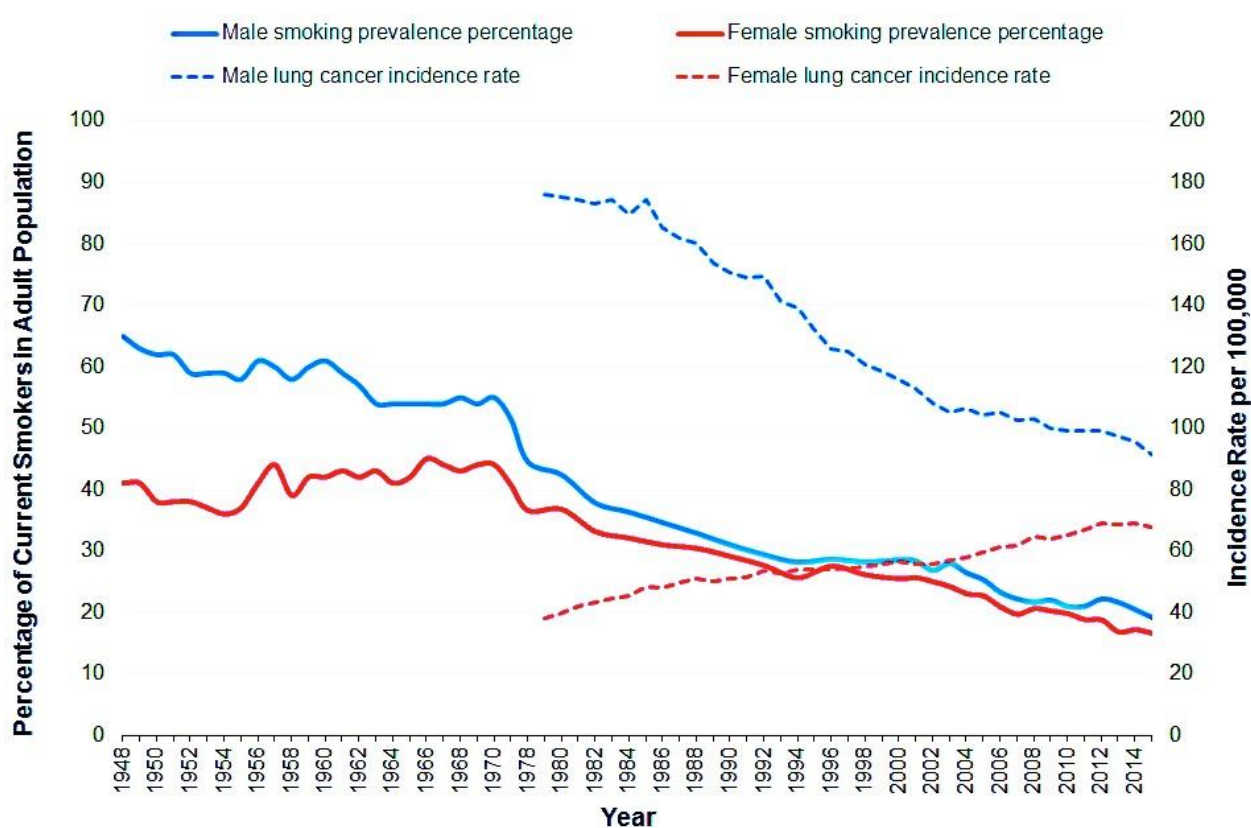


Figure 1-2 Trends of smoking incidence of lung cancer in the UK reproduced with permission from Cancer Research UK

1.2.3 Electronic cigarettes

The electronic cigarette is a handheld device that heats and aerosolizes a liquid containing nicotine, propylene glycol, glycerine and flavourings. This aerosolized vapour is subsequently inhaled. The modern electronic cigarette was invented in China during 2003 and since then its use has steadily increased.¹⁴ From 2017 to 2018 electronic cigarette use was estimated to be 5.4-6.2% of all adults in the UK and amongst tobacco smokers it was 14.9-18.5%.¹⁵ The UK department of health and NICE have stated that smokers should not be discouraged from using electronic cigarettes as a means of stopping tobacco smoking. This statement is supported by a Cochrane review that suggests electronic cigarette users are twice as likely to stop smoking than those using placebo.¹⁵ In addition, based on analyses of the composition of carcinogens within the vapour (of which there are significantly less than tobacco) the Royal college of physicians have estimated that the harm of long term vapour inhalation is about 5% of that for smoking tobacco.¹⁶

Conversely, countries such as Australia, which is viewed as a world leader in tobacco control, do not promote electronic cigarettes as a cessation method. This is because there is evidence to suggest that electronic cigarettes can encourage people to smoke tobacco and start a nicotine addiction via a different route.¹⁷ Indeed, some of the marketing strategies used by electronic cigarette manufacturers bare similarities to that of the tobacco industry with strong use of sexualised branding. Likewise, there is a lack of long-term safety data for electronic cigarette. These concerns are rightly justified as the construction of devices varies significantly and hence the composition of the vapour may also differ. In some analyses formaldehyde and heavy metals, such

as chromium, aluminium and arsenic have been detected at levels similar to, or greater than those found in tobacco.¹⁸

On balance it is reasonable to conclude that the long term health risks of electronic cigarettes and their subsequent impact on the different histological prevalences of lung cancer are currently unknown. Clearly, there are challenges for epidemiological studies to truly quantify the risk of lung cancer amongst electronic cigarette users as many people who vape have also smoked tobacco.

1.3 Other risk factors for lung cancer

1.3.1 Lung cancer in never-smokers

It has been estimated that 6,000 people who have never smoked die from lung cancer each year in the UK and this number is increasing.¹⁹ A never smoker is defined as someone who has smoked less than the equivalent of 100 cigarettes in their life-time. The following risk factors have all been associated with developing lung cancer and are the main aetiological drivers in never smokers.

1.3.2 Passive smoke inhalation

In addition to directly smoking tobacco there is evidence connecting passive smoke inhalation with the development of lung cancer. This risk is estimated to be approximately 24% for non-smokers who live with a smoking partner.²⁰ The other leading cause for passive smoke inhalation apart from tobacco is the burning of solid fuels on indoor cooking stoves. This practice has been associated with the development of lung cancer in addition to other lung diseases such as chronic obstructive pulmonary disease (COPD).²¹

1.3.3 Radon

Radon-222 gas is found in the air as a result of the radioactive decay of uranium-238 that is present in the earth's crust. It is estimated to cause approximately 2% of cancer deaths.²² Exposure is a considerable risk for some occupations such as miners. Outdoor concentrations are typically low however, there is concern that indoor radon gas concentrations can be significantly higher. In developed countries, where homes are well insulated, radon gas can accumulate as a result reduced ventilation. In the Southwest of England high indoor concentrations of radon are common and require action.²³ The UK Health Protection Agency recommends testing and has action levels for specific concentrations of radon gas in new and existing homes which property developers must abide to. Concentrations in newly built homes above 52Bq/m³ require preventative measures such as a sealed ground floor membrane.²⁴

1.3.4 Air pollution

The incomplete combustion of fossil fuels releases organic and inorganic compounds which make up the particulate matter in air pollution. Some of these particles are the same as those found in tobacco smoke. It is difficult to quantify a person's lifetime inhalation of air pollution however, many studies use postcode of residence along with recorded air pollution indices to estimate risk. A meta-analysis of 17 European cohorts found an increased risk of 22% for developing lung cancer in people who lived in areas with higher concentrations of air-born small particulate matter (particulate matter less than 10µm in diameter).²⁵ Presently the risks associated with air pollution have started to gain political traction and measures have been introduced to try and lower inner city concentrations, such as the London congestion fee.

1.3.5 Asbestos

Asbestos fibres, when inhaled into the lungs, cause a chronic inflammatory process leading to the development of lung cancer, mesothelioma and fibrosis. It is estimated to take a minimum of 10-15 years following asbestos exposure for lung cancer to develop.²⁶ Occupations in shipyards, construction and foundries prior to the 1960s are associated with heavy asbestos exposure. During 1969 the UK government introduced regulations for handling asbestos. This, in addition to better public health awareness means that we have probably hit the peak incidence of mesothelioma (currently 6 per 100,000 people) and this is expected to fall by 53% from 2014-2035.²⁷

1.3.6 Family history

There is evidence suggesting a genetic preponderance for developing lung cancer within families. For people with a first degree relative diagnosed with lung cancer under 60 years of age this risk has been estimated to be two to five-fold.^{28 29} However, shared environmental and genetic factors in addition to ascertainment bias (a person is more likely to see a doctor regarding symptoms after a relative has been diagnosed) make this risk difficult to truly quantify.

1.3.7 Iatrogenic

There has been a considerable increase in exposure to ionising radiation on the population through diagnostic imaging over the past 30 years.³⁰ While the risk of developing lung cancer as a result of diagnostic radiation in an individual is small, the extent of its use in the overall population may well translate into a significant number of new lung cancers in the future. The United States (USA), for example, conducted 70

million CT scans in 2007 and this is estimated to cause 29,000 cases of cancer in the future, of which lung would be the commonest.³¹

1.3.8 Comorbidities

Idiopathic pulmonary fibrosis, a disease characterised by inflammation, scarring and fibrosis of the lung parenchyma is independently associated with developing lung cancer.³² Compared to the general population the risk is estimated to be 7 fold. COPD may cause increased levels of oxidative stress, which in turn can drive the development of lung cancer.³³ However, given that smoking and age are confounders to developing COPD this relationship is less clear.

1.4 Histological classification of lung cancer

Histological samples are needed in order to further identify and define a tumour. These can be obtained directly, by sampling the tumour, or indirectly from metastases or a pleural effusion. The sampling methods used include: radiologically guided percutaneous biopsy or fine needle aspiration, bronchoscopic biopsy with or without ultrasound guided trans-bronchial needle aspiration (EBUS TBNA) and surgical resection. Following biopsy tissues are routinely fixed in 10% formalin and then embedded in paraffin. The sample is then cut into 4-5µm slices. The paraffin wax is then removed and the samples are stained with haematoxylin and eosin or used for other special stains, such as chromogranin (for neuroendocrine tumours) and immunohistochemistry, which is particularly useful at identifying subtypes of lung cancer.

There are two histological groups of lung cancer; Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). Approximately 10-15% of lung cancer cases are

SCLC and the rest are NSCLC.⁴ The proportion of SCLC has changed over time as previously it accounted for 20-25% of all lung cancers. This changing incidence is related to the decline of tobacco smoking.³⁴ A study conducted in 2007 examined the incidence of SCLC in the south east of England from 1970 to 2007 and found the age standardised incidence rates have decreased ((males 21% in 1972 to 15% in 2007) and (females 32% in 1972 to 17% in 2007)).³⁵

Mesothelioma, another form of lung cancer, affects the pleural cavity and carries a different prognosis and treatment to other lung cancers and hence will not be discussed further in this thesis.

1.4.1 Non-small cell lung cancer

NSCLC is composed of several histological subtypes. Adenocarcinoma accounts for 50% followed by squamous cell (30%) and large cell (4%) other mixed subtypes exist. In practice there is a further sub-group called NSCLC not specified. This group consists of individuals where the pathologist is unable to distinguish between the NSCLC subgroups. More recently the size of this group has decreased from 12.8% in 2014 to 9% in 2016, partly due to advanced immune-histochemical staining and increased pressure for a more precise diagnosis as many novel therapies are only effective in specific subtypes/mutations.^{36 37} Common immunohistochemical stains used to determine adenocarcinoma are thyroid transcription factor-1 (TTF-1) and cytokeratin 7. Whereas, p40, p63, and cytokeratin 5/6 are associated with squamous cell carcinoma.

1.4.2 *Small cell lung cancer*

Originally SCLC was described as a mediastinal sarcoma.³⁸ It was first classed as a bronchial “oat cell carcinoma” by WG Barnard in 1926 owing to its microscopic appearance resembling the shape of oat grains. Histologically SCLC can be diagnosed on a haematoxylin and eosin stained section. This typically shows cells that are small with prominent nuclei and have minimal cytoplasm (demonstrated in *Figure 1.3*). Sometimes immune-histochemical staining is required to identify SCLC as it can be combined within a NSCLC tumour (1-3%). The stains associated with SCLC are TTF-1, chromogranin, cd56 (neural cell adhesion molecule) and synaptophysin.³⁹

Some of these stains are specific neuro-endocrine markers as SCLC arises from neuroendocrine and neuroendocrine progenitor cells within the central airways, although the exact cell of origin is not known.⁴⁰ Other cells that line the bronchi, but are not associated with SCLC, are; mucous, basal, ciliated and non-ciliated cells.

As a result of its cellular origin SCLC has been categorised under the umbrella of neuroendocrine tumours (NET) by the World Health Organisation (WHO). Other tumours within this WHO spectrum are carcinoid tumours and large cell neuroendocrine carcinomas (LCNEC). It is clear there are major clinical, histological and genetic differences between tumours in this grouping as, for example, carcinoid tumours typically occur in younger people, are slow growing and can often be resected when diagnosed which is in stark contrast to SCLC.⁴¹ One method of differentiating the different NETs is by measuring the mitotic count i.e. the total amount of cells in prophase, metaphase, anaphase and telophase. Mitoses are counted per 2mm² in the areas of highest activity. This can be particularly useful in differentiating typical from atypical carcinoids and high-grade SCLC and LCNEC. Immuno-histochemical testing for

Ki-67 protein, a marker for cellular proliferation, can also be used to determine the amount of cellular division. Lastly, the presence or absence of necrosis (cell death) can also assist differentiation. Neuroendocrine cells, as the name suggests, have endocrine properties where-by they secrete hormones. SCLC shares this characteristic and has been associated with several paraneoplastic syndromes, such as the syndrome of inappropriate antidiuretic hormone. This results in hyponatraemia. Similarly, SCLC expresses antigens similar to those on the surface of neural cells causing the formation of onco-neural antibodies which can cause autoimmune destruction of neuronal cells giving arise to syndromes such as Lambert–Eaton myasthenia.⁴² The culminating effect of these characteristics means that SCLC is very aggressive and spreads rapidly resulting in many people (approximately 70%) being diagnosed with metastatic disease.³⁶ This thesis will now focus on topics related to SCLC instead of other histological types of lung cancer.

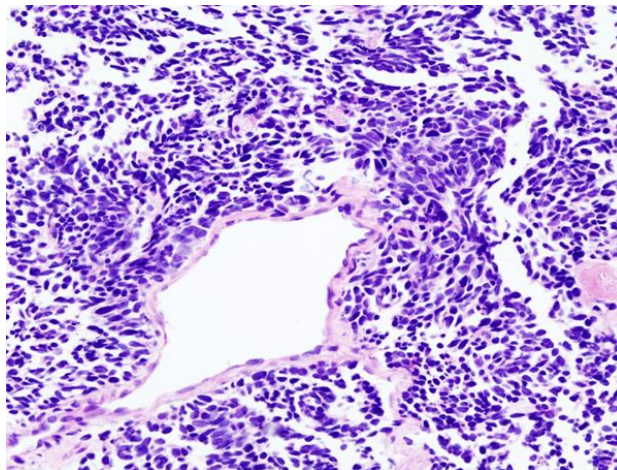


Figure 0-1 Histological template of SCLC with prominent nuclei (purple) in each cell, reproduced from Wikimedia.

1.4.2.1 Association with tobacco

Of all the lung cancer subtypes SCLC correlates the most with tobacco consumption,

however, it can occur in never smokers. The prevalence of SCLC in people who have never smoked varies considerably, most notably between Caucasian (2.0%-2.5%) and East Asian (13%-22.8%) populations. In Asian cohorts there is also evidence to suggest never smokers with SCLC have better survival than people who have ever smoked, an observation more pronounced in females. However, this observation maybe confounded by environmental exposures such as indoor air pollution from cooking oils at high temperatures in a wok.⁴³

1.5 Staging in SCLC

Staging patients with lung cancer is important as it determines treatment and prognosis. Individuals are staged through a combination of diagnostic imaging and histological sampling. The Tumour Node Metastasis system (TNM), which is now in its 8th edition, is an accepted method of staging SCLC, but is more commonly used in NSCLC.⁴⁴ The sub-divisions are as follows.

1.5.1 Tumour

Primary tumour classification is sub-divided according to the maximal tumour diameter, these are: T1a ≤ 1 cm, T1b >1 to 2 cm, T1c >2 to 3 cm, T2a >3 to 4 cm, T2b >4 -5 cm, T3 >5 -7 cm and T4 >7 cm. Tis and T1mi were introduced for adenocarcinoma in-situ and minimally invasive adenocarcinoma. In addition to the tumour size, the position and after effects from it are considered. Endobronchial tumours with any involvement of the main bronchus without the carina are classed as T2 as are tumours causing visceral pleural invasion or total lung atelectasis/pneumonitis extending to the hilum. Tumours of any size that invade the chest wall, pericardium, phrenic nerve or have nodules within the same lobe are T3. Similarly, any sized tumour invading the

diaphragm, mediastinum, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine or have an additional tumour in a different lobe of the ipsilateral lung are classed as T4.

1.5.2 Node

N denotes the lymphatic involvement of the tumour. The lymph node station descriptors are: N0 no lymph node involvement, N1 ipsilateral hilar node, N2 ipsilateral mediastinal or sub carinal node, N3 contralateral mediastinal or supraclavicular/scalene node.

1.5.3 Metastases

M0 signifies that no metastases are present. M1a represents intrathoracic metastases such as tumour in the contralateral lung or pleural effusion. Extra-thoracic metastases are classified as M1b (a single extra-thoracic metastasis in a single organ) or M1c (multiple extra-thoracic metastases in a single organ or multiple organs).

1.5.4 Veterans Administration Lung cancer Study Group (VALSG)

In comparison to TNM the VALSG staging system is more routinely used in everyday clinical practice for SCLC. This system divides SCLC into limited (LD-SCLC) and extensive stage (ED-SCLC). LD-SCLC is defined as any tumour that is confined to one hemi-thorax and regional lymph nodes (including ipsilateral supraclavicular nodes) that can be safely encompassed in one radiotherapy field. ED-SCLC accounts for any tumour/s that cannot be encompassed in one radiotherapy field i.e. spread beyond one hemi-thorax, malignant pleural effusion or metastasis to other organs. The National Institute for Health and Care Excellence (NICE) broadly equates limited disease as T1-4, N0-3, M0 (7th edition) whilst extensive disease is any T or N with M1a/b spread. Over time,

radiotherapy techniques have improved allowing more tumour to be encompassed, which in some cases, has resulted in the line between LD-SCLC and ED-SCLC becoming less clear. Indeed, some hospitals may lack the expertise to treat some N3 disease in a single radiotherapy field which leads to individuals being managed as ED-SCLC. Ultimately, for both stages of cancer the mainstay of treatment is the same, chemotherapy.

1.6 Treatment of SCLC

In the UK NICE published the clinical guideline CG121. This outlines the diagnosis and treatment for individuals with suspected/diagnosed lung cancer.⁴⁵ During the process of writing this thesis these NICE recommendations have undergone minor alterations to accommodate new evidence. These changes state that thoracic radiotherapy and prophylactic cranial irradiation (PCI) should be “considered” instead of “offered” to all patients who have responded to chemotherapy.⁴⁶ Regardless of these minor changes the guideline recommendations are similar worldwide, except for subtle differences due to the variations in healthcare infrastructure.^{47 48} I will focus on the treatments for SCLC recommended within the UK by NICE.

1.6.1 *Chemotherapy*

First line

Chemotherapy is the mainstay of treatment for individuals with SCLC as initial response rates have been quoted as high as 80%.⁴⁹ The treatment has remained the same since the 1980s and is a combination of a platinum drug, typically cisplatin or carboplatin with etoposide (a topoisomerase II inhibitor). Other drugs, such as irinotecan, are sometimes favoured ahead of etoposide in Asia.⁴⁸ Principally these drugs effect deoxyribonucleic acid (DNA) replication and, as such, rapidly dividing

cancer cells like SCLC are most susceptible. Cisplatin and carboplatin interfere with DNA replication by a process of aquation which causes DNA damage and triggers cellular apoptosis when DNA cannot be repaired. Etoposide is derived from the American Mandrake plant (*Podophyllum*) and similarly effects cell division by inhibiting the topoisomerase II enzyme that is needed to unravel DNA from the double helix in order for mitosis to occur.

The platinum combination of treatment has been demonstrated in several systematic reviews to have comparable survival outcomes to alkylator and anthracycline based regimens. Its advantage lies with the ability for the platinum and etoposide to be given at full dose alongside radiotherapy as well as having more favourable side effects.⁵⁰⁻⁵²

The associated side effects of cisplatin typically are: nephrotoxicity, severe vomiting and alopecia. Prior to starting treatment patients are given intravenous hydration in order to reduce the risk of kidney injury. This poses a significant time burden in addition to the distress caused by vomiting and alopecia. These factors are important to consider, particularly when cure is not an objective and more often a holistic approach to treatment is taken. Hence, carboplatin is favoured as it does not require pre-hydration and is less emetogenic. Here the main side effect is bone marrow suppression and whilst this is generally better tolerated by patients it carries a significant risk of neutropaenic sepsis and death. This risk is highest around two weeks after treatment as the white cell nadir occurs at this time. Granulocyte colony-stimulating factors can be given to increase white cell count but prophylaxis with these is not recommended with the first chemotherapy cycle.⁵³

Each cycle of platinum combination therapy is usually 21-28 days and it is recommended patients receive 4-6 cycles in total. Drugs are administered intravenously and response is assessed during (usually cycle 3) and after completion of a regimen.⁵⁴ Continuing chemotherapy beyond 6 cycles as “maintenance” has been shown (in a meta-analysis of 11 trials) to result in marginally improved survival (HR 0.89 %95%CI 0.81-0.92).⁵⁵ However, there was considerable heterogeneity between trial results and maintenance therapy exposed patients to more side effects, therefore it is not recommended in practice.

Second line

Unfortunately progression occurs for many patients within the first year of receiving initial chemotherapy. Patients with recurrent disease can be divided into two categories based on the likelihood of response to second-line therapy: resistant disease (progression within 3 months of first line treatment) and sensitive (progression after 3 months from initial therapy). Second-line treatments are limited in number and their benefits are questionable as response rates are low and side effects can be significant. NICE recommends second-line treatment with cyclophosphamide, doxorubicin and vincristine (CAV) or a different platinum doublet regimen initially. If these cannot be given then single agent oral topotecan can be used. This has similar response rates to CAV (approximately 7%) but has a lower risk of causing haematological toxicity.^{56 57 45}

1.6.2 Novel systemic therapies

The systemic treatments for SCLC have remained the same for 30 years but novel therapies, in particular immunotherapies, are beginning to show promise.

Immunotherapies “weaponise” the body’s immune system against cancer cells. The cellular immune pathway commonly targeted is the programmed cell death-1 receptor (PD-1 on the surface of T cells) and its ligand programmed cell death ligand 1 (PD-L1 overexpressed on the surface of tumour cells). One would think that SCLC seems to be the perfect tumour for novel immunotherapies owing to its rapid proliferation and immunogenic nature, however, these drugs have had limited success. The most promising result of their efficacy in SCLC has been the IMPOWER 133 study.⁵⁸ In this trial patients with ED-SCLC were randomized to receive atezolizumab (an anti-programmed death ligand 1 antibody) in addition to standard chemotherapy. The results showed a better median overall survival of 12.3 months vs 10.3 months in the experimental group, however this improvement in survival was lower than anticipated. Similarly, early clinical trials using nivolumab (anti-PD1 antibody) + ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4 antibody) in recurrent SCLC have shown sustained anti-tumour activity with up to 19% 1-year progression free survival.⁵⁹ However, other trials using nivolumab as maintenance therapy (Checkmate-451) and second line therapy (Checkmate-331) have failed to show a survival benefit and have tempered enthusiasm.^{60 61} Another anti-PD1 therapy, pembrolizumab, has also shown no survival benefit in comparison to chemotherapy, however, it is thought that a small subset of patients with higher PD-L1 expression may respond and further research is planned.⁶² In practice these small gains in survival may not be enough to justify the costs of immunotherapy in SCLC. The list cost of pembrolizumab is estimated to be £84,000 per patient but in June 2018 National Health Service (NHS) England managed to agree a deal of an undisclosed amount so that pembrolizumab can be routinely used within the NHS to treat NSCLC.⁶³

In addition to immunotherapies anti-angiogenic drugs, such as thalidomide and bevacizumab, have been trialled but have failed to augment survival in phase III randomized controlled trials despite promising earlier results.^{64 65}

1.6.3 Radiotherapy

Principally there are three forms of radiotherapy given in SCLC. These are thoracic radiotherapy, Prophylactic Cranial Irradiation (PCI) and palliative radiotherapy to metastatic sites.

For people with LD-SCLC who have a good performance status (PS 0-1) concurrent chemoradiotherapy is recommended.⁴⁵ Thoracic radiotherapy should start within the first 2 cycles of chemotherapy. This recommendation is supported by findings from 2 meta-analyses that have demonstrated an increase in overall survival with early radiotherapy in comparison to sequential radiotherapy of 5.2% at 2 years and 1.8% at 5 years.^{66 67} Concurrent treatment does have a greater risk of side effects, chiefly oesophagitis and pneumonitis, hence it is reserved for fitter individuals.

Sequential thoracic radiotherapy is recommended for individuals with LD-SCLC who are unfit for concurrent treatment and have stable or responsive disease following chemotherapy. A seminal meta-analysis found that 5-year survival was 14.3% with sequential radiotherapy and 8.9% without radiotherapy.⁶⁸ The effectiveness of thoracic radiotherapy in ED-SCLC is less clear however, it is recommended for individuals who have responded to chemotherapy and have persistent thoracic disease.⁶⁹ This recommendation is supported by a prospective randomized study that administered radiotherapy to chemotherapy responders and saw an improvement in median survival of 6 months in comparison to no radiotherapy.⁷⁰ A subsequent meta-

analysis has also indicated the survival benefits of thoracic radiotherapy in ED-SCLC.⁷¹ In contrast to both these findings *Slotman et al* did not see a significant improvement in 1-year survival with the addition of thoracic radiotherapy following chemotherapy for ED-SCLC.⁷²

The lowest total radiation dose used to treat LD-SCLC both concurrently or sequentially is 40Gy divided into 15 fractions. Other commonly used schedules for LD-SCLC include: 45Gy in 30 fractions and 66Gy in 33 fractions.⁶⁹ The optimum dosing schedule for LD-SCLC remains a subject of much discussion. *Turrisi et al* compared 45Gy in once daily 1.8Gy fractions with 45Gy in twice daily 1.5Gy fractions and found twice daily conferred better survival.⁷³ However, in clinical practice a once daily regimen is much easier to deliver. The CONVERT trial compared the *Turrisi* twice daily schedule with 66Gy in once daily 2Gy fractions and found that survival and toxicity in the once daily group was not superior to the twice daily schedule.⁷⁴ For ED-SCLC, there is less variability in radiotherapy schedules. The recommended schedule for chemotherapy responders and for palliation of thoracic symptoms is 30Gy split into 10 fractions over 2 weeks.⁶⁹

PCI aims to lower the chances of developing brain metastases following chemotherapy as the brain is a common site of relapse, owing to limited penetration of drugs through the blood brain barrier. PCI is recommended for patients <75 years with PS 0-2 whose cancer has not progressed on first-line treatment.⁷⁵ The typically recommended doses for PCI are 20 or 25Gy in 5 or 10 fractions respectively.⁶⁹ In some initial studies PCI reduced the incidence of brain metastases but unfortunately caused dementia and leukoencephalopathy in long term survivors.⁷⁶ The people most at risk of these

complications have been identified as individuals >65 years and with vascular disease.⁷⁷ Hence, with better patient selection and lower dosing schedules these side effects are now rare. Instead, the main adverse effects are fatigue and headache (approx. 25%).⁷⁸ For LD-SCLC the benefit of PCI is widely accepted. A systematic review which included mostly LD-SCLC patients from 7 clinical trials found PCI improved overall survival for people who were in complete remission following chemoradiotherapy for SCLC.⁷⁹ The evidence supporting PCI for ED-SCLC is less clear. The study showing a survival benefit, conducted by the European Organisation for Research and Treatment of Cancer (EORTC) had pitfalls, as initial responses to chemotherapy were not recorded and participants were not screened for asymptomatic brain metastases.⁸⁰ With these concerns addressed, a similar trial, that recruited mostly partial chemotherapy responders, failed to show any survival benefit with PCI.⁸¹

Other radiotherapy modalities exist but their use is not recommended in SCLC and they remain experimental. Stereotactic Ablative Body Radiotherapy (SABR) is able to deliver large doses of radiation with a high precision of 1-2mm to small lesions of <1cm³ using an external 3D co-ordinated system that is linked with movements during the respiratory cycle. SABR is recommended for NSCLC where surgical resection is not possible and individuals have early stage (≤5cm in largest diameter) and peripherally located (2cm outside of main airways and proximal bronchi) tumours. There is a small evidence base that suggests this modality of radiotherapy in combination with chemotherapy is a viable strategy for treating similar SCLC tumours.⁸² Case reports have described treating early stage peripheral tumours with radiofrequency or microwave ablation.⁸³ Here a probe is percutaneously inserted into the tumour under

computerised tomography (CT) guidance and a radiofrequency current or microwaves are used to thermally destroy the tumour.

1.6.4 Surgery

Surgical treatment has a limited role in SCLC but is recommended for the small proportion of patients (<5%) that present with very early stage (T1-2a, N0, M0).⁴⁵

Research by the International Association for the Study of Lung Cancer (IASLC) has estimated the 5-year survival following surgical resection for stage IA disease to be 53%.⁸⁴ Patients undergoing surgical resection must have adequate performance status (a measure of wellbeing) and physiological reserve. This is usually measured with pulmonary functions tests and in moderate to high risk patients exercise tests are recommended.⁴⁵ More recently, with the development of modern surgical techniques, such as Video Assisted Thoracoscopic Surgery (VATS) and the experimental robotic assisted thoracic surgery, the boundaries of surgical fitness are changing as these operations typically cause less tissue trauma than open resections and offer quicker recovery.⁸⁵

1.6.5 Palliative and supportive care

Specialist palliative and supportive care has an important role for managing symptoms and psychological well-being of people with SCLC, furthermore there is evidence suggesting it can augment survival. *Temel et al* examined the effect of early specialist palliative care involvement compared with standard care in patients with metastatic NSCLC.⁸⁶ They discovered a considerable difference in median survival with the early supportive care group faring better than those in standard care (11.6months vs 8.9 months, $p=0.02$). In addition these patients scored better quality of life and fewer

depressive symptoms and were less likely to require aggressive end of life care support. This finding of improved survival is backed by another randomised controlled trial (RCT) across all types of cancer.⁸⁷

The American Society of Clinical Oncology (ASCO) has recommended integrating early enhanced supportive care into standard oncology care for people with advanced cancer after systematically reviewing the available evidence. They concluded that early palliative care improves quality of life, reduces depression and improves satisfaction with care. However, they deduced that there was less evidence showing it improves survival.⁸⁸

1.7 Structure of cancer care in the UK

Until the publication of the Calman-Hine report in 1995, cancer care was provided by individual surgeons and physicians, some of whom may not have had respiratory expertise.⁸⁹ This report highlighted the need for uniform high quality care across England and Wales, raising patient awareness and the creation of specialist cancer units, or Multidisciplinary teams (MDTs) as they are now called. The MDTs consist of respiratory and oncology physicians, thoracic surgeons, pathologists, radiologists as well as specialist nurses. Here patient cases are discussed and a treatment plan is created and documented based on the collective expert opinion. Clearly, there are benefits to the patient, clinician and lung cancer community by this system however it poses a substantial time burden to cancer service providers and can cause significant delays to treatment if information is not available for discussion.⁹⁰ Since the publication of the Calman-Hine report there has been further restructuring of cancer care. The national cancer plan in 2000 set out targets for referral to diagnosis and treatment.⁹¹

These targets have been challenging for some hospitals to meet due to inefficiencies in the diagnostic pathway. The National Optimum Lung cancer Pathway, published in 2017, addresses these inefficiencies by introducing same day reporting of chest X-rays with subsequent CT imaging on the same day or within 72 hours for those with a high suspicion of cancer (flow chart of early pathway in *Figure 1.4*). This, combined with other measures, reduces the length of the pathway to 49 days from date of referral to the start of treatment which is well within the current 62 day target set by NHS England.

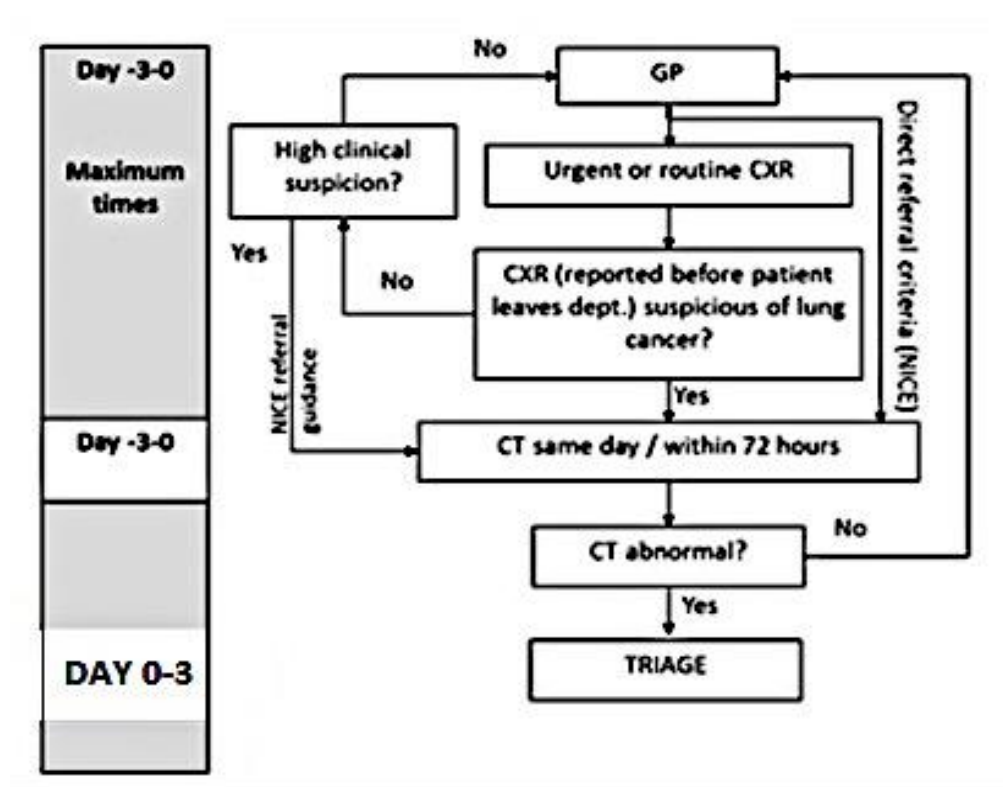


Figure 0-1 First stage of the national optimum lung cancer pathway. Zero corresponds to the date of referral.

Variation in access to cancer therapies still exists despite the optimism of the national cancer strategies in 2000 and 2007. The Department of Health have acknowledged this

and in the 2011 document “Improving outcomes: A strategy for cancer” they have set out plans to improve data collection for cancer diagnostics, treatments and survival. Better data capture and quality will help improve the understanding of these variations in care and survival and will aid health care providers in directing their services in the future.⁹²

1.7.1 Access to treatment by institutional factors

Across the UK cancer services are based upon a “hub and spoke” model. Whereby, smaller hospitals with fewer resources and expertise feed into larger units that have on-site specialist thoracic services such as surgeons, radiotherapy and diagnostics. This model, although successful, is partly the cause of inequalities in access to treatments.⁹³ The treatment rate of chemotherapy for SCLC in England and Wales has remained approximately 68% in recent years.³⁶ However, there is considerable variation in this between hospitals with some treating 28% whilst others treat close to 100%.³⁶ The variation in chemotherapy use as a result of the hub and spoke model has been described by *Rich et al* whereby hospitals that recruited more patients for clinical trials (hub units) were more likely to administer chemotherapy to people with SCLC than hospitals that did not.⁹⁴ Other research has shown after case mix adjustment patients are more likely to receive chemotherapy if they are diagnosed in a hospital that provides $\geq 75\%$ of chemotherapy on site.⁹⁵ These findings are reproduced when examining radiotherapy and surgery for lung cancer.^{93 96}

1.7.2 Access to treatment by patient factors

Access to treatment for lung cancer not only differs by institutional factors but has been shown to vary by patient characteristics. PS has consistently been shown to

influence receipt of treatment as people with a worse PS are less likely to receive it.⁹⁴

⁹⁵ Similarly older patients, typically greater than 70 years age, are less likely to receive chemotherapy in SCLC even after adjustment for PS and comorbidities. Nihilism amongst patients and clinicians in this age group is thought to be a key reason behind this observation. The increasing number of comorbidities a person has is independently associated with a lower chance of receiving chemotherapy.⁹⁴ The evidence for socioeconomic status (SES) and stage is mixed as some studies have shown a relationship between receiving chemotherapy whilst others have not.^{97 94 98} Receipt of treatment by SES might be a result of access to transportation and the distance travelled as poorer individuals are less likely to own a car. Indeed, centralisation of lung cancer services can make attending appointments extremely difficult if you do not own a car. A study in northern England demonstrated that poorer people who lived furthest away from hospital were less likely to receive active treatment for lung cancer.⁹⁹ Interestingly, in SCLC there were no differences by distance, which the authors concluded was due to chemotherapy for SCLC being more available in smaller district hospitals.

1.8 Survival

The natural life expectancy for people with SCLC is approximately 5 weeks for ED-SCLC and 12 weeks for LD-SCLC. This observation came from work conducted by *Zelen et al* during the 1970s where the survival of patients in the placebo arm of early VALSG randomized controlled trials were studied.¹⁰⁰ After receiving chemotherapy median survival is estimated to be 7-11 months and 12-16 months for ED-SCLC and LD-SCLC respectively.¹⁰¹ In the UK survival for all histological subtypes of lung cancer has

consistently lagged behind other countries with similar gross economic product. When compared to Canada, where the age standardised 5-year survival is 18.4%, the UK's 5-year survival of 8.8% is significantly less.¹⁰² Proposed reasons for this include: increased later stage diagnoses, fewer surgical resections and suboptimal patient selection for treatment. The Department of Health has addressed the issue of patient selection by dividing survival into early and late. They propose that early deaths (within 30 days of treatment) are a metric of poor selection as these indicate that treatment was unsuitable or unnecessary.⁹²

1.8.1 Early survival

Previously defined early survival endpoints are 30 and 90 days. Deaths that occur within 30-days of treatment are largely related to direct toxicity or inappropriate use of treatment, where perhaps it should have been avoided. Early deaths following lung cancer surgery have been examined extensively and mortality risk prediction scores have been developed to help select patients.^{103 104} By comparison the evidence base surrounding early mortality following chemotherapy is sparse. This is particularly true for SCLC where in fact the risks and rewards of treatment are greater, as this cohort have appreciable smoking related comorbidities and a prognosis of weeks without treatment. *Wallington et al* estimated the 30-day mortality following systemic anti-cancer therapy for lung cancer to be 8%, which is considerably higher than the 2% observed for breast cancer.¹⁰⁵ They did not examine SCLC in detail but found for NSCLC PS, age, treatment intent and sex were all independently associated risk factors for early death. The leading causes of early death in SCLC have been identified as disease

progression and neutropaenic sepsis.¹⁰⁶⁻¹⁰⁹ Several scores have been developed to estimate the risk of neutropaenic sepsis but none have been validated in an external dataset. The factors identified and included in these scores are: age (>50 years), 3 chemotherapy drugs, PS, previous sepsis and white cell count.

1.8.2 Late survival

Long term prognosis for people with SCLC is poor and 5-year survival following treatment is 10-13% for LD-SCLC and 1-2% for ED-SCLC.¹¹⁰ A person's sex, age, PS, stage, PS and laboratory measures (sodium and lactate dehydrogenase (LDH)) are important in determining the chances long term survival. Females have better survival than males, probably due to the protective effects of oestrogen.¹¹¹ Elderly patients are defined as people >70years in SCLC and have been shown to have shorter survival.⁹⁴ However, when comorbidities and PS have been adjusted for (as these also determine receipt of chemotherapy) the association with age is less clear. The IASLC have validated TNM staging in SCLC and have shown differences in survival between patients with LD-SCLC. Based on pathological staging people with N0 disease had 82% 1-year survival in comparison to those with N2 disease which was 54%.⁸⁴ Similarly, survival disparities exist within ED-SCLC as individuals with brain and liver metastases have the poorest prognosis in comparison to bone and soft tissue metastases.^{112 113}

Perhaps the most widely known prognostic score in SCLC is the Manchester score.¹¹⁴ It remains one of the few scores to be validated in an external dataset and is used to predict 2-year survival.¹¹⁵ The score estimates survival from PS and stage in addition to the serum: LDH, sodium, alkaline phosphatase and bicarbonate. Scores of 0-1 correlate to good prognosis (2-year survival 16.2%), whilst scores of 2-3 and ≥ 4 are

classed as medium (2-year survival 2.5%) and poor (2-year survival 0%) respectively. The Marsden prognostic score was created after eleven pre-treatment factors were evaluated. The researchers found PS, stage, alkaline phosphatase, sodium and albumin were associated with survival.¹¹⁶ The score divides patients into good, intermediate and poor prognosis based on their stage, PS and elevation or reduction of serum markers. Despite the Manchester and Marsden scores being externally validated neither are recommended by NICE or other international guidelines.⁴⁵

1.9 Justification of thesis

Reducing variation in treatment administration and encouraging appropriate patient selection are important targets set by successive UK governments. This research will directly address these targets and investigate factors associated with receipt of treatment and survival in SCLC. This will be achieved by examining national audit data as well as conducting a comprehensive systematic review and meta-analysis of early and late survival in SCLC. This knowledge will benchmark survival based on the currently recommended treatments and will better inform treatment choices and patient selection in the future. In addition, this thesis will investigate treatment and survival variation by hospital networks in England in order to better inform national healthcare commissioning.

1.10 Thesis objectives

This thesis aims to answer the following research objectives by examining original audit data and conducting a systematic review of the historical literature in SCLC. These objectives are:

1. Determine the factors associated with receipt of chemotherapy in SCLC and how these are related to early mortality.
2. Examine how the access to chemotherapy, radiotherapy and PCI vary by geographic location.
3. Determine what patient, tumour, treatment and hospital factors are associated with early and late survival for SCLC.
4. Establish early and late survival benchmarks following platinum based chemotherapy for SCLC.

In addition to these objectives over the course of this PhD I have increased my knowledge and skills as a lung cancer physician by conducting smaller research projects in other aspects of lung cancer care. These can be found in Appendix B.

1.11 Outline of thesis

Chapter 2: Description of databases- A description of the datasets used in the analyses outlining their background, variables used and strengths and weaknesses.

Chapter 3: Factors influencing treatment selection and thirty-day mortality following chemotherapy for people with small cell lung cancer: an analysis of national audit data- Linked national audit data are used to determine the factors associated with receipt of chemotherapy and how these are related to 30-day mortality.

Chapter 4: Quantifying factors associated with 1-year survival for people with SCLC using national audit, chemotherapy and radiotherapy data- This study linked national audit data to determine the patient, tumour, treatment and hospital factors that are associated with 1-year survival.

Chapter 5: A systematic review and meta-analysis of survival following anti-cancer treatment for SCLC- a systematic review and meta-analysis of survival was conducted following platinum based chemotherapy for SCLC. Survival was benchmarked at 30 and 90 days, 1 and 2 years, 5 years and median survival.

Chapter 6: Conclusions and future research- This chapter will summarise all the research in this thesis and discuss potential topics for research in the future.

1.11.1 Statistical methods, data management and word processing

All analyses were conducted using the statistical software package STATA version 14 & 15 (StataCorp, Texas, USA). Microsoft Excel 2013 was used for data collection during the systematic review. In order to acquire the knowledge to use these software and conduct the statistical analyses myself I attended training modules at the University of Nottingham.

1.11.2 Acknowledgements

I developed the research questions for all the studies in this thesis. Two studies utilised national data; the National Lung Cancer Audit (NLCA), Systemic Anti-Cancer Therapies (SACT), National Radiotherapy Dataset (RTDS) and Hospital Episode Statistics (HES). I acquired these data through a sharing agreement with Public Health England (PHE) (contract in Appendix C). Dr *Aamir Khakwani* organises the data and performs the statistical analysis for the annual NLCA report. He is an expert working with these data and provided a method to define some variables in the datasets, these included: stage, histological type and Charlson index (adapted from Dr *Anna Rich's* MD thesis 2008).¹¹⁷ I modified the aforementioned variables for this thesis and performed all other data

organisation and statistical analyses myself. Prof *Tricia McKeever* provided additional statistical support if needed. I interpreted the results from these tests and drew conclusions of their meaning by extensively searching and studying the current evidence base and comparing my findings.

Chapter 2 Databases

This chapter introduces the data sources used for chapters 3 and 4 in this thesis. I will discuss their background, the variables used and their strengths and limitations.

2.1 Ethical approval

The datasets used in this thesis were the National Lung Cancer Audit (NLCA), Hospital Episode Statistics (HES), Office of National Statistics (ONS), Systemic Anti-Cancer Therapies (SACT) and the national Radiotherapy Dataset (RTDS). These data are owned by PHE and access to these was obtained through a data sharing agreement with them. Before obtaining a data sharing agreement I acquired ethical approval for the proposed studies. This was obtained by writing and submitting a study protocol (Appendix D) through the Integrated Research Application System. This submission was subsequently reviewed by the NHS Health Research Authority, London Camden & Kings Cross research ethics committee (REC reference 16/LO/0503) and ethical approval was granted. The raw data extracts from PHE were received by Dr Aamir Khakwani, at the University of Nottingham, (who conducts the statistical analysis for the NLCA report) and these raw “uncleaned” files were shared with me. All data were anonymised by PHE England prior to my receipt and I conducted all the data cleaning and statistical analyses myself.

2.2 The National Lung Cancer Audit

2.2.1 Background

The NLCA was developed in response to an increasing need to monitor lung cancer care and variation across the UK as survival lagged behind other countries with similar health systems and wealth. It includes all patients diagnosed with SCLC, NSCLC, mesothelioma and carcinoid tumours. Established in 2002, by the Royal College of Physicians, the NLCA benchmarks standards of care for lung cancer and aims to reduce variation by comparing hospitals to these standards and taking action if they fall

significantly below these. In its earlier years data submission was non-mandatory and was done individually by each hospital trust to a bespoke dataset, Lung Cancer Data (LUCADA). This resulted in poor case ascertainment initially but improved with time (2004 ascertainment 19%, 2013 ascertainment 98%).¹¹⁸ In 2014, the method of data collection changed and submissions are now mandatory and monthly. Data are submitted by different hospital information technology (IT) systems (MDT software, Patient administration systems and pathology systems) to the Cancer Outcomes and Services Dataset (COSD). COSD is then processed by the National Cancer Registration Service (NCRAS) at NHS England to form the NLCA data. This new method ensures 100% case ascertainment and in its first year identified an additional 6,000 cases of lung cancer that were not accounted for by the previous method.¹¹⁹ The University of Nottingham is commissioned to carry out all statistical analyses of the audit data for the annual report. This annual report, published in December/January, details national and trust level results in comparison to audit standards e.g. 1-year survival. If trusts fall below 2 or 3 standard deviations from this standard an alert process is triggered to ensure a cause is identified and an action plan is created. This process provides an incentive for trusts to ensure accurate data entry and makes the NLCA an excellent resource for research. Indeed, the Roy Castle Lung Cancer Foundation stated in 2014 that the NLCA had been referenced in 175 research articles.¹²⁰

2.2.2 How the data were processed

I received raw data extracts from PHE. NLCA data is presented in a wide format and is composed of individual patient data that have been pseudo-anonymised. This means identifiable information such as name, date of birth address have been removed and instead are replaced by a unique identifier number. A person's unique identifier is the

same across all the datasets used in this thesis, which is how records were linked for the studies in chapters 3 and 4. In order to perform statistical analyses and ensure the data were accurate I had to process them. Each line of data corresponded to a record of that patient's cancer journey from diagnosis through to treatment and survival. However, in the raw extracts I received there were duplicate records for each patient. Duplicate records were found by searching the identifier numbers. Each duplicate was examined and the record with most complete and up to date survival data was kept. I ensured that the date of death did not pre-date the date of diagnosis or date of treatment. Records with diagnosis dates after death dates were removed and treatment was classed as not given if the death date preceded it.

Each variable within the dataset was examined for data completeness. I decided that if a variable had >50% missing data it should be dropped from the dataset and subsequent analysis. This was done to ensure analyses were performed on the most accurate and best quality data. Examples of variables that were not used were forced expiratory volume in 1 second and smoking status as data were missing in 87% and 66% of patients respectively. Many variables such as dates, histological code and staging were coded in a "string" format i.e. alphabetical rather than numerical. These string variables cannot be used in statistical analyses and the values are dependent on spelling and punctuation. Therefore, in order to be grouped effectively and used in analyses I converted them to a "float" (numerical format). The differences in spelling and punctuation were identified by using the tab command in STATA. This generated a list of values/entries for that variable. I then systematically reviewed this list and ensured that each entry was captured under a numerical code in the newly generated float variable (using the gen command). Examples of variables where this process was

used was hospital trust (this was grouped by cancer network instead of trust as not every hospital can give systemic anti-cancer treatment), stage and ethnicity. Ethnicity was not used in the final analyses as approximately 87% of patients were Caucasian and 10% had missing data. This meant all other ethnic groups contained too few numbers to perform statistical analyses using these data.

2.2.3 Variables used in this thesis

Patient demographics: age at diagnosis and sex.

Socioeconomic Status: The NCRAS have postcode data for a person and are able to calculate a Townsend score of deprivation based upon this. This score is divided into quintiles where 5 is most deprived and 1 is least deprived. The post code data were removed from the NLCA extracts I received.

Performance Status: PS is a subjective measure by the clinician of an individual's wellbeing and level of independence. PS is coded as 0-5 in alignment with the WHO criteria, as shown in *Table 2.1*. PS is taken at the point when the patient is first seen in hospital. An individual's PS was classed as missing if it was not recorded or coded as 5 (dead).

Table 2.1 WHO definition of performance status

Grade	Explanation of activity
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Stage: Pre-treatment and pathological stage are recorded in the NLCA. For this thesis the pre-treatment records were used as pathological staging is only carried out following surgery, a treatment rarely used in SCLC. Stage is recorded in the Tumour Node Metastases format version 7 (as outlined in chapter 1). The TNM stages were adapted into the equivalent VALSG stage. Limited stage equated to T1-4, N 0-3, M0 and extensive stage was any M1a/b disease. Stage was classed as missing if TNM records were incomplete or contained ambiguous values such as “T=4c” or “T=3s”.

Histological subtype: The histological code of each patient was examined to identify the SCLC cases. Histology is recorded using Systematised Nomenclature of Medicine (SNOMed) codes. The codes used to identify SCLC were: M8041/3, M8042/3,

M8043/3, M8044/3 and M8045/3 (full code list included in Appendix E). Patients with no record for histological diagnosis were assumed to have NSCLC as this accounts for the majority of lung cancer cases.

Date of diagnosis: Records were removed if the date of diagnosis was after the date of death as these represent diagnoses made at post mortem.

Hospitals first seen: All patients have a hospital trust where they were first seen for their diagnosis of lung cancer. As there are fewer SCLC diagnoses per year than NSCLC hospital trusts were grouped by lung cancer network. A lung cancer network was a system within the NHS to organise the integrated care of cancer patients across a geographical region. In England there were 13 lung cancer networks these are: London Cancer alliance, Cheshire and Merseyside, Greater Manchester, Lancashire and South Cumbria, Northern England, Yorkshire and Humber, East of England, East Midlands, West Midlands, South West, South East Coast, Thames Valley, Wessex and London Cancer. In September 2016 cancer networks were replaced by cancer alliances, of which there are 19 in England.¹²¹

2.2.4 Strengths and limitations

The NLCA has many strengths. Annually there are nearly 40,000 new lung cancer cases added, making it larger than other European datasets. We can be certain that 100% of lung cancers diagnosed in secondary care are included due to the new method of data collection. There are strong incentives for trusts to ensure accurate data entry and the NLCA has been validated by *Rich et al* to show it truly represents cases of lung cancer.¹¹⁷ The NLCA provides a picture of the real world diagnostic and treatment

pathways used for patients and there are well established research methods of processing the data as the recorded variables have remained the same.

Its limitations are the same as any other observational data. There are many confounders and biases that influence receipt of treatment and survival in the real world and not all these can be adjusted for in statistical analyses. The NLCA is still reliant on the accurate coding and entry of data and some variables, such as PS and stage frequently have missing data, however, this is improving with time (2016 completion for PS and stage were 81% and 96% respectively).³⁶ In my analyses missing data were assumed to be missing completely at random and were included in statistical analyses. This is because these data are not deliberately withheld by hospitals and were missing due to either problems with extracting the data or they were simply not recorded at the time. In addition, previous analyses of the NLCA data have included these missing values in analyses instead of performing imputation or excluding them.^{93 94} Some variables, such as PS, can only be entered once and are taken at the time of diagnosis and when a person receives treatment their PS may have changed. For similar reasons I was unable to see if there has been a stage shift in response to treatment. Lastly, the NLCA does not state whether a case of lung cancer is a recurrence from a previously treated lung cancer.

2.3 Hospital episode statistics

2.3.1 Background

In England HES data are recorded when a person is admitted to an NHS hospital. Every admission is called an episode and a patient can have multiple episodes corresponding to each hospital admission or care under a specific consultant. Episodes contain clinical data relevant to the admission such as: admission/discharge dates, primary and secondary diagnoses, procedures and treatment. The data are collected as part of the commissioning dataset and are submitted to NHS digital for processing. The main purpose of HES is to track the care patients receive so that hospitals are paid for the services they deliver. HES data were not considered for research purposes until 1997, as completeness of the data prior to this was poor. Now the data are used frequently for research and have become an important asset to the annual NLCA analysis as the HES comorbidity data are used to infer case-mix adjustment between trusts. The NLCA and HES can be linked through the unique patient identifier.

2.3.2 Processing data and variables used in this thesis

Extracted HES data were received for all patients diagnosed with lung cancer during 2015 and 2016. The raw HES data were in wide format and each patient had multiple lines corresponding to different hospital stays. Each patient was identified by a unique identifier number (the same number as in the NLCA data). The list of diagnoses during each hospital episode are recorded in a string format of the ICD 10 code. For the purposes of my studies I merged the date of lung cancer diagnosis/date of first receiving chemotherapy for each patient from the NLCA/SACT record with the corresponding HES record. I then created a new float indicator variable for each of the

diagnoses that are included in the Charlson comorbidity index. Each patient with an ICD 10 code for that diagnosis would have a 1 value in this indicator variable. The Charlson score was originally created in 1987 and consists of 19 individually weighted medical conditions according to their mortality risk. *Table 2.2* provides a breakdown of the score.¹²² Lung cancer diagnosis was excluded from the modified Charlson score. Individuals with no HES data or people with no coded medical diagnoses were assumed to have no comorbidities and were given a score of 0.

Table 2.2 Weighted comorbidity scores in the Charlson index

Assigned weight/score	Conditions
1	Myocardial infarct Congestive cardiac failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic lung disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate/severe Renal disease Diabetes with organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour Acquired Immunodeficiency syndrome.

From my indicator variables I was then able to create a new variable that was the charlson score. Once this score was complete I deleted duplicate patient records and dropped all the other variables except the charlson score and patient identifier. These data were then merged with the NLCA data file using the merge command by the patient identifier number in STATA.

2.3.3 Strengths and limitations

HES data allow an accurate way to calculate an individual's comorbidity, which is an important factor to adjust for in treatment and survival analyses. This would not be possible without these data. Since Hospitals have a financial interest in ensuring HES data are accurate (as it determines how much a hospital is paid for a person's care) we can be certain that significant comorbidities diagnosed in secondary care are captured. Conversely, patients with no hospital admissions that have comorbidities diagnosed in primary care are not captured by HES and as such may receive an incorrect comorbidity score of 0. Similarly, commissioning data are typically uploaded after a hospital stay, often by administrative staff who have no clinical knowledge, which can lead to inaccuracies in the data.

2.4 Office of National Statistics

2.4.1 Background

The ONS is responsible for collecting information related to the British economy, population and society for the government. In the UK reporting and registration of death are mandatory and these data are continuously gathered by the ONS.

2.4.2 Use for this thesis

Over the course of this thesis two extracts of death data from the ONS (via PHE) were received. These data included the unique patient identifier number and the date that the person died. I merged these death dates with the NLCA records through the unique patient identifier number. Patients who had no recorded date of death at these times were assumed to be alive.

2.4.3 Strengths and limitations

It can be assured that death data are accurate as death registration in the UK is mandatory and has been in place for many years. A death certificate is needed in order to register a death and in cases referred to the coroner a death certificate cannot be produced until it has been authorised by them. This can cause delays in registering the death and may inadvertently lead to small minority of patients being classed as alive in these data.

2.5 Systemic Anti-Cancer Therapies

2.5.1 Background

The SACT dataset was launched in a phased process across English NHS hospitals during 2012 in line with the 2011 Department of Health policy.⁹² By 2014 data submission became mandatory and these are sent in monthly submissions to the NCRAS at PHE. SACT gathers data for all prescriptions of systemic anti-cancer therapies, such as chemotherapy, immunotherapy and targeted treatments. The objective of the dataset is to assist in commissioning these drugs and demonstrate the trends in practice and outcomes following their receipt. Data are quality assured and a Commissioning for Quality and Innovation (CQUIN) is set so that trusts receive a financial incentive if data are accurate. The data completeness has improved with time and during 2017-2018 variables such as start date and drug name were recorded in 100% of people.¹²³ Information is collected from e-prescribing systems and is uploaded through an online portal (CancerStats) where trusts can view reports. Reporting of trusts is matched to reasonable requirements and when apparent unacceptable clinical practice is seen a formal staged investigation is undertaken.

2.5.2 How these data were processed

For this thesis access to SACT data for 2015 and 2016 was obtained and these were linked with NLCA records via the patient identifier number. The raw SACT data were recorded in long format with each attendance for chemotherapy being recorded on a new line. The number of cycles of treatment a person received was calculated by sorting the cycle numbers for a given chemotherapy regimen and generating a variable that was the maximum cycle number. The number of planned chemotherapy cycles

was created by sorting the planned number of cycles for a given chemotherapy regimen and keeping the largest number. The data were converted into a wide format by keeping the row that contained the earliest date of chemotherapy administration, leaving one row per patient. Chemotherapy regimens and dates were recorded in “string” format. There was significant variation in spelling and punctuation of drug names. This was rectified by systematically converting “string” values to a “float” format. The extract of data I received did not include everything that was requested in my data sharing agreement with PHE, notably weight and height. PS at the start of treatment was included however this was not used as PS data were more complete from the NLCA (approximately 30% missing in SACT vs 20% in NLCA).

2.5.3 Variables used in this thesis

Start date of regimen- This is the date that the first dose of chemotherapy was administered. If no date was given then patients were classed as not receiving chemotherapy.

Regimen- Is the chemotherapy drugs administered to a patient and is coded in a string format, allowing free text entry of drug names. These string coded entries were converted to float by grouping them based on the combination of drugs prescribed.

Planned cycles- This is the number of cycles of SACT planned for a chemotherapy prescription. This may be a standard amount or can be modified by the prescriber.

Cycle number- Cycles are numbered sequentially within a chemotherapy regimen and are only assigned if a drug is given. The largest cycle number was taken to represent the maximum amount of drug cycles a person received.

2.5.4 Strengths and limitations

SACT records can be linked to the NLCA by the patient identifier. There are financial and professional incentives to ensure good quality data are submitted. Records are derived from electronic prescriptions, meaning they are directly inputted by clinicians and not administrative staff who may have limited knowledge of the treatments.

Using SACT for research purposes is relatively new in comparison to the NLCA. Local validation of data is encouraged but it is likely that only trusts who have been marked as outliers undergo this. Drugs are sometimes recorded by freehand entry which means spelling errors and abbreviations can occur that can make drug identification difficult.

2.6 National Radiotherapy Dataset

2.6.1 Background

The RTDS was created in 2009 and all English NHS hospitals that provide radiotherapy services, of which there are 50, are required to submit data. RTDS collects information for all tele and brachytherapy administered in hospitals. Originally the RTDS was managed by the National Clinical Analysis and Specialised Applications Team (NATCANSAT), however, in April 2016 PHE took full responsibility and data are now managed by the NCRAS. The RTDS provides intelligence for service planning, commissioning, clinical practice and research. It has been used by the government to provide an up-to date report on the state of radiotherapy services in England which has in turn set standards for service implementation in the future.¹²⁴ RTDS data are extracted from oncology management system software that are interfaced with radiotherapy machines as well as planning and patient scheduling IT programs. Like

SACT, information must be submitted monthly through an online portal. Following submission a quality assurance report is created (based on number of records, data completeness, validation of field format) and informs trusts whether their data has passed or failed the first quality inspection. Further quality assurance is carried out at the NCRAS. All radiotherapy data can be linked with the NLCA and SACT to provide a comprehensive picture of cancer care.

2.6.2 How these data were processed

One RTDS extract was received for this thesis, as PHE took full responsibility during 2016. The data were originally in long format with each patient assigned the unique identifier number. Each row within the dataset corresponded to a radiotherapy appointment. Radiotherapy regimens were dropped at this stage if the primary diagnosis field did not include an ICD 10 code for lung cancer. Following this the maximal total prescribed radiotherapy dose (gray (Gy)) was extracted from the radiotherapy prescription data along with its associated fractionation.

I then examined records to determine whether PCI had been given and generated an indicator variable for this. This PCI variable was defined as radiotherapy given to the skull (derived from z codes recorded in string format) or radiotherapy with prophylactic intent (a string variable that I had previously sorted) at 20 or 25Gy in 5 or 10 fractions for people with ED-SCLC and 25Gy in 10 fractions for people with LD-SCLC. Stage data and chemotherapy data were merged from NLCA and SACT data respectively in order to do this. I validated the PCI variable by confirming that all PCI were given after chemotherapy and checking the time interval from chemotherapy

prescription to PCI (median 127days range 56-165 days). These PCI data were saved as a separate file and merged with the master NLCA data.

The radiotherapy data format were changed from long to wide by keeping the largest total radiotherapy dose given to a patient, thus each patient had one line of data. These radiotherapy data were saved in a separate file and were merged with NLCA data.

2.6.3 Variables used in this thesis

The following variables from RTDS were kept for the final statistical analyses along with the PCI variable I created.

Appointment date- The appointment date is the date that radiotherapy was given. The earliest date following receipt of chemotherapy was used to represent when radiotherapy was started. If no date was present then it was assumed that radiotherapy was not given.

Treatment region- Is the broad definition of the area where radiotherapy was delivered i.e. primary tumour, regional nodes, not specific, prophylactic, metastases and unknown. This was used to identify PCI which is explained in greater detail in chapter 4.

Treatment anatomical site- Gives a specific anatomical site where radiotherapy was administered and is based on Operation Procedure Codes (OPCS) version 4 (found in Appendix F). These OPCS Z codes were used to help identify PCI.

Dose- This is the total dose of radiotherapy prescribed in a schedule (in Gray units (Gy)). The largest dose prescribed was taken to represent the radiotherapy a person

received. PCI schedules were identified prior to sorting these radiotherapy doses so that they could not be classed as the highest dose prescribed.

Fraction- This is the amount of times the total radiotherapy dose was to be divided. Fractions were used to identify PCI schedules but no other radiotherapy regimens.

2.6.4 Strengths and limitations

These data provide an in-depth picture of the radiotherapy used to treat lung cancer and have not been available to previous researchers using the NLCA. The data are extracted at source from radiotherapy machines and are quality assured so I am confident they are accurate. However, unlike SACT there is no attached CQUIN to RTDS data collection. The RTDS is the latest dataset to come under ownership of the NCRAS and PHE and they are still developing methods of processing the data effectively so it can be used for research purposes.

2.7 Linkage of the datasets

In order to get a comprehensive picture of a person's lung cancer journey I needed to connect these individually processed data extracts to form a master file. As outlined above, each dataset was individually processed into a wide format first i.e. one row per patient. These processed data were linked in a stepwise approach to the master NLCA dataset. This was achieved by using the "merge" command in STATA. Records were merged by using the unique patient identifier assigned to each person as this was the same number in all the datasets. If records from SACT, RTDS and HES were not successfully merged with NLCA records these were dropped from the final master data file as they would not have been treatments for lung cancer. Following this merge

process dates were cross checked again to ensure diagnosis, treatment and death were in a chronological order. I checked for duplicate patient records once more.

2.8 Chapter Summary

The five datasets that have been linked in order to conduct the analyses in this thesis; the NLCA, HES, ONS, SACT and RTDS have been introduced. These are routinely collected data and are primarily used to assist in healthcare commissioning and monitoring outcomes nationally. All records are pseudo-anonymised and can be linked via a unique patient identifier number. This allows researchers to get a comprehensive picture of the care a person receives after a diagnosis of lung cancer.

Chapter 3 Factors influencing treatment selection and thirty-day mortality following chemotherapy for people with small cell lung cancer: an analysis of national audit data

This chapter uses national lung cancer audit, SACT, HES and ONS data to determine the factors associated with receiving chemotherapy and early death following treatment for SCLC.

3.1 Introduction

The median survival for people with SCLC who do not receive chemotherapy is short and has been estimated by *Zelen et al* to be 5 weeks for ED-SCLC and 11.7 weeks for LD-SCLC.¹⁰⁰ This poor prognosis without treatment coupled with the fact that this aggressive tumour is responsive to chemotherapy is reflected in the treatment guidelines which recommend chemotherapy for ED-SCLC even in elderly people with poor PS and significant comorbidities.^{45 48 100 125} Administration of chemotherapy in this frail population means some individuals die shortly after treatment. It is recognised that deaths within 30 days of anti-cancer treatment are an indicator of avoidable harm and sub-optimal patient selection as they reflect that treatment was either; directly toxic or, in the case of non-treatment related early death e.g. disease progression, was futile and unnecessary.⁹² This study aims to determine the factors that influence receipt of chemotherapy and how these are associated with 30-day mortality from the first chemotherapy dose. This knowledge may improve patient selection for chemotherapy and reduce 30-day mortality in the future.

3.2 Materials and methods

3.2.1 Study population

I used NLCA data to identify people diagnosed with SCLC in English hospitals between 1st January 2015 and 31st December 2015. These individuals were identified by their SNOMED histological code as outlined in Chapter 2. These NLCA data were then linked with corresponding SACT, HES and ONS data by the unique patient identifier number.

3.2.2 Chemotherapy

If an individual had a date for administration of chemotherapy recorded within 6 months from the date of diagnosis, they were defined as having received chemotherapy. Those who did not have a date for chemotherapy administration or received chemotherapy after 6 months from diagnosis were assumed not to have received chemotherapy. The location where chemotherapy was received was used to define lung cancer network. The chemotherapy received was grouped according to the combination administered, predominantly cisplatin + etoposide and carboplatin + etoposide. The remaining groups were: single platinum (cisplatin or carboplatin), other (single agent etoposide, topotecan and clinical trials) and missing (date of administration present but no drug details given).

3.2.3 Death date

The death date derived from the ONS records was used to define whether a person had died. For this study, the date of death had last been updated on the 19th October 2016. This, along with the SACT record for the date when chemotherapy was first administered was used to calculate 30-day mortality.

3.2.4 Covariates

In addition to the chemotherapy prescribed (30-day mortality model only) and lung cancer network the following variables were used in the multiple logistic regression model and were defined using the methods outlined in Chapter 2.

- Sex
- Age- Grouped into 10 year bands starting at <50 years and finishing at >80 years

- SES- Formatted into Townsend index of deprivation (1- least to 5 –most))
- PS- At time of diagnosis based on WHO criteria.
- Charlson index- Grouped into 4 categories (0, 1, 2-3 and ≥ 4)
- Stage- Divided into LD-SCLC and ED-SCLC. ED-SCLC consisted of any tumour with M1a/b spread. A sensitivity analysis was performed with ED-SCLC defined as any tumour with M1a/b or any T and M0 with N3 nodal involvement, as some N3 disease cannot be treated as LD-SCLC.

3.2.5 *Statistical analysis*

A descriptive analysis of the whole cohort and those who received chemotherapy was carried out followed by a univariate analysis to estimate the odds ratios (OR) for receiving chemotherapy. Factors that were significantly associated on univariate testing ($p \leq 0.05$), or were considered a-priori, were included in a multiple logistic regression model which also included lung cancer network.

The proportion of deaths within 30 days for people who received chemotherapy was calculated and univariate and multivariate logistic regression models were created by a similar method in order to estimate odds ratios for 30-day mortality by patient, tumour, chemotherapy and network factors in this group. The significance of each variable was assessed by using the likelihood ratio test or Wald's p value.

The above analyses were repeated in a sensitivity analysis where N3 disease, in addition to any M1a/b, was re-classified as ED-SCLC owing to some N3 disease being managed as ED-SCLC in clinical practice.

Lastly, lung cancer network performance with administration of chemotherapy and 30-day mortality were compared by generating a pooled national mean proportion for

both outcome measures. Then, in a separate multiple logistic regression model, adjusting for the measured factors, patients were clustered by network and odds ratios of receiving chemotherapy and early death were generated for each network in comparison with the national mean proportion.

3.3 Results

There were 3,715 individuals identified with SCLC. The cohort demographics are shown in *Table 3.1*. The median age was 70 years (interquartile range (IQR) 63-76). Most people had ED-SCLC (n=2,438 (65.6%)) whilst 1,165 (31.4%) had LD-SCLC. Stage and PS were not recorded in 112 (3.0%) and 1,031 (27.8%) people respectively.

A total of 2,235 people (60.2%) received chemotherapy, 1,133 (50.7%) were male. The median age of those who received chemotherapy was 69 years (IQR 62-74) and 1,130 (50.5%) had a PS of 0-1, 421 people (18.8%) had a PS of 2 and 160 (7.2%) had a PS of 3-4. PS was not recorded for 524 (23.5%) people. The median time between the date of diagnosis and the first dose of chemotherapy was 18 days (IQR 13-27 days) and the median time from the decision to treat MDT to receiving chemotherapy was 12 days (IQR 6-21 days). Different chemotherapy regimens were used and the proportion of their use is shown in *Table 3.2*.

3.3.1 Receiving chemotherapy

There was a reduction in the odds of receiving chemotherapy with increasing age. These odds are displayed in *Table 3.1*. The adjusted OR for those aged 50-59 years vs. those aged 60-69 years was 1.39 (95% confidence interval (CI) 1.08-1.79). Worsening PS was associated with less chance of receiving chemotherapy (PS 3 vs PS 0, adjusted OR 0.28 95% CI 0.21-0.38). People with a Charlson comorbidity index of ≥ 4 , were less

likely to receive chemotherapy compared to those with no comorbidity (adjusted OR 0.53 95% CI 0.43-0.66). Sex, social deprivation and stage did not affect receipt of chemotherapy. When compared to the national proportion of people treated there was significant variation in the odds of receiving chemotherapy by cancer network, this is demonstrated in *Figure 3.1* Three networks were less likely to administer chemotherapy and 3 were more likely. The odds ranged from 0.70 (95% CI 0.56-0.88) to 1.96 (95% CI 1.37-2.80). When a sensitivity analysis was conducted with ED-SCLC reclassified to include N3 disease the number of individuals diagnosed with LD-SCLC and ED-SCLC changed to 785 and 2,818 respectively, however, the independently associated factors remained the same; age, PS, comorbidity and network. The table for this analysis can be found in Appendix G.

Table 3.1 Features of patients who had chemotherapy and the odds ratios for receiving chemotherapy									
	Total population		Had chemotherapy		OR	95% CI	Adjusted OR*	95% CI	P value (LR test)
Factor	N= 3,715	%	N=2,235 (60.2%)	%					
Sex									
Female	1,797	48.4	1,102	61.3	1		1		
Male	1,918	51.6	1,133	59.1	0.91	0.80-1.04	0.97	0.84-1.13	*0.71
Age group									
<50	104	2.8	69	66.3	1.05	0.69-1.61	1.04	0.66-1.63	<0.01‡
50-59	477	12.8	342	71.7	1.35	1.07-1.71	1.39	1.08-1.79	
60-69	1,211	32.6	789	65.2	1		1		
70-79	1,401	37.7	852	60.8	0.83	0.71-0.97	0.86	0.73-1.03	
≥80	522	14.1	183	35.1	0.29	0.23-0.36	0.32	0.25-0.40	
Townsend Quintile									
Least deprived-1	466	12.5	278	59.7	1		1		0.55
2	659	17.8	400	60.7	1.04	0.82-1.33	1.01	0.77-1.33	
3	698	18.8	424	60.7	1.05	0.82-1.33	1.11	0.85-1.45	
4	841	22.6	509	60.5	1.04	0.82-1.31	1.02	0.79-1.32	
Most deprived- 5	1,051	28.3	624	59.4	0.99	0.79-1.23	0.91	0.71-1.18	
Performance status									
0	450	12.1	334	74.2	1		1		<0.01
1	1,031	27.8	796	77.2	1.18	0.91-1.52	1.44	1.10-1.88	
2	663	17.9	421	63.5	0.60	0.46-0.79	0.85	0.65-1.13	
3	423	11.4	148	35.0	0.19	0.14-0.25	0.28	0.21-0.38	
4	117	3.2	12	10.3	0.04	0.02-0.07	0.05	0.03-0.10	
Missing	1,031	27.8	524	50.8	0.36	0.28-0.46	0.45	0.34-0.58	
Charlson comorbidity index									
0	625	16.8	445	71.2	1		1		<0.01
1	575	15.5	426	74.1	1.16	0.90-1.549	1.19	0.91-1.57	
2-3	514	13.8	330	64.2	0.73	0.56-0.93	0.86	0.65-1.14	
≥4	2,001	53.9	1,034	51.7	0.43	0.36-0.53	0.53	0.43-0.66	
Stage									
Limited	1,165	31.4	809	36.2	1		1		0.09
Extensive	2,438	65.6	1,371	61.3	0.57	0.49-0.66	0.85	0.72-1.02	
Missing	112	3.0	55	49.1	0.42	0.29-0.63	0.68	0.44-1.04	
Network (separate logistic regression model to other factors)									
National pooled	3,715		2,235	60.2	1		1		<0.01‡
N1	214	5.8	108	50.5	0.67	0.52-0.87	0.88	0.66-1.18	
N2	207	5.6	120	58.0	0.91	0.70-1.19	0.75	0.57-1.00	
N3	441	11.9	276	62.6	1.11	0.92-1.33	1.00	0.82-1.22	
N4	341	9.2	178	52.2	0.72	0.59-0.89	0.70	0.56-0.88	
N5	490	13.2	318	64.9	1.22	1.03-1.46	1.31	1.08-1.58	
N6	382	10.3	237	62.0	1.08	0.89-1.32	0.93	0.75-1.15	
N7	287	7.7	182	63.4	1.15	0.91-1.43	1.24	0.96-1.58	
N8	358	9.7	196	54.7	0.80	0.66-0.98	0.71	0.57-0.88	
N9	294	7.9	191	65.0	1.23	0.98-1.55	1.30	1.00-1.69	
N10	273	7.4	137	50.2	0.67	0.53-0.84	0.70	0.54-0.90	
N11	103	2.8	67	65.0	1.23	0.83-1.84	1.32	0.87-2.03	
N12	162	4.4	119	73.5	1.83	1.30-2.58	1.96	1.37-2.80	
N13	163	4.4	106	65.0	1.23	0.90-1.69	1.45	1.03-2.05	
LR= likelihood ratio test, Adjusted for all other variables ‡: LR test trend *: Wald's P value. ‡:LR test in multivariate logistic model without clustering									

Table 3.2 Chemotherapy regimens used to treat different stages of SCLC		
Chemotherapy regimen	Number of people	% of those who received chemotherapy
Limited stage		
Carboplatin + etoposide	560	69.2%
Cisplatin + etoposide	133	16.4%
CAV	4	0.5%
Single platinum	47	2.2%
Other chemotherapy	18	5.8%
Missing	47	5.8%
Extensive stage		
Carboplatin + etoposide	1,065	77.7%
Cisplatin + etoposide	76	5.5%
CAV	15	1.1%
Single platinum	36	2.6%
Other chemotherapy	103	7.5%
Missing	76	5.5%

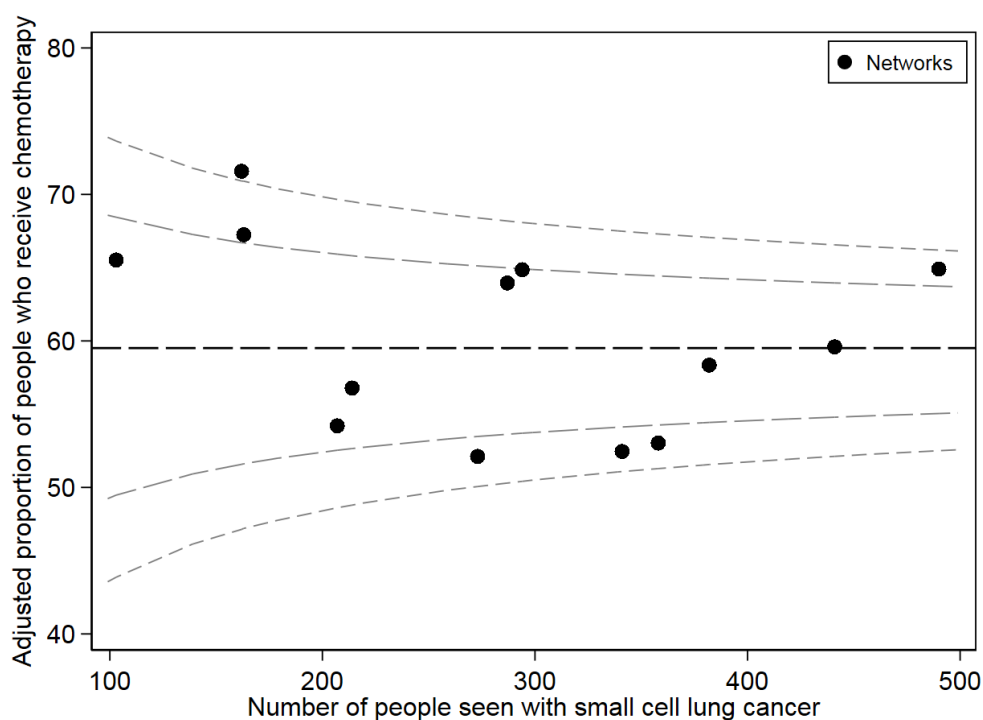


Figure 3-1 Adjusted proportion of patients who receive chemotherapy by an individual lung cancer network. The black dashed line represents the national mean proportion treated and the grey dashed lines represent 2 and 3 standard deviations from the mean.

3.3.2 Median survival

The median survival from diagnosis to death for individuals who received chemotherapy was calculated by “setting” the survival data within the dataset. This was achieved using the `st set` command in STATA (failure was date of death, origin was the date of diagnosis and the censoring date was the 19th October 2016). The median was 388 days (95% CI 371-404) and 228 days (95% CI 219-241) for LD-SCLC and ED-SCLC respectively. This was markedly different for people who did not receive chemotherapy (LD-SCLC 251 days (95%CI 201-284 days) and ED-SCLC 32 days (95% CI 28-36 days)). *Figure 3.2* is two Kaplan-Meier survival plots for individuals with LD-SCLC and ED-SCLC who do and do not receive chemotherapy and demonstrates the disparities in survival from the date of diagnosis.

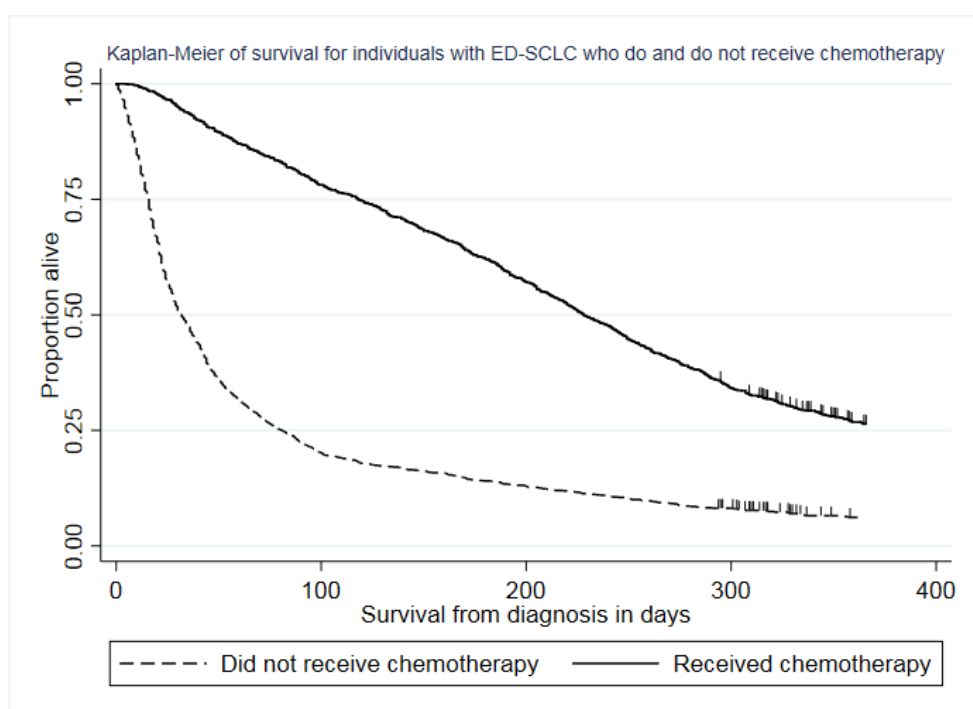
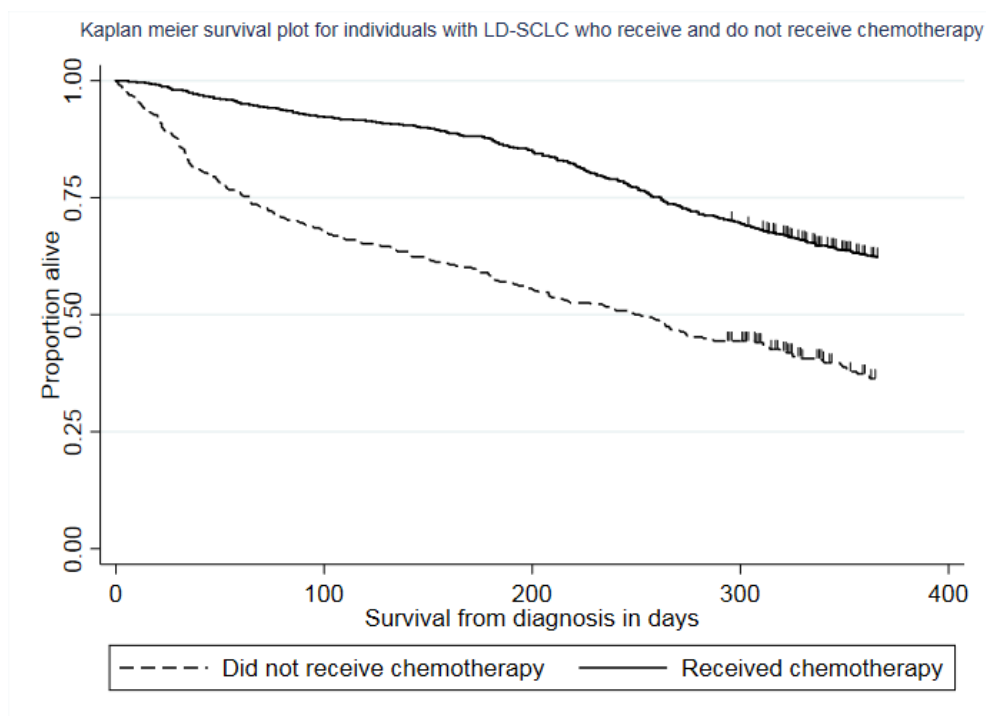


Figure 3-2 Kaplan-Meier survival plots of individuals with limited stage and extensive stage SCLC who receive and do not receive chemotherapy (vertical line represents censoring (censoring date was 19th October 2016)).

3.3.3 Thirty-day mortality

The overall 30-day mortality after chemotherapy was 7.8% (n=174). This was associated with patient, tumour and geographical factors. *Table 3.3* demonstrates the features of patients who died within 30 days of chemotherapy and the odds of 30-day mortality by these different factors. Worsening PS, was overwhelmingly associated with 30-day mortality. The adjusted odds ratio for people with PS 2 vs PS 0 was 3.76 (95% CI 1.71-8.26). People ≥ 80 years were less likely to die within 30 days compared to people aged 60-69 years (adjusted OR 0.38 95% CI 0.17-0.82) there was no trend across all ages (p trend= 0.054). ED-SCLC was associated with greater odds of early death (adjusted OR 1.53 95% CI 1.02-2.28). Early mortality was not independently associated with the chemotherapy received, however, there was a signal that a single platinum agent increased 30-day mortality risk compared to carboplatin+etoposide (adjusted OR 1.71 95% CI 0.99-2.95). *Table 3.4* demonstrates the proportion of people who died within 30-days of the first day of chemotherapy (with 95% confidence intervals) by the two independently associated factors, stage and PS.

There was significant variability in 30-day mortality by cancer network (p=0.01). *Figure 3.3* shows the case-mix adjusted proportion of patients who died within 30 days of chemotherapy by different network and demonstrates that one network had an increased proportion of deaths while another had significantly fewer. There was no correlation between the proportion of individuals treated and the proportion of early deaths by network (p=0.497) as shown in *Figure 3.4*. The sensitivity analysis, where stage was re-classified, demonstrated the same independently associated factors as above. The table showing this can be found in Appendix H.

Table 3.3 Features of patients who died within 30 days of receiving chemotherapy and odds ratios for death within 30 days.							
Factor	Total 30-day deaths N=174	% who died from those who received chemotherapy	OR of 30-day mortality after receiving chemotherapy	95% CI	Adjusted OR 30-day mortality after receiving chemotherapy	95% CI	P value (LR test)
Sex							
Female	80	7.3	1		1		
Male	94	8.3	1.16	0.85-1.58	1.12	0.81-1.55	*0.49
Age group							
<50	5	7.3	0.82	0.32-2.09	0.79	0.30-2.10	
50-59	19	5.6	0.61	0.36-1.04	0.62	0.36-1.07	
60-69	69	8.8	1		1		
70-79	73	8.6	0.98	0.69-1.38	0.88	0.61-1.26	
≥80	8	4.4	0.48	0.23-1.01	0.38	0.17-0.82	¥0.054
Townsend quintile							
Least deprived- 1	14	5.0	1		1		
2	32	8.0	1.64	0.86-3.13	1.44	0.74-2.80	
3	38	9.0	1.86	0.99-3.49	1.56	0.81-2.99	
4	41	8.1	1.65	0.88-3.09	1.56	0.82-2.97	
Most deprived- 5	49	7.9	1.61	0.87-2.96	1.60	0.84-3.04	0.64
Performance status							
0	8	2.4	1		1		
1	42	5.3	2.27	1.05-4.89	2.15	0.99-4.67	
2	43	10.2	4.64	2.15-10.00	3.76	1.71-8.26	
3-4	30	18.8	9.40	4.20-21.05	6.91	3.02-15.81	
Missing	51	9.7	4.39	2.06-9.38	4.19	1.93-9.08	<0.01
Charlson comorbidity index							
0	25	5.6	1		1		
1	19	4.5	0.78	0.43-1.45	0.71	0.38-1.34	
2-3	20	6.1	1.08	0.59-1.99	0.92	0.49-1.73	
≥4	110	10.6	2.00	1.28-3.13	1.25	0.77-2.01	0.16
Stage							
Limited	39	4.8	1		1		
Extensive	132	9.6	1.72	1.19-2.47	1.53	1.02-2.28	
Missing	3	5.5	0.79	0.24-2.61	0.98	0.28-3.41	0.07
Chemotherapy							
Carbo+ etoposide	130	7.8	1		1		
Cisp + etoposide	7	3.2	0.39	0.18-0.85	0.47	0.21-1.06	
CAV	2	10.5	1.39	0.32-6.08	1.58	0.34-7.46	
Other	5	9.1	1.18	0.46-3.01	0.97	0.36-2.59	
Single platinum	22	14.6	2.01	1.24-3.27	1.71	0.99-2.95	
Missing	8	6.3	0.79	0.38-1.66	0.84	0.38-1.82	0.13
Network (separate logistic regression model to other factors)							
Pooled networks	174	7.8	1		1		
N1	10	9.3	1.21	0.64-2.28	1.10	0.58-2.10	
N2	6	5.0	0.62	0.28-1.40	0.66	0.29-1.51	
N3	23	8.3	1.08	0.72-1.60	1.10	0.73-1.67	
N4	6	3.4	0.41	0.19-0.92	0.40	0.18-0.88	
N5	32	10.1	1.33	0.95-1.85	1.17	0.84-1.64	
N6	20	8.4	1.09	0.71-1.68	1.26	0.81-1.96	
N7	23	12.6	1.71	1.14-2.58	1.79	1.14-2.80	
N8	10	5.1	0.64	0.34-1.18	0.66	0.36-1.23	
N9	23	12.0	1.62	1.08-2.44	1.50	0.97-2.31	
N10	7	5.1	0.64	0.30-1.34	0.65	0.31-1.35	
N11	2	3.0	0.36	0.09-1.48	0.39	0.09-1.67	
N12	4	3.4	0.41	0.15-1.10	0.43	0.16-1.15	
N13	8	7.6	0.97	0.48-1.96	1.03	0.49-2.14	‡0.01
*: Wald's P value test ¥: LR test for trend ‡: LR test in multivariate logistic model without clustering. Adjusted OR for all other factors							

Table 3.4 Proportion of 30-day mortality (after treatment and diagnosis) by independently associated factors, PS and stage, for treated and untreated patients					
Treated					
		Performance Status			
		PS 0	PS 1	PS 2	PS 3-4
Received chemotherapy	Limited	1.0%	3.0%	7.8%	21.1%
		0.3%-5.5%	2.0%-6.0%	4.2%-14.0%	10.6%-37.4%
		(n=143)	(n=333)	(n=128)	(n=38)
	Extensive	3.2%	6.8%	11.3%	18.2%
		1.4%-7.0%	4.8%-9.5%	8.2%-15.5%	12.2%-26.2%
		(n=186)	(n=455)	(n=291)	(n=121)
Untreated					
Did not receive chemotherapy	Limited	3.5%	6.5%	13.6%	28.8%
		0.9%-13.3%	2.7%-14.9%	6.8%-25.1%	19.0%-41.0%
		(n=57)	(n=77)	(n=59)	(n=66)
	Extensive	26.3%	30.9%	42.5%	61.4%
		1.6%-39.5%	24.0%-38.8%	35.5%-49.9%	55.8%-66.7%
		(n=57)	(n=152)	(n=181)	(n=308)
Parenthesis contains 95% confidence interval, n represents the total number of individuals who received and did not receive chemotherapy in that group.					

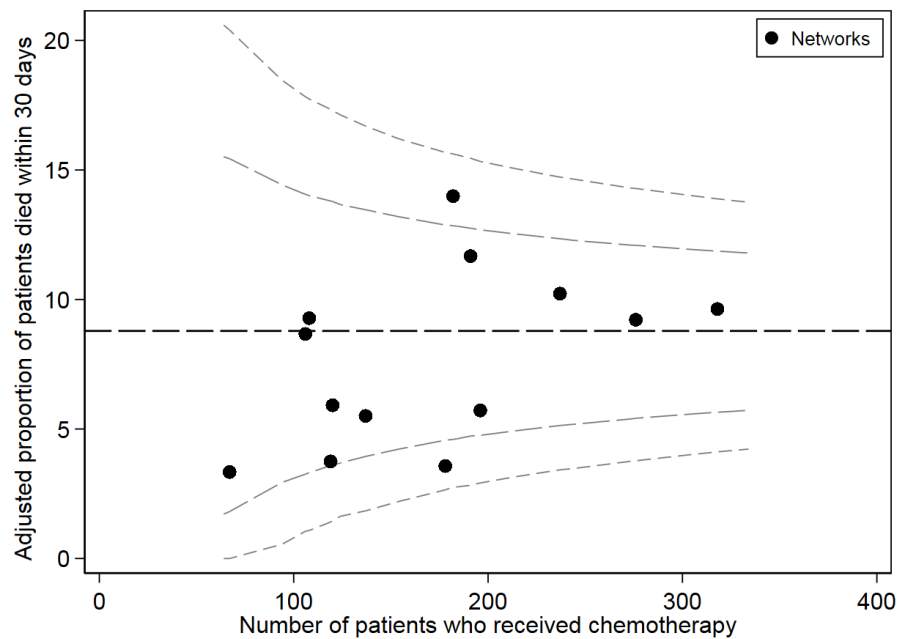


Figure 3-3 Case mix adjusted proportion of deaths within 30 days of chemotherapy by lung cancer network. The black dashed line represents national mean proportion of deaths and the grey dashed lines represent 2 and 3 standard deviations from this mean.

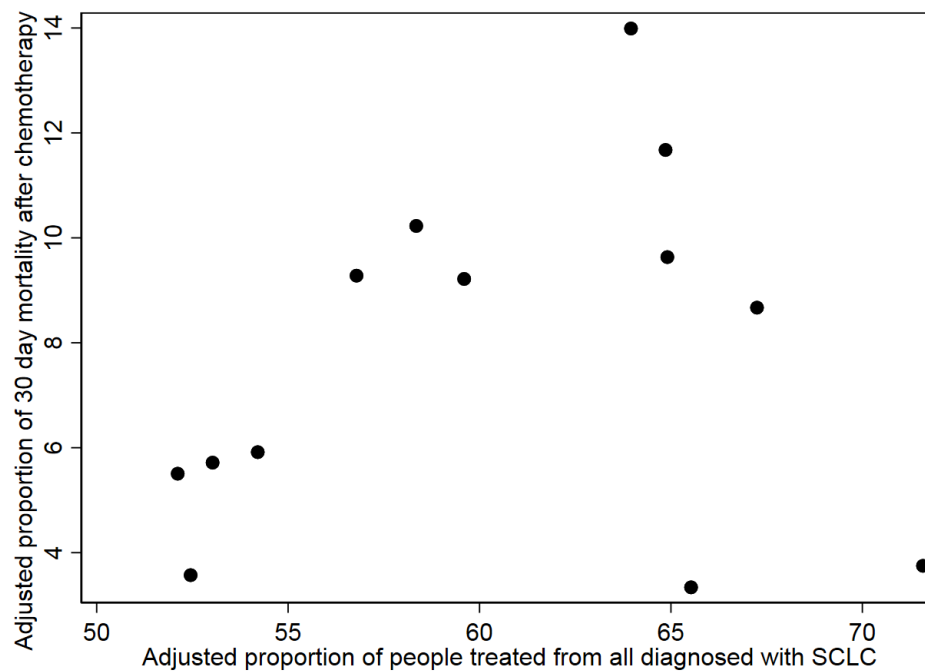


Figure 3-4 Scatter plot of the case-mix adjusted proportion of people treated with chemotherapy versus 30-day mortality by lung cancer network.

3.4 Discussion

3.4.1 *Main findings*

These observational data have illustrated that the administration of chemotherapy for SCLC was associated with PS, age, comorbidity and cancer network. The preferred choice of chemotherapy in LD-SCLC was carboplatin+etoposide followed by cisplatin + etoposide. In ED-SCLC carboplatin+etoposide was preferred followed by single platinum.

The data have helped to quantify the up to date median survival for people who do not receive chemotherapy in SCLC and have shown that the difference between ED-SCLC and LD-SCLC is much greater than previously thought.¹⁰⁰ Thirty-day mortality was associated with stage and PS and varied by network. Although increasing age did not show a trend, people aged ≥ 80 years were less likely to die within 30 days, yet, were also less likely to receive chemotherapy.

3.4.2 *Strengths*

This is the first time that factors associated with 30-day mortality have been explored in detail for SCLC using real-world data. Clinical trials provide limited data on 30-day mortality and compared to these, this current study's population is unselected and therefore more relevant to clinical practice. The data illustrate variation in SCLC treatment and outcomes in England but this finding will be relevant to other countries. The untreated median survival in SCLC is often cited from VALSG research conducted in the 1970s but this study describes the current median survival, this is important as healthcare has changed with time.¹⁰⁰ This study quantifies the time taken to administer chemotherapy from diagnosis and the regimens being used, which allows

comparison with national recommendations. These findings set an important baseline that can be used to improve standards of care in the future.

3.4.3 Limitations

The cohort consisted of histologically confirmed SCLC but there is a small proportion of patients who were diagnosed with lung cancer that were too frail to obtain a histological diagnosis. This number is too small to affect the findings as histological confirmation for lung cancers diagnosed in 2015 was reported as 74% in the NLCA.¹¹⁹ Radiotherapy data was limited but this treatment may add further toxicity to chemotherapy, however, it is not usually given in the first 30 days. The data do not describe the causes of early death, though, the information that matters to the patient is the risk of death from any cause. Stage was reported based on VALSG criteria. TNM staging offers a more precise method of grouping patients, however, using this would result in subgroups being too small for the statistical analysis. Nevertheless, guidelines use VALSG criteria to recommend treatment, hence, the findings in this study can be easily related to these. Comparing the survival of people who receive treatment with those that do not can introduce immortal time bias, as those who receive treatment will naturally live longer as they have to survive to receiving it. Similarly, there is selection bias to consider when comparing survival in relation to receipt of chemotherapy, as those who do not receive chemotherapy are probably individuals who have a very bad prognosis. *Figure 3.2* attempts to reduce this bias by comparing survival for patients with similar PS (0-2).

3.4.4 Comparisons with other research

Receipt of chemotherapy

The findings of increasing age, poorer PS, greater comorbidity and network have all been associated with a negative effect on the likelihood of receiving chemotherapy.⁹⁴

^{95 98} PS is a subjective measure by the clinician and therefore one expects this to correlate with receiving chemotherapy as the clinician also controls the prescription.

Rich et al identified that patients were more likely to receive chemotherapy if they were diagnosed in a hospital recruiting for clinical trials.⁹⁴ This may explain the differences between networks in this study as some contain more clinical trial units than others. However, ambiguous selection criteria and expertise may also contribute to variation.

Chemotherapy administered

Some of the chemotherapy given, such as CAV, is not recommended as first-line treatment in current guidelines. Previously CAV was favoured in poor prognosis SCLC, unlike cisplatin+etoposide, which was not used for this group.¹²⁶ A survey conducted 20 years ago found carboplatin+etoposide was favoured over cisplatin+etoposide because of patient convenience, toxicity and quality of life.¹²⁶ This may explain why carboplatin+etoposide was favoured for LD-SCLC in this study.

There was a considerable delay between the decision to treat and receipt of chemotherapy. NICE recommends that all patients with SCLC who are eligible for chemotherapy should be seen within 1 week of the decision to treat by an oncologist. Likewise, the NLCA report uses 14 days from diagnosis to chemotherapy administration as a quality standard. Indeed, during 2016 approximately 34% of

individuals with SCLC in England and Wales received chemotherapy within 2 weeks of diagnosis.³⁶

Thirty-day mortality

The finding that 30-day mortality was 4.0% and 9.1% for people with LD-SCLC and ED-SCLC respectively, is similar to *Wallington et al's* study (4.0% for curative intent chemotherapy and 12.0% for palliative intent).¹⁰⁵ Likewise, a systematic review of phase III clinical trials in SCLC found that 2.95% of people died within 4 weeks of completing chemotherapy.¹⁰⁷ In this systematic review the population mostly consisted of individuals with PS 0-1 and deaths that were a result of disease progression were excluded. With these caveats considered their findings are similar when 30-day mortality risk is stratified by PS and stage in my data, as shown in *Table 3.4*.

The oldest age group had a lower risk of death with no significant trend across all ages. Despite this, the oldest group were less likely to receive chemotherapy. This contrasts with previous research which assessed overall survival in patients entered into clinical trials for chemotherapy in SCLC.¹²⁷ They found that increasing age was a risk factor for death. The most likely explanation is that the oldest patients in this current study who received chemotherapy were in fact fitter than their younger counterparts. This originates from them either being less likely to be offered or accept chemotherapy when fitness levels are equivalent to younger patients.

Comorbidity was not independently associated with early mortality. In previous work *Rich et al*, found that an increase in Charlson index was associated with reduced overall survival.⁹⁴ These discrepancies are explained by the different length survival was

measured. Thirty days is a short time-frame and if survival is measured over longer periods it permits an increased exposure time to the slower rate of death from comorbidities to occur (attrition bias).¹²² Similarly, chemotherapy given to people with more comorbidities might be under-dosed.

Using more than 2 chemotherapy drugs in combination is linked with increased early treatment-related deaths in SCLC.^{108 109} Contrary to this there was a signal that a single platinum agent increased 30-day mortality risk when compared to carboplatin+etoposide. Selection bias may explain this i.e. frailer individuals were given a single chemotherapy drug to limit toxicity. If this is the case then it implies that an “all or nothing” approach should be taken for combination chemotherapy.

3.4.5 Median survival

In this study, the median survival for untreated LD-SCLC was considerably longer than *Zelen et al's* estimate of 11.7 weeks.¹⁰⁰ This difference is explained by the broad range of TNM stages captured under the limited stage umbrella (i.e. this study may have more early stage LD-SCLC), differing cohort sizes (*Zelen et al* n=38) and the advances of routine healthcare since the 1970s.

3.4.6 Relevance

This research demonstrates geographical variation in the administration of chemotherapy for SCLC with no apparent correlation to the risk of 30-day mortality, indicating that there is some uncertainty in patient selection across England. In surgery for lung cancer global risk scores have been proposed as an aid to inform shared decision making, but none are yet considered accurate enough for this purpose.^{103 104} ¹²⁸ Instead, tables have been produced showing recent mortality figures stratified by the most important associated factors.¹⁰⁴ Going forward, a similar method could be used in order to assess eligibility for chemotherapy by utilising *Table 3.4* as it stratifies 30-day mortality risk by the two independently associated factors PS and stage. This is where this research adds much more clinical relevance and evidence than the other studies that have previously investigated 30-day mortality (of which there are few). The 30-day mortality risk table could be incorporated into NICE guidelines in order to better quantify risk to patients as the decision of whether to treat a less fit individual is a relatively common dilemma in clinical practice. However, further work is needed to develop a robust risk prediction model for 30-day mortality following chemotherapy that could incorporate other biological markers which are not included within the data used for this research.^{114 116 129}

3.5 Conclusion

The degree of physical impairment, as reflected in PS, is the overwhelming factor determining receipt of chemotherapy and 30-day mortality. However, it is evident that age and comorbidity are given too much weight in the decision to administer chemotherapy which may result in suboptimal decision making and variation between

networks. The risk of 30-day mortality can be used in conjunction with median survival estimates to assist the patient selection process. *Table 3.4* provides a practical solution to this, conveying 30-day mortality risk by the independently associated factors, PS and stage allowing better informed treatment decisions in the future.

Chapter 4 Quantifying factors associated with 1-year survival for people with small cell lung cancer using national audit, chemotherapy and radiotherapy data.

This chapter uses linked NLCA, SACT, RTDS, HES and ONS data to identify the factors associated with 1-year survival for people diagnosed with SCLC and the people who subsequently receive chemotherapy.

4.1 Introduction

Many people that survive 1-year with SCLC have received chemotherapy. The international treatment consensus is to give platinum doublet chemotherapy, however, the optimal duration of this (4 or 6 cycles) remains unclear.^{45 47 48} Thoracic radiotherapy is an adjunct to chemotherapy and can be given either: concurrently (within the first 2 chemotherapy cycles to people with LD-SCLC and PS 0-1) or sequentially (patients that have shown response to chemotherapy who are unfit for concurrent irradiation or have ED-SCLC). PCI is reserved for individuals whose cancer has not progressed following first-line treatment. The aforementioned therapies are often confined to tertiary hospitals and hence there are likely to be variations in their use.⁹⁴ In addition, the side effects of these treatments and the time spent in hospital pose a significant burden to patients which can drastically lower their limited quality and quantity of life. Hence, with these harms considered it is important that individuals are offered appropriate treatment with an understanding of its long-term survival gains.

The objectives of this study were to quantify the patient, treatment and hospital factors associated with 1-year survival and furthermore the variability in access to these therapies between geographical regions so that better informed treatment decisions can be made.

4.2 Materials and methods

4.2.1 *Study population*

This study used English NLCA, SACT and HES data from 2015 and 2016. RTDS data were also used but were limited to 2016 only, owing to the limited extract received from

PHE. The most recent survival data by the ONS were from 21st September 2017. Individuals diagnosed with SCLC were identified based on their histological code from NLCA data (as outlined in chapter 2) and were linked with data in the other datasets by the unique patient identifier number.

4.2.2 Validating long term survival

1-year survival is a frequently used statistic for describing lung cancer survival. In order to confirm that 1-year survival represented long term outcomes in these data a survival time analysis for all SCLC cases was performed (stset command in STATA). Survival was calculated from the date of diagnosis up to the date of death or the censoring date, 21st September 2017, as this was the date of the last ONS search. A Kaplan-Meier survival curve by SCLC stage was created and is shown in *Figure 4.1*. It was evident that 1-year survival was longer than the median for ED-SCLC (129 days) and somewhat shorter than the median for LD-SCLC (415 days). With this considered, 1-year was used as the long-term survival benchmark for this study. One-year survival was defined as survival greater than or equal to 365 days from the date of diagnosis. In order to meet this definition patients who were diagnosed with SCLC after 21st September 2016 were excluded from the analysis as these did not have complete 1-year survival data

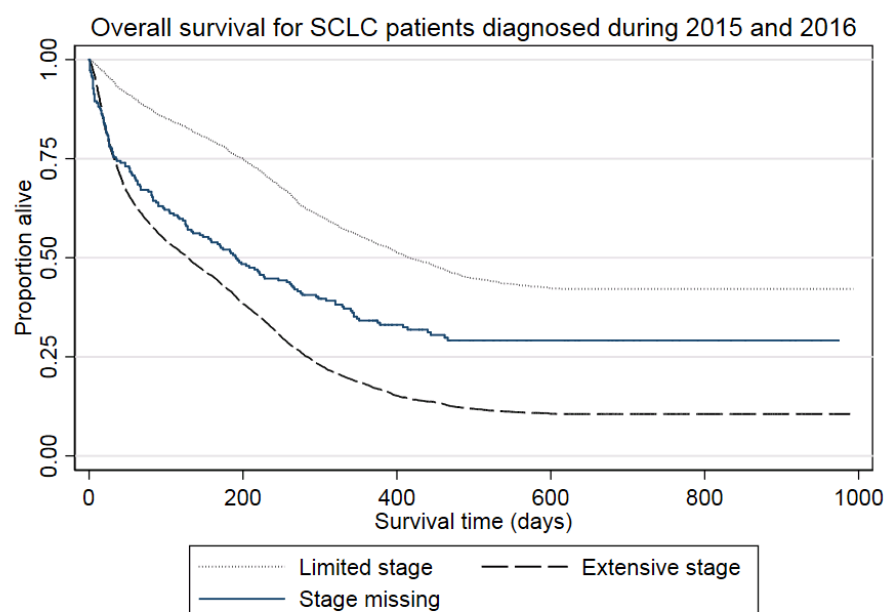


Figure 4-1: Survival in all people diagnosed with SCLC during 2015 and 2016

4.2.3 Variables

Treatment factors

An individual was defined as receiving chemotherapy if there was a record of administration within 6 months after diagnosis. If no date was present or it was beyond 6 months of diagnosis chemotherapy was classed as not given. The chemotherapy regimens were grouped according to the drugs administered except “other”. This consisted of drugs given in small quantities e.g. gemcitabine+cisplatin. Chemotherapy regimen was classed as “missing” if the administration date was present but drug details were not given. The planned chemotherapy cycles were taken at the time of first prescription. The amount of cycles received was derived from the number of consecutive drug administration dates an individual had for a single chemotherapy regimen.

Radiotherapy was classed as given if an administration date was present after diagnosis. Thoracic radiotherapy was stratified by the maximal dose prescribed (radical intent $\geq 40\text{Gy}$ and palliative $< 40\text{Gy}$). This dose threshold was chosen as it aligned with the Royal College of Radiologists recommendations.⁶⁹ In addition, I conducted a sensitivity analysis with a dose threshold at $\geq 30\text{Gy}$ for radical intent. PCI was defined as radiotherapy given to the skull or with prophylactic intent following chemotherapy at 20 or 25Gy in 5 or 10 fractions for people with ED-SCLC and 25Gy in 10 fractions for people with LD-SCLC.

Patient and hospital factors

These factors were generated as outlined in Chapter 2 and consisted of:

- Age- grouped into 3 categories, < 60 , 60-79 and ≥ 80 years
- Sex
- SES- (Townsend index of deprivation 1-least deprived to 5-most deprived)
- PS- Who criteria
- Stage- LD-SCLC and ED-SCLC (any M1a/b spread).
- Comorbidity- Charlson index categorised as 0, 1, 2-3 and ≥ 4 .
- Lung cancer network.

4.2.4 Statistical analysis

The whole cohort that were diagnosed from 1st January 2015 to 21st September 2016 were described and univariate and multivariate logistic regression for the odds of 1-year survival were performed. This multivariate model for 1-year survival included factors that were a-priori or significant on univariate testing ($p \leq 0.05$). These factors were age, sex, socioeconomic status, PS, stage, co-morbidities and chemotherapy. A

similar sub-analysis in the 2016 population that received chemotherapy was conducted as the radiotherapy data were limited to this time. The multivariate logistic regression model in this sub-analysis included receipt of radiotherapy, PCI and chemotherapy cycles in addition to the aforementioned factors. The significance of each variable was assessed using the likelihood ratio test.

Network performance by 1-year survival, receipt of chemotherapy, radiotherapy and PCI were compared. A pooled mean national proportion for these outcomes was created and a multiple logistic regression model, adjusting for the aforementioned factors, generated odds ratios for each network in comparison to the national mean. An additional 6-month survival analysis between networks was also performed.

4.3 Results

4.3.1 *All SCLC diagnoses*

There were 6,438 people diagnosed with SCLC whose demographics are summarised in *Table 4.1*. Approximately 51.3% (n=3,303) were male and the median age was 70 years (IQR 63-76). The majority of individuals had ED-SCLC (n=4,264 (66.2%)). There were 1,860 (28.9%) people that survived 1-year. For people with LD-SCLC 1-year survival was 53.8% (n=1,068) in contrast to ED-SCLC where this was 17.0% (n=725). A total of 1,578 (84.8%) people who survived 1-year received chemotherapy. Chemotherapy was mostly carboplatin+etoposide (n=1,170) or cisplatin+etoposide (n=274). The median time from the date of diagnosis to the first dose of chemotherapy was 18 days (IQR13-26days). The majority of patients received 4 cycles (n=506 (27.7%)) whereas 6 cycles were given to 418 people (23.7%) and 1 cycle was given to 326 (18.5%).

Table 4.1 Features of patients diagnosed with SCLC and people that survived 1-year from diagnosis with odds ratios for 1-year survival.									
	Total population		Survived one year		OR 1-year survival	95% CI	Adjusted OR* 1-year survival	95% CI	P value (LR test)
Factor	n= 6,438	%	N=1,860	%					
Sex									
Female	3,135	48.7	1,043	33.3	1		1		
Male	3,303	51.3	817	24.7	0.66	0.59-0.73	0.70	0.62-0.80	0.01
Age group									
<60	997	15.5	381	38.2	1.48	1.28-1.71	1.25	1.06-1.49	
60-79	4,527	70.3	1,335	29.5	1		1		
≥80	914	14.2	144	15.8	0.48	0.37-0.54	0.66	0.53-0.82	0.01¥
Townsend Quintile									
Least deprived-1	806	12.5	243	30.2	1		1		
2	1,117	17.4	334	29.9	0.99	0.81-1.20	1.06	0.83-1.32	
3	1,268	19.7	345	27.2	0.87	0.71-1.05	0.92	0.73-1.15	
4	1,516	23.6	444	29.3	0.96	0.80-1.16	0.92	0.74-1.14	
Most deprived- 5	1,731	26.9	494	28.5	0.93	0.77-1.11	0.92	0.74-1.14	0.79
Performance status									
0	869	13.5	442	50.9	1		1		
1	1,918	29.8	742	38.7	0.61	0.52-0.72	0.69	0.57-0.83	
2	1,286	20.0	274	21.3	0.26	0.22-0.32	0.38	0.31-0.48	
3	806	12.5	65	8.1	0.08	0.06-0.11	0.19	0.14-0.26	
4	234	3.6	3	1.3	0.01	0.00-0.04	0.04	0.01-0.14	
Missing	1,325	20.6	334	25.2	0.33	0.27-0.39	0.55	0.45-0.68	<0.01
Charlson comorbidity index									
0	1,822	28.3	659	36.2	1		1		
1	1,306	20.3	514	39.4	1.15	0.99-1.33	1.15	0.97-1.37	
2-3	1,227	19.1	340	27.7	0.68	0.58-0.79	0.76	0.63-0.92	
≥4	2,083	32.4	347	16.7	0.35	0.30-0.41	0.62	0.52-0.74	<0.01
Stage									
Limited	1,984	30.8	1,068	53.8	1		1		
Extensive	4,264	66.2	725	17.0	0.18	0.16-0.20	0.21	0.19-0.25	
Missing	190	3.0	67	35.3	0.47	0.34-0.64	0.60	0.42-0.85	<0.01
Chemotherapy									
Did not have chemo	2,443	37.9	282	11.5	0.21	0.18-0.24	0.28	0.24-0.33	
Carbo + etoposide	3,040	47.2	1,170	38.5	1		1		
Cisp + etoposide	416	6.5	274	65.9	3.08	2.49-3.83	1.57	1.23-1.99	
CAV	24	0.4	3	12.5	0.23	0.07-0.77	0.26	0.07-0.86	
Other chemo	83	1.3	26	31.3	0.73	0.46-1.17	0.73	0.43-1.19	
Single platinum	273	4.2	45	16.5	0.32	0.23-0.44	0.42	0.30-0.61	
Missing drug name	159	2.5	60	37.7	0.97	0.70-1.35	0.86	0.55-1.15	<0.01
LR= likelihood ratio test, *Adjusted for all other variables in table ¥: LR test trend									

LR= likelihood ratio test, *Adjusted for all other variables in table ¥: LR test trend

4.3.2 One-year survival for all diagnosed

After adjusting for age, sex, socioeconomic status, PS, comorbidities, stage and chemotherapy the multivariate analysis showed significant differences in the odds of 1-year survival by patient factors (*Table 4.1*). Males were less likely to survive compared with females (males adjusted OR 0.70 95%CI 0.62-0.80). Similarly, increasing age was associated with poorer survival (LR trend p=0.01). Individuals with

worse PS were less likely to survive 1-year (PS 2 vs PS 0 adjusted OR 0.38 95%CI 0.31-0.48) as were people with more co-morbidities (Charlson index ≥ 4 vs 0 adjusted OR 0.62 95%CI 0.52-0.74). Individuals with ED-SCLC were less likely to survive 1-year in comparison to LD-SCLC (adjusted OR 0.21 95%CI 0.19-0.25). There was significant variation in 1-year survival by receipt of chemotherapy. Individuals who did not receive chemotherapy were less likely to survive than those who were given carboplatin+etoposide (adjusted OR 0.28 95%CI 0.24-0.33). In contrast, people receiving cisplatin+etoposide were more likely to survive (vs carboplatin+etoposide adjusted OR 1.57 95%CI 1.23-1.99) however, PS, comorbidities and stage were confounders to this. Receipt of a single platinum drug conferred poorer survival (vs carboplatin+etoposide adjusted OR 0.42 95%CI 0.30-0.61). Socioeconomic status was not associated with survival ($p=0.79$).

4.3.3 Survival following receipt of chemotherapy

There were 1,761 individuals diagnosed in 2016 that received chemotherapy. The cohort consisted of 891 (50.6%) females and 870 (49.7%) males. The median age was 68 years (IQR 62-75). Most people had a PS of 0-2 ($n=1,464$ (83%) and 144 (8.2%) and 13 (0.7%) had PS 3 and 4 respectively. Approximately 50.6% ($n=891$) of people were Townsend quintiles 4 and 5 (most deprived) in comparison to 28.5% ($n=507$) who were Townsend quintiles 1 and 2 (least deprived) and of these 695 (39.5%) survived 1-year. The median Charlson Index was 1 (IQR 0-5). Approximately 792 (45.0%) people received radiotherapy and 365 (20.7%) received PCI. The median total dose of radiotherapy prescribed was 30Gy (IQR 25-40) and the median time from the first dose of chemotherapy to receiving any form of radiotherapy was 110 days (IQR 77-138.5days). The mixed stage 1-year survival was 39.5% ($n=695$) however, this varied

considerably by stage, hence the results are presented by LD-SCLC and ED-SCLC separately. A table of combined stage survival can be found in Appendix I.

Limited stage

There were 628 people who received chemotherapy for LD-SCLC. This was mostly carboplatin + etoposide (n=243(67.7%)) and cisplatin + etoposide (n=100(27.9%)). Radiotherapy was given to 359 people and the median dose was 40Gy (IQR 30-45Gy) most commonly divided into 15 fractions. From the 628 that received chemotherapy 60.7% (n=381) survived to 1 year. *Table 4.2* displays the result of 1-year survival by the different variables for LD-SCLC patients. After adjustment for patient, tumour, chemotherapy and radiotherapy factors 1-year survival was associated with PS (PS 3-4 vs PS 0 adjusted OR 0.32 95%CI 0.13-0.77). However, PS 1 and 2 showed no significant difference in comparison to PS 0. Survival was associated with SES but only those with Townsend 2 had poorer 1-year survival (vs Townsend 1 adjusted OR 0.46 95%CI 0.23-0.92). Individuals who were given cisplatin + etoposide were more likely to survive 1-year compared with carboplatin + etoposide (adjusted OR 2.09 95%CI 1.17-3.74), PS was a confounder to this. Receipt of radical radiotherapy was associated with better survival in comparison to not receiving radiotherapy (radical adjusted OR 3.32 95%CI 2.07-5.31). This association remained, although less pronounced, when the radical threshold was set to 30Gy (vs nil radiotherapy adjusted OR 2.83 95%CI 1.84-4.34, shown in *Table 4.3*). PCI augmented the odds of 1-year survival (adjusted OR 2.42 95%CI 1.33-4.39). There was no association between survival and age (p=0.59), sex (p=0.07), comorbidity score (p=0.32) and the chemotherapy cycles administered (p=0.53).

Table 4.2: Features of patients with limited stage who receive chemotherapy and survived 1-year with odds ratios for 1-year survival.							
Factor	Number surviving 1-year (n=381 from 628)	% who survived 1-year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival*	95% CI	P value (LR test)
Sex							
Female	220	65.1	1		1		
Male	161	55.5	0.67	0.49-0.92	0.71	0.49-1.03	0.07
Age group							
<60	78	73.6	1.92	1.20-3.08	1.20	0.69-2.09	
60-79	271	59.2	1		1		
≥80	32	50.0	0.69	0.41-1.17	0.86	0.47-1.57	0.59¥
Townsend quintile							
Least deprived- 1	56	65.9	1		1		
2	53	52.5	0.57	0.32-1.04	0.46	0.23-0.92	
3	74	61.7	0.83	0.47-1.49	1.03	0.53-2.00	
4	98	58.3	0.73	0.42-1.25	0.73	0.39-1.36	
Most deprived- 5	100	64.9	0.96	0.55-1.67	1.10	0.57-2.10	0.04
Performance status							
0	110	69.2	1		1		
1	171	65.8	0.86	0.56-1.31	1.04	0.64-1.69	
2	63	48.8	0.43	0.26-0.69	0.63	0.36-1.11	
3-4	11	28.2	0.18	0.08-0.38	0.32	0.13-0.77	
Missing	26	63.4	0.77	0.38-1.58	1.00	0.44-2.27	0.02
Charlson comorbidity index							
0	128	67.7	1		1		
1	115	66.5	0.94	0.61-1.47	1.19	0.71-2.00	
2-3	86	52.8	0.53	0.35-0.82	0.75	0.45-1.24	
≥4	52	50.5	0.49	0.30-0.79	0.83	0.47-1.47	0.32
Chemotherapy							
Carboplatin+ etoposide	254	57.0	1		1		
Cisplatin + etoposide	107	82.3	3.52	2.16-5.73	2.09	1.17-3.74	
Other	8	72.7	2.02	0.53-7.70	3.64	0.84-15.66	
Single platinum	9	29.0	0.31	0.14-0.67	0.55	0.23-1.34	
Missing	3	30.0	0.32	0.08-1.27	0.43	0.08-2.27	0.01
Chemotherapy cycles received							
More than planned (mean 4 cycles)	10	71.4	0.75	0.21-2.64	0.80	0.19-3.34	
Less than planned (mean 3 cycles)	169	56.0	0.38	0.22-0.65	0.67	0.37-1.24	
4 planned and received	70	76.9	1		1		
6 planned and received	80	67.8	0.63	0.34-1.18	0.97	0.48-1.97	
Received planned amount excluding 4 & 6 cycles (mean 2 cycles)	18	52.9	0.34	0.15-0.78	0.70	0.24-2.04	
Missing planned cycles	34	49.3	0.29	0.15-0.57	0.57	0.26-1.23	0.53
Received radiotherapy							
Did not receive radiotherapy	119	44.2	1		1		
Radical (≥40Gy)	197	81.4	5.52	3.69-8.26	3.32	2.07-5.31	
Palliative (<40Gy)	65	55.6	1.58	1.02-2.44	1.53	0.94-2.49	<0.01
Received PCI							
No	261	53.4	1		1		
Yes	120	86.3	5.52	3.29-9.24	2.42	1.33-4.39	<0.01
¥: LR test for trend, *Adjusted OR for all other factors in table							

Table 4.3: Sensitivity analysis of individuals with LD-SCLC who survived to 1-year following chemotherapy with different radiotherapy thresholds.							
	Number surviving 1-year n=381	% who survived 1-year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95%CI	P value likelihood ratio test
Received radiotherapy							
Did not receive radiotherapy	119	44.2	1		1		
Radical ($\geq 40\text{Gy}$)	197	81.4	5.52	3.69-8.26	3.32	2.07-5.31	
Palliative ($< 40\text{Gy}$)	65	55.6	1.58	1.02-2.44	1.53	0.94-2.49	<0.01
Received PCI							
No	261	53.4	1		1		
Yes	120	86.3	5.52	3.29-9.24	2.42	1.33-4.39	<0.01
Received radiotherapy							
Did not receive radiotherapy	119	44.2	1		1		
Radical ($\geq 30\text{Gy}$)	236	77.6	4.37	3.15-6.28	2.83	1.84-4.34	
Palliative ($< 30\text{Gy}$)	26	47.3	1.13	0.63-2.02	1.31	0.69-2.47	<0.01
Received PCI							
No	261	53.4	1		1		
Yes	120	86.3	5.52	3.29-9.24	2.44	1.34-4.43	<0.01
Adjusted OR for all other factors in table 4.2							

Extensive stage

There were 1,091 people with ED-SCLC who received chemotherapy. Carboplatin + etoposide was most commonly used (n=900(82.5%)) followed by a single platinum (n=95(8.7%)) and cisplatin + etoposide (n=59(5.41%)). Radiotherapy was given to 409 (37.5%) people and the median total dose prescribed was 30Gy (IQR 20-30) divided into 10 fractions. Radiotherapy doses ranged from a maximal of 55Gy in 20 fractions to 3Gy in 1 fraction. From the 1,091 people with ED-SCLC who received chemotherapy 286 (26.2%) survived 1-year. *Table 4.4* demonstrates the demographics of those that survived to 1 year and the odds of 1 year survival. The associated patient factors differed to LD-SCLC, in particular sex (male vs female adjusted OR 0.53 95%CI 0.39-0.73) and comorbidity (comorbidity score ≥ 4 vs 0 adjusted OR 0.64 95%CI 0.43-0.94). PS was a significant prognostic factor ($p < 0.01$) whereas SES ($p = 0.16$) and age (p trend=0.30) were not. The odds of survival differed by the chemotherapy cycles received. Individuals receiving less than the planned amount of cycles (mean 3 cycles received) were less likely to survive 1-year (vs 4 cycles adjusted OR 0.37 95%CI 0.23-0.61). Similarly, people that received the planned amount of cycles which did not include 4 or 6 cycles (mean 2 cycles) were less likely to survive (vs 4 cycles adjusted OR 0.27 95%CI 0.09-0.76). Six chemotherapy cycles did not augment survival in comparison to 4 (6 vs 4 adjusted OR 1.34 95%CI 0.81-2.21). Receipt of PCI was associated with improved 1-year survival (received PCI adjusted OR 2.04 95%CI 1.42-2.93). The median radiotherapy dose prescribed in ED-SCLC was 30Gy. At 40Gy threshold radical and palliative radiotherapy favoured survival but lacked statistical significance (radical vs nil adjusted OR 1.88 95%CI 0.91 3.87 and palliative vs no

radiotherapy adjusted OR 1.37 95%CI 0.99-1.90). Reducing the threshold to ≥ 30 Gy caused radical radiotherapy to be associated with improved survival and reduced the effect of palliative radiotherapy (radical vs nil adjusted OR 1.78 95%CI 1.22-2.59, *Table 4.5*). Chemotherapy regimen was not independently associated with survival ($p=0.12$). However, individuals that received single platinum therapy were less likely to survive 1-year (vs carboplatin+etoposide adjusted OR 0.36 95%CI 0.14-0.92)

Table 4.4: Features of patients with extensive stage who received chemotherapy and survived 1-year with odds ratios for 1-year survival							
Factor	Number surviving 1-year (n=286 from 1,091)	% who survived 1-year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival*	95% CI	P value (LR test)
Sex							
Female	166	31.4	1		1		
Male	120	21.4	0.59	0.45-0.78	0.53	0.39-0.73	<0.01
Age group							
<60	64	29.6	0.88	0.63-1.23	1.10	0.75-1.62	
60-79	210	27.1	1		1		
≥80	12	12.1	0.33	0.17-0.64	0.59	0.28-1.26	0.30¥
Townsend quintile							
Least deprived- 1	34	28.1	1		1		
2	48	26.4	0.92	0.55-1.53	1.01	0.57-1.80	
3	65	27.2	0.96	0.59-1.56	0.98	0.57-1.70	
4	81	30.3	1.11	0.69-1.79	1.29	0.76-2.21	
Most deprived- 5	58	20.6	0.66	0.41-1.08	0.73	0.42-1.27	0.16
Performance status							
0	82	42.7	1		1		
1	125	29.7	0.57	0.40-0.81	0.53	0.36-0.79	
2	51	18.4	0.30	0.20-0.46	0.32	0.20-0.51	
3-4	12	10.5	0.16	0.08-0.31	0.22	0.10-0.45	
Missing	16	18.4	0.30	0.16-0.56	0.29	0.14-0.57	<0.01
Charlson comorbidity index							
0	102	31.4	1		1		
1	72	38.9	1.39	0.96-2.03	1.76	1.14-2.70	
2-3	37	21.0	0.58	0.38-0.90	0.80	0.49-1.30	
≥4	75	18.5	0.50	0.35-0.70	0.64	0.43-0.94	<0.01
Chemotherapy							
Carboplatin+ etoposide	254	28.2	1		1		
Cisplatin + etoposide	20	33.9	1.30	0.75-2.28	1.02	0.53-1.95	
Other	4	16.0	0.48	0.16-1.43	1.05	0.32-3.52	
Single platinum	5	5.3	0.14	0.06-0.35	0.36	0.14-0.92	
Missing	3	25.0	0.85	0.23-3.16	2.63	0.50-13.74	0.12
Chemotherapy cycles received							
More than planned (mean 5 cycles)	6	37.5	1.06	0.36-3.14	1.19	0.36-3.88	
Less than planned (mean 3 cycles)	91	17.0	0.36	0.23-0.57	0.37	0.23-0.61	
4 planned and received	39	36.1	1		1		
6 planned and received	117	44.8	1.44	0.91-2.28	1.34	0.81-2.21	
Received planned amount excluding 4 & 6 cycles (mean 2 cycles)	8	13.8	0.28	0.12-0.66	0.27	0.09-0.76	
Missing planned cycles	25	22.5	0.51	0.28-0.93	0.46	0.24-0.88	<0.01
Received radiotherapy							
Did not receive radiotherapy	142	20.8	1		1		
Radical (≥40Gy)	21	51.2	4.00	2.11-7.57	1.88	0.91-3.87	
Palliative (<40Gy)	123	33.4	1.91	1.44-2.54	1.37	0.99-1.90	0.07
Received PCI							
No	191	21.8	1		1		
Yes	95	44.6	2.90	2.12-3.96	2.04	1.42-2.93	<0.01
¥: LR test for trend, *Adjusted OR for all other factors in table							

Table 4.5: Sensitivity analysis of individuals with ED-SCLC who survived to 1-year following chemotherapy with different radiotherapy thresholds							
	Number surviving 1-year N=286	% who survived 1-year from all who received chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95%CI	P value likelihood ratio test
Received radiotherapy							
Did not receive radiotherapy	142	20.8	1		1		
Radical (≥ 40 Gy)	21	51.2	4.00	2.11-7.57	1.88	0.91-3.87	
Palliative (< 40 Gy)	123	33.4	1.91	1.44-2.54	1.37	0.99-1.90	0.07
Received PCI							
No	191	21.8	1		1		
Yes	95	44.6	2.90	2.12-3.96	2.04	1.42-2.93	< 0.01
Received radiotherapy							
Did not receive radiotherapy	142	20.8	1		1		
Radical (≥ 30 Gy)	113	45.2	3.14	2.30-4.28	1.78	1.22-2.59	
Palliative (< 30 Gy)	31	19.5	0.92	0.60-1.42	0.96	0.59-1.55	< 0.01
Received PCI							
No	191	21.8	1		1		
Yes	95	44.6	2.90	2.12-3.96	1.76	1.19-2.60	< 0.01
Adjusted OR for all other factors in table 4.4							

4.3.4 Network evaluation

Treatment administration by network

There was significant variation in chemotherapy use by lung cancer network following diagnosis ($p < 0.01$ Table 4.6). There was variation in access to radiotherapy and PCI for people who had been treated with chemotherapy (radiotherapy $p < 0.01$ and PCI $p < 0.01$). Tables 4.7 and 4.8 show the amount and odds of people being treated with radiotherapy/PCI from all the people who received chemotherapy by lung cancer network. Despite network variation being statistically significant the absolute difference in the proportions treated from the national average were small (mean difference in proportion treated vs pooled national proportion: chemotherapy (0.25% (SD+/-5.15%)), radiotherapy (-1.87% (SD+/-9.2%)) and PCI (0.25% (SD+/-5.3%))).

Table 4.6: Odds of receiving chemotherapy for individuals diagnosed with SCLC.								
Network	Number receiving chemotherapy (N)	Proportion treated with chemotherapy from total diagnosed	Difference in proportion treated from national proportion treated %	OR receiving chemotherapy	95% CI	Adjusted OR receiving chemotherapy	95% CI	P value (LR test)
Pooled networks	3,995	62.1		1		1		
N1	232	59.3	-2.8	0.89	0.73-1.08	1.20	0.97-1.48	
N2	201	57.3	-4.8	0.82	0.67-1.01	0.67	0.53-0.84	
N3	493	65.2	3.1	1.15	1.00-1.32	1.08	0.92-1.25	
N4	342	58.2	-3.9	0.85	0.73-0.99	0.85	0.71-1.01	
N5	571	65.8	3.7	1.18	1.03-1.34	1.26	1.09-1.46	
N6	375	59.6	-2.5	0.90	0.78-1.05	0.82	0.70-0.97	
N7	325	65.4	3.3	1.16	0.97-1.38	1.19	0.98-1.45	
N8	370	58.6	-3.5	0.87	0.75-1.01	0.75	0.64-0.89	
N9	308	64.2	2.1	1.10	0.91-1.31	1.09	0.89-1.33	
N10	252	52.6	-9.5	0.68	0.57-0.81	0.67	0.55-0.81	
N11	117	66.1	4.0	1.19	0.88-1.62	1.49	1.06-2.08	
N12	216	71.5	9.4	1.54	1.20-1.96	1.52	1.17-1.99	
N13	193	66.8	4.7	1.23	0.97-1.56	1.44	1.11-1.87	<0.01
Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and chemotherapy drugs received								

Table 4.7: Odds of receiving radiotherapy for individuals who were treated with chemotherapy.								
Network	Number receiving radiotherapy (N)	Proportion receiving radiotherapy from those treated with chemotherapy	Difference in proportion treated from national proportion treated (%)	OR Receiving radiotherapy	95% CI	Adjusted OR Receiving radiotherapy	95% CI	P value (LR test)
Pooled networks	792	45.0		1		1		
N1	57	50.9	5.9	1.27	0.89-1.81	1.29	0.88-1.88	
N2	24	29.6	-15.4	0.52	0.32-0.82	0.49	0.30-0.79	
N3	134	61.8	16.8	1.98	1.53-2.55	2.48	1.88-3.28	
N4	80	48.5	3.5	1.15	0.86-1.54	1.22	0.90-1.65	
N5	110	43.8	-1.2	0.95	0.76-1.20	1.10	0.86-1.41	
N6	69	46.0	1.0	1.04	0.77-1.42	1.02	0.74-1.39	
N7	62	42.8	-2.2	0.91	0.67-1.25	0.83	0.59-1.17	
N8	58	35.6	-9.4	0.68	0.50-0.92	0.63	0.45-0.87	
N9	50	38.8	-6.2	0.77	0.55-1.09	0.73	0.51-1.04	
N10	45	40.9	-4.1	0.85	0.59-1.22	0.76	0.52-1.12	
N11	14	29.2	-15.8	0.50	0.27-0.93	0.43	0.22-0.82	
N12	54	53.5	8.5	1.41	0.96-2.05	1.38	0.94-2.02	
N13	35	39.3	-5.7	0.79	0.52-1.20	0.64	0.42-0.98	<0.01
Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and chemotherapy drugs received								

Table 4.8: Odds of receiving PCI for individuals who were treated with chemotherapy								
Network	Number receiving PCI (N)	Proportion receiving PCI from those treated with chemotherapy	Difference in proportion treated from national proportion treated (%)	OR Receiving PCI	95% CI	Adjusted OR Receiving PCI	95% CI	P value (LR test)
Pooled networks	730	20.7		1		1		
N1	56	25.0	4.3	1.27	0.84-1.92	1.35	0.87-2.10	
N2	40	24.7	4.0	1.25	0.77-2.05	1.34	0.80-2.26	
N3	128	29.5	8.8	1.60	1.22-2.09	1.77	1.33-2.37	
N4	76	23.0	2.3	1.14	0.81-1.61	1.29	0.91-1.83	
N5	94	18.7	-2.0	0.88	0.66-1.18	1.00	0.73-1.36	
N6	40	13.3	-7.4	0.59	0.37-0.93	0.56	0.35-0.89	
N7	48	16.6	-4.1	0.76	0.50-1.16	0.65	0.41-1.02	
N8	40	12.3	-8.4	0.53	0.34-0.84	0.47	0.29-0.76	
N9	48	18.6	-2.1	0.87	0.57-1.34	0.90	0.59-1.39	
N10	46	20.9	0.2	1.01	0.65-1.58	0.95	0.59-1.52	
N11	20	20.8	0.1	1.01	0.51-2.00	1.03	0.49-2.19	
N12	58	28.7	8.0	1.54	1.02-2.33	1.38	0.91-2.08	
N13	36	20.2	-0.5	0.97	0.59-1.61	0.87	0.51-1.48	<0.01
Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and chemotherapy drugs received								

Survival by network

Survival was not associated with lung cancer network ($p=0.58$). *Table 4.9* demonstrates this as it displays the number of individuals diagnosed in a network, the number/proportion treated with chemotherapy and the odds of 1 year survival. Likewise, there was no correlation with the proportion receiving chemotherapy per network and 1-year survival ($p=0.802$). This is demonstrated in a *scatter plot*, *Figure 4.2*. The secondary analysis of six-month survival per network demonstrated similar results to 1-year ($p=0.100$, *Table 4.10*).

Lung cancer network was not associated with 1-year survival for people that received chemotherapy ($p=0.52$). *Table 4.11* shows the number of people treated in that network with chemotherapy and the odds of 1-year survival. However, one network (N12) did have better odds of 1-year survival in comparison to the national mean (adjusted OR 1.43 95%CI 1.08-1.90). This is demonstrated in the funnel plot *Figure 4.3* that compares the number of patients treated with chemotherapy in a network by the case-mix adjusted 1-year survival. This network (N12) had a tendency to give more radiotherapy and PCI than others (as previously shown in *Tables 4.7 and 4.8*).

Table 4.9: Number of patients diagnosed and subsequently treated with chemotherapy with the odds of 1-year survival in all patients diagnosed by network.								
Network	Number of patients seen in network (N)	Number of patients receiving chemotherapy	Proportion receiving chemotherapy from all diagnosed (%)	OR 1-year survival	95% CI	*Adjusted OR 1-year survival	95% CI	P value (LR test)
Pooled networks	6,438	3,995	62.1	1		1		
N1	391	232	59.3	1.00	0.81-1.24	1.20	0.95-1.53	
N2	351	201	57.3	1.15	0.93-1.43	1.14	0.89-1.48	
N3	756	493	65.2	1.05	0.91-1.21	0.96	0.81-1.13	
N4	588	342	58.2	0.95	0.80-1.13	1.06	0.87-1.29	
N5	868	571	65.8	0.87	0.76-1.00	0.90	0.76-1.07	
N6	629	375	59.6	1.03	0.88-1.22	1.01	0.83-1.22	
N7	497	325	65.4	1.01	0.84-1.22	0.96	0.77-1.18	
N8	631	370	58.6	0.99	0.84-1.17	0.96	0.79-1.17	
N9	480	308	64.2	0.88	0.72-1.07	0.86	0.68-1.09	
N10	479	252	52.6	0.92	0.76-1.11	1.03	0.82-1.28	
N11	177	117	66.1	1.02	0.74-1.41	0.94	0.58-1.22	
N12	302	216	71.5	1.39	1.11-1.75	1.27	0.87-1.65	
N13	289	193	66.8	1.10	0.86-1.40	1.07	0.82-1.41	0.58
*Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and receipt of chemotherapy								

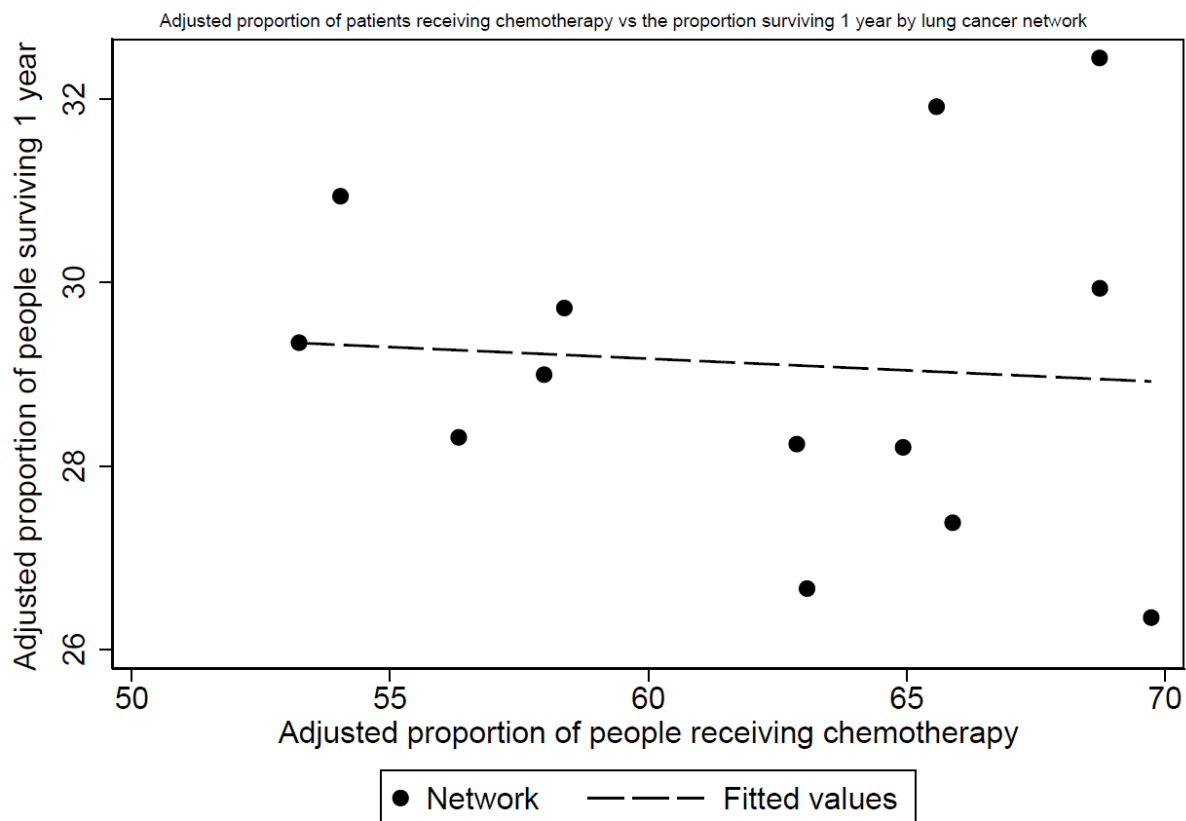


Figure 4-2: Scatter plot comparing the proportion of patients treated per lung cancer network with the corresponding proportion of 1-year survival in that network. Each dot represents a lung cancer network. *Adjusted for sex, age, PS, stage, socioeconomic status and comorbidity.

Table 4.10 Number of patients diagnosed in a lung cancer network and the odds ratios of 6 month survival								
Network	Number of patients seen in network (N)	Total number of patients surviving 6 months	% of total patients surviving 6 months	OR 6 month survival	95% CI	Adjusted OR 6 month survival	95% CI	P value (LR test)
Pooled networks	6,438	3,405	52.9	1		1		0.100
N1	391	199	50.9	0.92	0.76-1.12	1.06	0.85-1.33	
N2	351	197	56.1	1.14	0.93-1.40	1.23	0.94-1.61	
N3	756	406	53.7	1.03	0.90-1.18	1.01	0.85-1.19	
N4	588	328	55.8	1.12	0.96-1.31	1.37	1.13-1.66	
N5	868	453	52.2	0.97	0.86-1.10	1.01	0.86-1.17	
N6	629	316	50.2	0.90	0.78-1.04	0.84	0.70-1.01	
N7	497	270	54.3	1.06	0.89-1.26	0.94	0.77-1.17	
N8	631	324	51.4	0.94	0.81-1.09	0.92	0.75-1.12	
N9	480	249	51.9	0.96	0.81-1.14	0.91	0.72-1.15	
N10	479	230	48.0	0.82	0.69-0.98	0.93	0.75-1.14	
N11	177	90	50.9	0.92	0.69-1.23	0.71	0.49-1.02	
N12	302	180	59.6	1.31	0.05-1.65	1.09	0.83-1.43	
N13	289	163	56.4	1.15	0.92-1.45	1.04	0.76-1.42	
Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and receipt of chemotherapy								

Table 4.11 Odds of 1-year survival after receiving chemotherapy by lung cancer network.						
Network	Number treated with chemotherapy (N)	OR 1-year survival after receiving chemotherapy	95% CI	*Adjusted OR 1-year survival after receiving chemotherapy	95% CI	P value (LR test)
Pooled networks	3,995	1		1		
N1	232	1.04	0.81-1.35	1.15	0.87-1.52	
N2	201	1.19	0.91-1.56	1.10	0.81-1.47	
N3	493	1.01	0.85-1.20	1.02	0.84-1.24	
N4	342	0.89	0.72-1.10	0.98	0.78-1.24	
N5	571	0.81	0.69-0.95	0.88	0.74-1.06	
N6	375	1.14	0.94-1.38	1.04	0.83-1.29	
N7	325	0.98	0.79-1.22	0.92	0.73-1.17	
N8	370	1.01	0.83-1.23	0.96	0.77-1.20	
N9	308	0.82	0.66-1.04	0.86	0.66-1.11	
N10	252	1.15	0.90-1.46	1.14	0.88-1.48	
N11	117	1.07	0.74-1.53	0.92	0.60-1.40	
N12	216	1.42	1.10-1.84	1.43	1.08-1.90	
N13	193	0.97	0.73-1.29	0.86	0.65-1.16	0.52
*Adjusted for sex, age, social deprivation, performance status, cancer stage, Charlson score and receipt of chemotherapy						

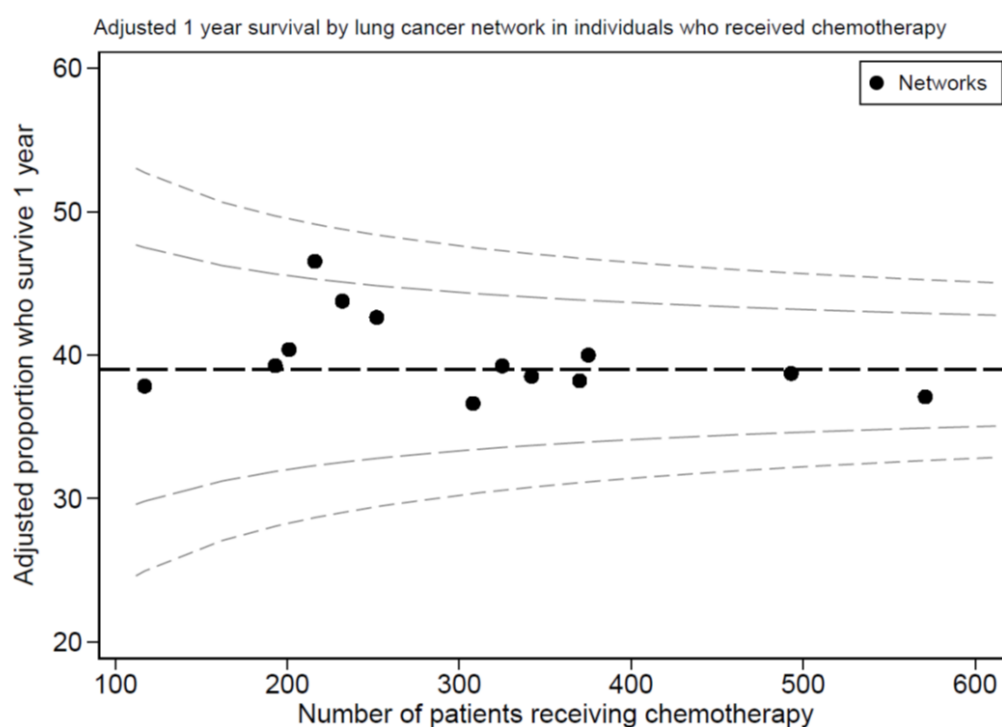


Figure 4-3: : Funnel plot demonstrating the case mix adjusted proportion of 1-year survival after receiving chemotherapy and the number of individuals treated with chemotherapy by each lung cancer network. Each network is represented by a dot. The central black dashed line represents the national mean proportion of 1-year survival. The other dashed lines represent 2 and 3 standard deviations from this mean. *Adjusted for sex, age, PS, stage, socioeconomic status and comorbidity.

4.4 Discussion

4.4.1 *Main findings*

It is evident from this research that sex, age, PS, comorbidity, stage and receipt of chemotherapy are independently associated with 1-year survival for all people diagnosed with SCLC. The majority of these factors with the addition of radiotherapy and PCI, but excluding age, were also associated with 1-year survival in people who received chemotherapy. Continuing chemotherapy to 6 cycles did not increase the chance of 1-year survival in comparison to 4.

There was variation in use of chemotherapy, radiotherapy and PCI between networks. However, there was no survival variation between them.

4.4.2 *strengths*

These results provide an up-to date “real world” benchmark of 1-year survival for SCLC. This complex linkage of national data provides a comprehensive picture of the treatments given for SCLC and importantly their survival impact. Many studies that inform treatment recommendations are clinical trials and have highly selected cohorts. This research demonstrates the efficacy of these treatments in the real world.

4.4.3 *Limitations*

Some variables are prone to immortal time bias, however, many of the therapies for SCLC are given within days of diagnosis. Hence, the few days survival advantage treated groups have is too small a proportion of the 1-year survival to significantly bias these results. Similarly, there might be residual selection bias i.e. fitter patients are more likely to receive treatments. However, by adjusting for PS and comorbidity this

bias will be lessened and in the case of chemotherapy cycles these biases would tend to favour 6 over 4.

4.4.4 Comparisons with other research

Patient factors

The associated survival factors identified in this research have been demonstrated previously for all people diagnosed with SCLC. Female sex and age (<70 years) have been shown to confer better long term survival in clinical trials as well as real world settings.^{130 131} However, age may be confounded by selective receipt of chemotherapy because amongst those receiving chemotherapy, age was not independently associated with survival. Survival was not considerably different for people with LD-SCLC who were PS 0 and 2. This finding is inconsistent with other research and is probably a result of small patient numbers impeding statistical significance. Indeed, PS was an independently associated factor with 1-year survival. This finding, in addition to stage, is consistent with other research and both are used in the Manchester prognostic score to estimate 2-year survival.¹¹⁴ Rich *et al* demonstrated that a worse Charlson Index was associated with poorer survival in all stages of SCLC.⁹⁴

Chemotherapy

Contrary to this study's observation of better survival with cisplatin+etoposide in LD-SCLC, a meta-analysis of individual patient data has shown no difference between carboplatin vs cisplatin regimens.¹³² The difference in these results may relate to residual selection bias in the NLCA and SACT data. Indeed, PS was a strong confounder to this, suggesting cisplatin was reserved for fitter individuals and those receiving concurrent chemo-radiotherapy. Clinicians may select carboplatin over cisplatin when

prognosis is short due to its favourable side effect profile and convenience of administration.

PCI

There is strong evidence to support PCI use in LD-SCLC. A systematic review which included mostly LD-SCLC patients from 7 clinical trials found that PCI improved survival for people who were in complete remission following chemo-radiotherapy for SCLC.⁷⁹

The evidence for the benefit of PCI in ED-SCLC is less clear. The EORTC showed, in 2007, that PCI augmented survival for individuals with ED-SCLC who had responded to chemotherapy.⁸⁰ However, this study did not report response to chemotherapy or screen for asymptomatic brain metastases in all participants. More recently, with the pitfalls of the EORTC study addressed, a phase III randomized controlled trial found that PCI did not augment survival in a cohort consisting mostly of partial chemotherapy responders with ED-SCLC.¹³³ The datasets used in this thesis do not contain information about the response to chemotherapy before PCI administration. However, one can assume that PCI was given to individuals who had responded to chemotherapy, in accordance with treatment recommendations.^{47 48}

Radiotherapy

Radical radiotherapy doses $\geq 40\text{Gy}$ augmented the odds of 1-year survival but lacked statistical significance in ED-SCLC. When reduced to $\geq 30\text{Gy}$ these odds decreased for LD-SCLC and became statistically significant for ED-SCLC. This is the resultant effect of 30Gy being used for palliative as well as radical (life prolonging) treatment in addition to it being the median dose prescribed for ED-SCLC. Indeed, the lowest recommended dose by the Royal College of Radiologists to treat LD-SCLC is 40Gy whereas, for ED-

SCLC, 30Gy can be used as consolidation therapy in chemotherapy responders (where the goal is to prolong survival) or as palliation of persistent thoracic symptoms following chemotherapy.⁶⁹

In LD-SCLC the survival benefits of early thoracic radiotherapy within the first 2 cycles of chemotherapy were established using a schedule of 40Gy in 15 fractions.¹³⁴ Other studies have also given ≥ 40 Gy but have investigated the delivery of radiotherapy i.e. once vs twice daily. *Turrisi et al* found that a total dose of 45Gy given twice daily was superior to once daily.⁷³ However, this finding was refuted by the CONVERT trial which demonstrated that a total dose of 66Gy given as 2Gy in once daily fractions was no better, in terms of survival and toxicity, than a total dose of 45Gy given in twice daily fractions.⁷⁴ Nevertheless, both these regimens would have been captured in the radical radiotherapy group.

For ED-SCLC the addition of thoracic radiotherapy in chemotherapy responders has been associated with improved survival before.⁷¹ A meta-analysis of two randomized controlled trials that gave 30Gy in 10 fractions and 54Gy in 36 fractions found that thoracic radiotherapy augmented survival in chemotherapy responders when compared to no radiotherapy (HR 0.81 95%CI 0.69-0.96).

Cycles of chemotherapy

There was no difference in 1-year survival between 4 and 6 cycles of chemotherapy and the supporting evidence in this area is limited. *Powell et al* found a reduction in the risk of death when more chemotherapy cycles were given but was unable to directly compare 4 with 6.⁹⁵ To my knowledge only one study has compared both and

found no difference in survival for LD-SCLC and a trend to improved survival with 6 cycles for ED-SCLC, but this lacked statistical significance ($p=0.09$).¹³⁵

Network

There was significant variation in receipt of treatment between networks, although the magnitude of the variation was small. This probably explains why no survival difference was seen. *Rich et al* described similar results to this, whereby hospitals with high clinical trial recruitment offered more chemotherapy than other units but there was no significant variation in survival.⁹⁴ Another explanation to this study's finding, but rebutted by the 6-month survival analysis, is that many treated patients relapse after first-line treatment and die within 1-year, hence the proportion treated does not correlate with 1-year survival.

In the population that received chemotherapy, one network (N12) had greater 1-year survival in comparison to the national average. Although not statistically significant, this network tended to administer more radiotherapy and PCI than others. This may relate to the main findings that radiotherapy treatments are important for survival and that this effect may even be seen on a larger population such as a network.

4.4.5 Relevance

These findings relate to clinical practice and add to the evidence base for treatment recommendations. It demonstrates that higher dose radiotherapy and PCI are associated with improved survival and that 6 cycles of chemotherapy is no better than 4. This may serve to ensure the emphasis is placed on delivering the more effective radiotherapy treatments as opposed to focussing on more than 4 cycles of chemotherapy.

4.5 Conclusion

This research adds further evidence to factors associated with long-term survival in SCLC. Receiving chemotherapy is one of the strongest predictors of survival yet there remains variation in its use. Balancing the survival benefits of chemotherapy with the toxicities is important if quality as well as quantity of life is to be preserved. This may be supported by giving 4 cycles of chemotherapy rather than 6, as there is no survival advantage from the latter. Access to radiotherapy and PCI remains disproportionate but their use should be encouraged because they provide a survival benefit. In the future, advances in SCLC survival may come from adding novel maintenance therapies to four cycles of optimally delivered chemo and radiotherapy.¹³⁶

Chapter 5 A systematic review and meta-analysis of survival following anti-cancer treatment for small cell lung cancer

This chapter includes a comprehensive systematic review and meta-analysis of survival for SCLC following platinum doublet chemotherapy.

5.1 Introduction

European guidelines, NICE and the European Society of Medical Oncology (ESMO), recommend 4-6 cycles of cisplatin or carboplatin doublet chemotherapy as first line treatment for all stages of SCLC.^{45 47} Thoracic radiotherapy and prophylactic cranial irradiation (PCI) are primarily reserved for individuals who respond to initial chemotherapy, with the exception of early concurrent chemoradiotherapy, which is encouraged in fit individuals with LD-SCLC. These treatments have remained largely unchanged for 30 years but novel immunotherapies are beginning to emerge that show promising results for SCLC. Indeed, one such immunotherapy, atezolizumab, has been approved by the US food and drug administration for the treatment of SCLC, whilst nivolumab has been granted priority review.¹³⁷⁻¹³⁹

Whether existing or new therapies are used to treat patients it is important to maximise their efficacy by ensuring patients are optimally selected. Deaths that occur early after chemotherapy (within 30-days) are a metric of poor selection and this is estimated to be 9.1% in SCLC, however the evidence base here is limited.¹⁰⁵ Hence, the objective of this systematic review is to examine early and late survival by current treatment recommendations in order to increase this evidence base and benchmark current survival. This survival benchmark will facilitate the appraisal of novel immunotherapies in the future.

5.2 Methods

5.2.1 Study question

The Cochrane Population, Intervention, Comparison and Outcome criteria (PICO) were used to frame the study question; What is the short and long term survival

following chemotherapy for SCLC and how is this influenced by treatment, study and population factors?

Population- Individuals with SCLC.

Intervention- All studies that administered first line, European recommended chemotherapy.

Comparison- By chemotherapy regimen, study factors, treatment factors and population factors.

Outcome- Overall early (30 and 90 days) and late (1, 2, 5-year and median) survival.

5.2.2 Registration of study

Prior to conducting this study an internet search was performed and the systematic review registry, Prospero (www.crd.york.ac.uk/prospero), was examined to identify whether this research question had previously been answered. It had not. The study protocol was written and registered on the Prospero website portal. The protocol can be found in Appendix J. The Prospero identification number assigned to this study is CRD42016037772.

5.2.3 Search strategy

English language RCTs or observational cohort studies that reported overall survival following receipt of cisplatin or carboplatin in combination with etoposide, irinotecan or topotecan for SCLC, in line with European recommendations were to be included. A search strategy that could be applied to EMBASE and MEDLINE was developed. EMBASE is an online biomedical and pharmacological bibliographic database. It contains over 32 million records of published research literature from 1947 until

present. MEDLINE is a similar database founded in the United States and contains records of published healthcare related literature since 1950. The search of these databases was conducted on 7th June 2016. The search strategy can be found in Appendix K. In addition to these two databases Google and the online conference libraries of the ASCO, ESMO and the IASLC were used to identify abstracts. Finally, a bibliographic search from all included manuscripts was performed. The search was completed on the 22nd November 2017.

5.2.4 Inclusion and exclusion criteria

The full details of the inclusion criteria are presented in *Table 5.1*. Overall survival in treatment naïve individuals with SCLC who received platinum based chemotherapy in-keeping with NICE and ESMO guidelines were included.^{45 47} Studies were excluded if “up front” prophylactic growth colony stimulating-factor or antibiotics were given before the first chemotherapy cycle as these are not routinely recommended in SCLC.¹⁴⁰ Studies administering colony stimulating-factors or antibiotics were included if these were used to treat an episode of neutropaenia/neutropaenic sepsis. Abstract only articles were included and manuscripts using the same study population were only used once and, if present, the study with the most comprehensive survival data was chosen. If a study changed the protocol throughout it’s duration and this change was not compatible with the inclusion criteria the study was excluded. The inclusion and exclusion criteria were applied by two reviewers (Dr Gavin Jones and Prof Tricia McKeever) to all the identified studies. If there was disagreement then a third reviewer was consulted (Prof David Baldwin or Prof Richard Hubbard) and a consensus was reached.

Table 5.1: Inclusion and exclusion criteria.

Inclusion	Exclusion
• Phase IIb, III or IV RCTs. • Observational studies. • First line therapy. • Etoposide + carboplatin. • Etoposide + cisplatin. • Irinotecan + cisplatin. • Gemcitabine + cisplatin. • Topotecan + cisplatin. • Any combination of the above mentioned drugs with a third non- chemotherapy drug which is part of routine hospital care e.g. enoxaparin, oxygen, analgesics. • Radiotherapy combined with the above chemotherapy drugs. • Limited stage and extensive stage small cell.	• Phase I, IIa clinical trials. • Systematic reviews/ review. • Editorials. • Second line or maintenance therapy. • Any chemotherapy drugs not in the inclusion criteria. • Any combination of the included chemotherapy drugs and another chemotherapy agent. • Any combination of approved chemotherapy with erythropoiesis stimulating drugs e. g GCSF, colony stimulating factors given with the 1st cycle • Any combination of approved chemotherapy that also includes prophylactic antibiotics. • Trials that include Chinese herbal medicines. • Any trial/ study arm that includes Immunotherapy. • Trials investigating radiotherapy alone or prophylactic cranial irradiation without chemotherapy. • Adjuvant chemotherapy (after surgery).

5.2.5 Screening process

There were 3 rounds to the screening process and the online reference manager Covidence (www.covidence.org) was used to assist with this. The three rounds consisted first reviewing titles, then abstracts and lastly the full manuscripts. Prof Tricia M McKeever and I independently reviewed each study once. At the end of each round the studies where there was disagreement were discussed and a final consensus for inclusion/exclusion was reached, involving the third reviewer if needed.

5.2.6 Data extraction

Once the final list of included manuscripts had been reached data were extracted. The information collected consisted of: trial design, participant characteristics, treatment schedule, survival (30-day, 90-day, 1-year, 2-year, 5-year and median survival), cause of 30-day mortality and the study quality. The data were extracted independently by three reviewers; myself, Dr Kelly Elimian and Prof Tricia M McKeever onto a bespoke Microsoft Excel spreadsheet that was designed for this study. Graph digitalizer software, Digitizelt V2.2, (Braunschweig, Germany) was used to extract survival data from Kaplan Meier plots if survival was not within the manuscript text. This method of digital extraction has been used in previous survival analyses and is a valid method of extracting these data.¹⁴¹⁻¹⁴³ Extracted values were cross-checked for accuracy with the other reviewers and if there were discrepancies of > 2% then a third value was taken with both reviewers in agreement and this value was used. A quality score was developed that was unique to this systematic review as RCTs and cohort studies were being examined. This score was an amalgamation of the Cochrane risk of bias (RCTs) and the Newcastle-Ottawa scoring method (Cohort studies). It assessed the quality of survival reporting and study design for risk of bias. RCTs and cohort studies could achieve a maximal score of 30 and 27 respectively. The breakdown of this score is shown in *Table 5.2*. Studies were grouped by their quality score (poor (0-9), moderate (10-14), good (15-19) and very good (20-27)). The scores were grouped in this way as “good” coincided with the median score and the IQR.

Table 5.2: Quality score table

Data ascertainment	Survival calculated from?	How were survival figures obtained?		Blinding of treatment (RCT only)	Representativeness of general SCLC population	Completeness of survival Data (censoring/ follow ups lost)	Reason of death given/ summarised	Patients excluded from survival analysis?
5	4	Specific time points (30-day, 90-day, 1-year etc.)	Median	3	3	3	4	3
Clinical trial records	Date of 1 st dose of chemotherapy			Triple blind	Unselected (any age, PS 0-3)	All followed up	All patients	Nil
4						2	3	2
Individual patient records	3	Published in text	Published in text	2	2	<20% follow ups lost	0-90 days	Yes- reason given
3	Date of randomisation	2	1	Double blind	(age <75, PS 0-2, severe comorbidity, > 3 months predicted survival)	1	2	1
Database/ registry		Mix of published in text and KM extraction/published in text but no KM plot	KM extraction/ can be extrapolated from survival data	1		>20% follow ups lost	0-30 days	Yes- early mortality/ toxicity
2	2	1	0	Single blind	1	0	1	0
Patient interview	Date of enrolment				tight selection (age <65, PS 0-1, single sex, any comorbidity > 6 months predicted survival)	No statement/ unable to quantify	Published but timing of deaths not given	Yes- No clear reason given
1		1	0	0			0	
Self report	1	KM extraction/can be extrapolated from survival data/ only 1 survival outcome reported with no KM plot	Unable to ascertain	Open label			Not published	
0	Date of diagnosis	0			0			
No description	0	0		N/A	No description			
	Not stated/other	Unable to ascertain						
Score:	Score:	Score:	Score:	Score:	Score:	Score:	Score:	Score:
Total: /30/27								

5.2.7 Statistical Analysis

All statistical analyses were carried out using STATA V15 (TX, USA). Pooled survival estimates were derived from individual treatment arms and not by study. For example, a single study that had two treatment regimens meeting the inclusion criteria would have two survival outcomes in the meta-analysis. Where possible, a pooled survival estimate from studies at: 30-days, 90-days, 1-year, 2-years and 5 years were calculated using a random effects model allowing for Freeman-Tukey arcsine transformation to stabilize variances between studies.¹⁴⁴ This was produced using the “metaprop” command in STATA. The median survival estimate was produced using the “metan” STATA command which is a random effects inverse-variance model (DerSimonian Laird).¹⁴⁵ In order to test for significant variation in median survival by study subgroups a metaregression analysis (metareg command) was performed, P values of ≤ 0.05 were considered significant. Heterogeneity was quantified using the I^2 statistic.¹⁴⁶ For studies where the median survival was presented without 95% CIs, a previously derived method by *R.P Jones et al* was used.¹⁴⁷ This method assumes that survival follows an exponential distribution in order to calculate λ (the average number of events occurring over a unit of time). Once λ was calculated the variance was estimated using the formula.

$$Variance = \frac{1}{(population \times \lambda^2)}$$

The standard error was calculated from this using the equation:

$$Standard\ error = \sqrt{Variance}$$

The 95% CIs were calculated using the standard error. This method was validated by conducting a sensitivity analysis which excluded the studies where 95% CIs were estimated. In addition, the studies where 95% CIs were known were examined to ensure that the confidence intervals were normally distributed around the median survival, as the estimated values were derived from the standard error, which is a statistic used to describe normally distributed data.

Combined stage pooled survival estimates with 95% CIs were presented along with LD-SCLC and ED-SCLC separately. Survival estimates were stratified by study factors and interventions. Studies were grouped by quality score (as previously described) and study design (RCT or cohort). The year that a study commenced and the median participant age were divided into 10 year groups. Study region was the continent where it originated and was classed as international if carried out across more than one. PS was based on inclusion criteria and was split into 0-1 to 0-4. Mixed reporting of survival by chemotherapy regimens was grouped into: platinum + etoposide (cisplatin/carboplatin+etoposide) and platinum+etoposide/irinotecan (cisplatin/carboplatin + etoposide/irinotecan). Thoracic radiotherapy, if given, was grouped according to start time (before (early) or after (late) the third chemotherapy cycle).

5.3 Results

5.3.1 Search process

There were 10,487 titles identified and after screening 130 remained. Another 30 studies were identified from references of included manuscripts giving a total of 160 studies. *Figure 5.1* is a flowchart of this process.

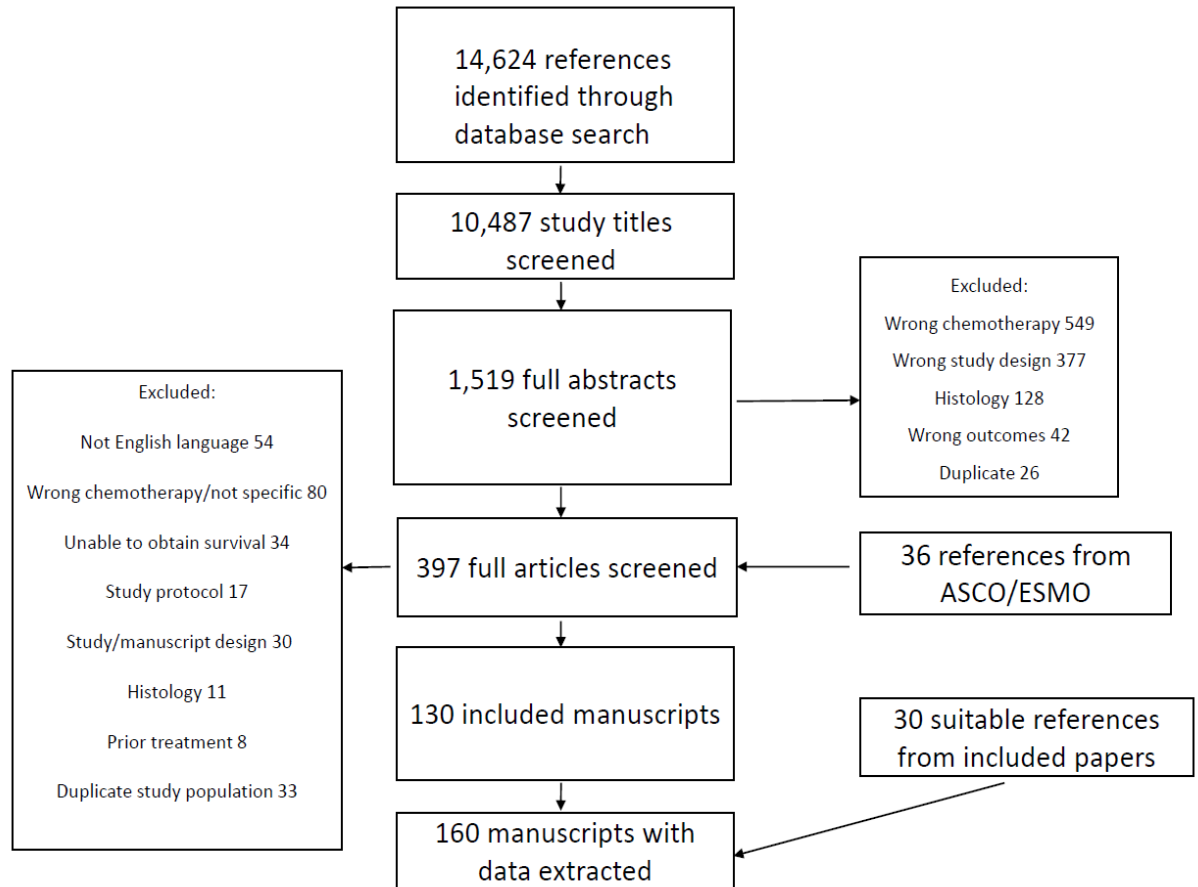


Figure 5-1: Prisma flow chart of the selection process.

5.3.2 Summary of studies

Appendix L is a summary table of all the included manuscripts, 11 of which were abstracts.^{51 65 73 74 135 148-303} The majority were observational cohort studies (100 (62.5%)) while the remaining were randomized/non-randomized controlled trials (60 (37.5%)). Study recruitment varied in size from 10 - 10,428 with a median recruitment of 78. Nearly 38% (n=56) of the included manuscripts examined patients with both LD-SCLC and ED-SCLC whereas 36.0% (58) and 28.8% (46) contained only LD-SCLC or ED-SCLC patients respectively. The earliest studies commenced in 1981, however, most were from 2000-2009 (67(41.9%)). Numerous manuscripts were Asian (60 (37.5%))

followed by European (45 (28.1 %)) and North American (36 (22.5%)). The average, median participant age was 63 years (SD 5.3 years) and most were male (median proportion 78.9%).

The median quality score for cohort studies was 18.5/27 (IQR 15.5-20.5, range 7.5¹⁶⁷ to 24²⁷⁶) and 18.5/30 (IQR 17.25-19.75, range 10²⁷⁹ to 19²⁴³) for RCTs. The causes for poorer quality were lack of reporting of early survival and cause of early death or not specifying the point from where survival was measured. In total, 63 (39.4%) studies used the first date of chemotherapy administration as the start of survival whereas 33 (20.6%) studies did not specify this. Other dates were: enrolment (20 (12.5%)), randomisation (21 (13.1 %)) and diagnosis (16 (10.0%)).

Many study populations were highly selected, most included people with PS 0-2 (107 (66.9%)). There were 31 (19.4%) studies that had minimum life expectancy criterion ranging from >8 weeks to >6 months. Many had pre-requisites for adequate bone marrow, hepatic and renal function. Common exclusion criteria were malignant pleural or pericardial effusions, recent cardiovascular disease and symptomatic brain metastases.

The chemotherapy regimens that were included in the survival meta-analysis are summarised in *Figure 5.2*. Cisplatin+etoposide (n=129(52.0%)), carboplatin+etoposide (n=54(21.8%)) and irinotecan+cisplatin (n=23(9.3%)) were predominantly used. Chemotherapy was mostly administered intravenously however 14 studies gave oral etoposide.^{156 165 176 202 204 218 225 234 235 240 248 257 261} On the whole, a maximum of 6 or 4 cycles of chemotherapy were given. The largest amount of cycles specified in a study was 12.¹⁶¹ Cycles were typically 21 or 28 days long.

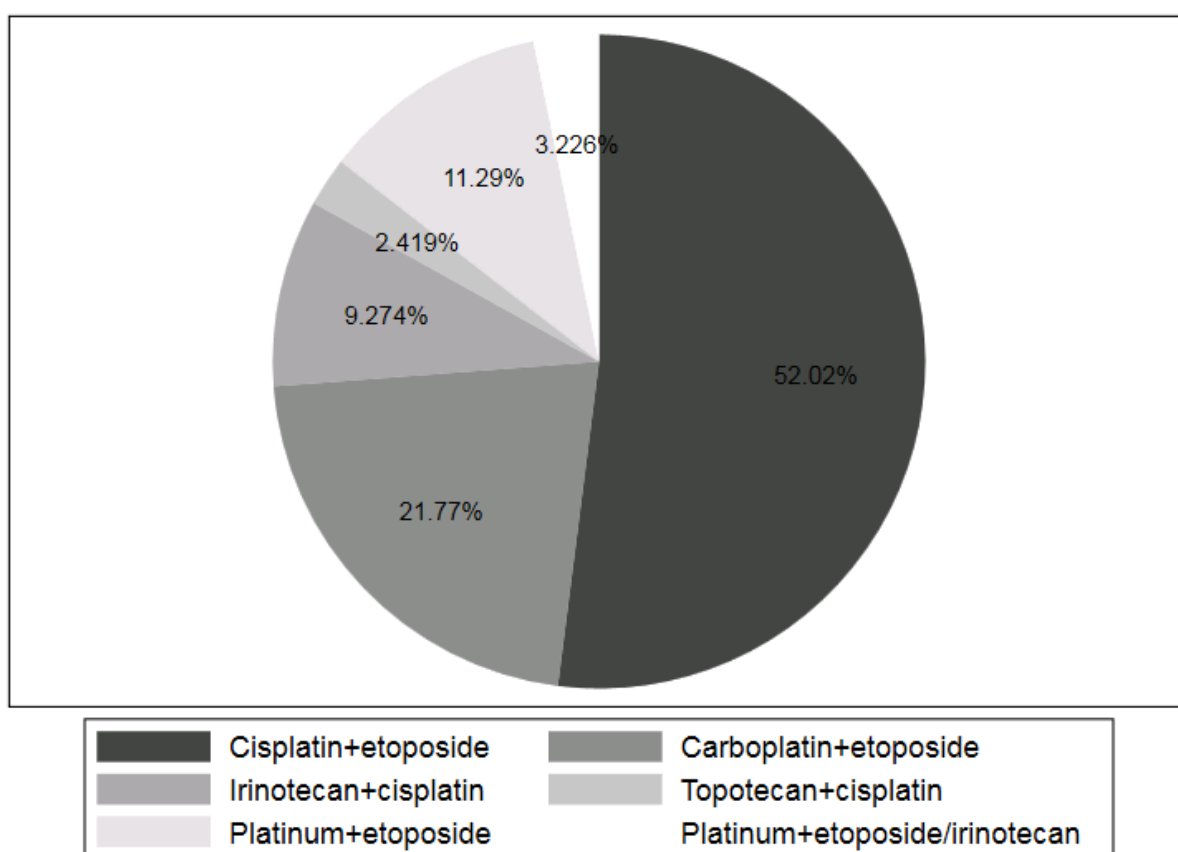


Figure 5-2: Chemotherapy regimens included in the survival meta-analysis

5.3.3 Early Survival

All forest plots from the meta-analysis of survival can be found in Appendix M.

Thirty day survival

The results of 30-day survival are summarised in *Table 5.3*. For LD-SCLC studies 30-day survival was 100% (95% CI 100%, I^2 0%, $n=76$) and for ED-SCLC it was 96% (95% CI 95-97%, I^2 67.3%, $n=71$). The variation of the proportion surviving 30 days by the study factors was small, however, for some factors this was statistically significant. For combined stage significant variation was seen by chemotherapy ($p<0.01$), study year ($p=0.02$), radiotherapy ($p<0.01$) and region ($p<0.01$). For ED-SCLC there was variation by PS and participant age ($p\leq 0.01$ in each).

Table 5.3: Pooled 30-day survival

	Overall					Limited stage					Extensive stage				
	30-day Observations=n	30-day survival %	95% CI	I ² %	P	30-day Observations=n	30-day survival %	95% CI	I ² %	P	30-day Observations=n	30-day survival %	95% CI	I ² %	P
All	167	98	98-99	66.2		76	100	100	-		71	96	95-97	67.3	
Quality															
Moderate (10-14)	15	99	96-100	66.4		6	100	100-100	-		9	97	93-100	76.3	
Good (15-19)	98	99	98-99	71.7		48	100	100-100	-		40	96	95-97	71.0	
Very good (20-25)	54	98	97-99	46.1	0.58	22	99	99-100	-	0.06	22	96	95-98	46.7	0.87
Design															
RCT	73	97	97-98	74.5		23	100	99-100	24.8		41	96	95-97	66.1	
Cohort	94	99	98-100	51.6	0.3	53	100	100-100	-	0.77	30	96	94-98	68.8	0.86
Chemotherapy															
Cisplatin+etoposide	84	98	98-99	70.3		39	100	100-100	-		34	96	95-97	73.8	
Carboplatin+etoposide	36	98	97-99	54.4		15	100	99-100	-		14	96	94-98	60.0	
Irinotecan+cisplatin	15	97	96-98	2.2		4	99	95-100	-		11	97	95-98	16.1	
Topotecan+cisplatin	6	95	92-96	17.1		-	-	-	-		6	95	92-96	17.1	
Platinum+etoposide	21	100	98-100	54.1		14	100	100-100	-		5	97	89-100	83.3	
Platinum+etoposide/irinotecan	5	100	100	-	<0.01	4	100	100-100	-	0.07	1	100	93-100	-	0.22
Year of study															
1980-1989	43	98	96-99	66.2		19	100	100-100	-		16	93	90-95	32.6	
1990-1999	53	98	96-99	70.7		27	100	100-100	-		19	95	92-97	70.0	
2000-2009	67	99	98-99	59.3		30	100	100	-		32	97	96-98	59.1	
2010-2015	4	98	93-100	74.6	0.02	-	-	-	-	0.86	4	98	93-100	74.6	<0.01
Radiotherapy															
Early <3 rd cycle	36	100	100	-		35	100	100-100	-		-	-	-	-	
Late > 3 rd cycle	29	99	99-100	20.4		22	100	100-100	-		-	-	-	-	
Yes/Timing not stated	41	98	97-99	71.5		16	100	100-100	17.6		19	97	95-98	69.6	
No/Not stated	61	97	95-97	64.6	<0.01	3	100	100-100	-	0.83	52	96	95-97	66.9	0.44
Region															
Europe	54	97	96-98	51.2		24	99	99-100	-		21	95	93-96	46.6	
North America	38	98	96-99	82.1		17	100	100-100	-		17	94	91-97	82.9	
Asia	59	100	100	-		30	100	100-100	-		23	100	99-100	-	
International	12	96	95-98	65.9		2	99	98-100	-		9	95	94-97	48.0	
Africa	1	98	85-100	-		1	98	85-100	-		-	-	-	-	
Australasia	3	99	92-100	-	<0.01	2	100	98-100	-	<0.01	1	93	83-97	-	<0.01
Included performance status															
0-1	11	98	96-100	77.7		5	100	100-100	5.2		6	96	94-98	67.7	
0-2	95	98	98-99	63.3		45	100	100-100	-		39	96	95-97	57.3	
0-3	29	97	95-98	55.3		12	100	99-100	-		15	95	92-97	55.0	
0-4	24	99	98-100	67.3		11	100	100-100	-		9	97	91-100	83.6	
Not stated	8	98	95-100	76.9	0.28	3	100	99-100	-	0.17	2	100	98-100	-	0.01
Median age of study participants															
50-59	36	99	98-99	20.7		17	100	99-100	-		17	98	97-99	40.1	
60-69	99	98	97-99	69.6		45	100	100-100	-		40	95	94-97	65.6	
≥70	18	100	98-100	54.9		9	100	100-100	-		6	100	99-100	-	
Not stated	14	96	91-99	81.0	0.08	5	100	99-100	29.0	0.48	8	100	99-100	56.3	<0.01

P= Between group heterogeneity test

Causes of death within 30 days

There were 31 studies where 75 people died within 30 days of chemotherapy and the cause of death was published. The results from individual studies are shown in *Table 5.4*. The majority of deaths were attributed to neutropenic sepsis (27 (36.0%)), disease progression (11 (14.7%)) and cardiovascular, gastrointestinal and others (8 (10.7%) in each).

Table 5.4 Published cause of death within 30 days of chemotherapy

Study Author	Chemotherapy	Number of 30-day deaths reported	Cause of death within 30 days
A Araujo ¹⁵²	Cisplatin + etoposide	1	Haemoptysis from grade 4 neutropenic infection
J Bishop ¹⁶⁰	Carboplatin + etoposide	3	1 neutropenic sepsis, 1 acute infarction, 1 road trauma
C Boni ¹⁶¹	Cisplatin + etoposide	1	Pulmonary embolism
B Chewaskulyong ¹⁶⁵	Cisplatin + etoposide	4	Neutropenic sepsis
P Cortazar ³⁰⁴	Cisplatin + etoposide	1	Myocardial infarction
W K Evans ¹⁷⁴	Cisplatin + etoposide	2	1 treatment related, GI haemorrhage
W K Evans ¹⁷⁵	Carboplatin + etoposide	1	Cardiac event
W K Evans ¹⁷⁶	Carboplatin + etoposide	1	Ischaemic colitis
F Figoli ¹⁷⁸	Cisplatin + etoposide	3	1 disease progression, 1 myocardial infarction, 1 "unknown"
J Hainsworth ¹⁸⁵	Cisplatin + etoposide	1	Neutropenic sepsis
J Y Han ¹⁸⁹	Cisplatin + irinotecan	2	1 neutropenic sepsis, 1 hepato-renal failure
J Y Han ¹⁹⁰	Cisplatin + irinotecan	1	Neutropenic sepsis
YS Hong ¹⁹³	Cisplatin + irinotecan	1	Neutropenic sepsis
A Hugli ¹⁹⁵	Cisplatin + etoposide	1	CMV colitis
M Kelley ²¹⁰	Cisplatin + irinotecan	1	Aspiration
S Kudoh ²¹⁵	Cisplatin + irinotecan	2	Diarrhoea following neutropenia and thrombocytopenia
P Lara ²¹⁷	Cisplatin + irinotecan	1	Treatment toxicity related
P Lara ²¹⁷	Cisplatin + etoposide	1	Treatment toxicity related
S H Lee ²²⁵	Cisplatin + etoposide	1	Neutropenic sepsis
P Loehrer ²²⁹	Cisplatin + etoposide	6	1 cardiac arrest, 5 disease progression
K Matsui ²³¹	Carboplatin + etoposide	2	Massive pleural effusions
D Mavroudis ²³²	Cisplatin + etoposide	1	GI haemorrhage
H Minami ²³⁵	Carboplatin + etoposide	3	1 disease progression, 1 neutropenic sepsis, 1 exacerbation of pulmonary fibrosis
P Murphy ²⁴⁰	Cisplatin + etoposide	3	1 peritonitis secondary to perforation. 2 Neutropenic sepsis
H Niell ²⁴²	Cisplatin + etoposide	6	4 neutropenic sepsis, 1 renal failure, 1 neurological event
K Noda ²⁴³	Cisplatin + irinotecan	3	1 Haemoptysis, 2 neutropenic sepsis
E Quoix ²⁵⁰	Carboplatin and etoposide	7	1 tumour lysis and renal failure, 1 neutropenic sepsis, 1 myocardial infarction, 2 arrhythmia, 1 pulmonary embolism and 1 haemoptysis
J Schiller ²⁶¹	Cisplatin + etoposide	5	4 neutropenic sepsis, 1 pulmonary embolism
D V Skarlos ²⁷²	Cisplatin + etoposide	1	Gastro duodenal perforation
M Sorensen ²⁷⁶	Cisplatin + topotecan	1	Pulmonary embolism
M Viren ²⁹⁰	Carboplatin + etoposide	4	2 sepsis, 2 cerebrovascular accident
J Walewski ²⁹¹	Cisplatin + etoposide	4	Disease progression

Survival at 90 days

Table 5.5 demonstrates survival at 90 days stratified by study factors. Overall survival was 95% (95% CI 94-96%, I^2 81.7%, n=166). In LD-SCLC survival was 99% (95% CI 98-99%, I^2 33.9%, n=77) and showed minimal differences by study factors. Survival was

shorter for ED-SCLC (90% (95% CI 89-92%, I^2 79.5%, n=73) but had more variation by study factors. In particular, recent studies (2010-2015 96% (95% CI 89-99%, I^2 81.6%, n=7)) and those conducted in Asia (97% (95% CI 95-98%, I^2 42.8%, n=26)) had better survival. Conversely, carboplatin + etoposide and cisplatin + topotecan had the poorest 90-day survival (88% (95% CI 83-92%, I^2 77.3%, n=14) and 86% (95% CI 83-89%, I^2 27.9%, n=35) respectively). Worse PS heralded lower 90-day survival (PS 0-4 87% (95%CI 74-96%, I^2 92.7%, n=9)).

Table 5.5: pooled 90-day survival by study factors

	Overall					Limited stage					Extensive stage				
	90-day	90-day	95% CI	I ² %	P	90-day	90-day	95% CI	I ² %	P	90-day	90-day	95% CI	I ² %	P
	Observations=n	Survival %				Observations=n	Survival %				Observations=n	Survival %			
All	166	95	94-96	81.7		77	99	98-99	33.9		73	90	89-92	79.5	
Quality															
Moderate (10-14)	14	96	92-99	81.8		6	99	98-100	3.6		8	94	85-99	88.9	
Good (15-19)	98	95	94-96	84.1		48	99	99-100	36.6		42	90	88-91	78.1	
Very good (20-25)	54	94	92-96	73.1	0.72	23	98	97-99	24.0	0.21	23	91	87-93	69.2	0.55
Design															
RCT	75	93	92-94	84.3		23	98	97-98	59.2		43	90	88-91	72.5	
Cohort	91	97	95-98	74.8	<0.02	54	100	99-100	11.4	0.39	30	91	87-95	84.0	0.74
Chemotherapy															
Cisplatin+etoposide	84	95	94-96	80.8		40	99	98-99	10.6		35	91	88-93	81.2	
Carboplatin+etoposide	34	94	91-96	80.6		15	99	97-100	46.4		14	88	83-92	77.3	
Irinotecan+cisplatin	17	93	91-95	32.7		5	98	94-100	-		12	91	89-92	-	
Topotecan+cisplatin	6	86	83-89	27.9		-	-	-	-		6	86	83-89	27.9	
Platinum+etoposide	20	97	93-99	80.6		13	99	98-100	36.8		5	91	74-100	93.0	
Platinum+etoposide/irinotecan	5	100	99-100	23.3	<0.01	4	100	98-100	42.4	0.32	1	100	93-100	-	<0.01
Year of study															
1980-1989	40	94	91-96	79.1		19	99	98-100	-		16	86	81-90	63.8	
1990-1999	52	93	91-95	81.0		28	98	97-99	39.6		18	87	83-90	74.1	
2000-2009	67	96	95-97	83.5		30	99	98-100	42.2		32	92	90-94	79.7	
2010-2015	7	96	89-99	81.6	0.03	-	-	-	-	0.09	7	96	89-99	81.6	<0.01
Radiotherapy															
Early <3 rd cycle	38	99	98-100	39.0		37	99	98-99	38.9		-	-	-	-	
Late > 3 rd cycle	28	97	96-99	43.8		22	99	98-99	-		-	-	-	-	
Yes/Timing not stated	38	94	91-96	84.2		15	98	97-99	56.9		19	90	86-94	83.3	
No/Not stated	62	91	89-92	76.7	<0.01	3	100	94-100	-	0.22	54	90	89-92	79.2	0.93
Region															
Europe	52	91	89-93	76.4		23	97	95-98	40.0		21	84	81-88	64.4	
North America	35	94	92-96	88.3		17	98	98-99	6.3		16	90	85-93	87.9	
Asia	63	99	98-99	43.9		32	100	100-100	1.8		26	97	95-98	42.8	
International	12	91	88-94	84.7		2	99	96-99	-		9	89	87-91	51.8	
Africa	1	98	85-100	-		1	98	85-100	-		-	-	-	-	
Australasia	3	94	78-100	-	<0.01	2	98	93-100	-	0.01	1	81	69-89	-	<0.01
Included performance status															
0-1	11	96	92-99	89.5		5	100	99-100	34.6		6	92	89-95	76.9	
0-2	95	95	94-96	79.0		46	99	98-99	4.4		40	90	88-92	65.2	
0-3	29	92	89-95	69.6		12	97	95-99	30.2		16	87	84-91	57.4	
0-4	24	95	91-98	85.9		11	100	99-100	17.8		9	87	74-96	92.7	
Not stated	7	97	92-100	87.4	0.13	3	98	92-100	-	0.10	2	100	98-100	-	<0.01
Median age of participants															
50-59	37	96	95-98	69.9		17	98	96-99	39.6		19	94	92-97	76.3	
60-69	97	94	93-96	83.3		46	99	98-99	30.1		40	89	87-91	76.4	
≥70	18	97	92-99	73.5		9	100	100-100	-		6	96	89-100	68.4	
Not stated	14	89	81-96	89.4	0.10	5	98	92-100	62.2	0.41	8	82	74-89	77.2	<0.01

P= Between group heterogeneity test

5.3.4 Late survival

Survival at 1 and 2 years

Late survival at 1-year is reported within this section (*Table 5.6*) as the data for 2-years showed similar trends by study factors (*Table 5.7*). Overall 1-year survival was 54% (95% CI 51-57%, I^2 93.3%, $n=189$) and 2-year survival was 23% (95% CI 20-26%, I^2 94.4%). Across both stages research in Asia had superior 1-year survival (62% (95% CI 57-67%, $I^2=88.6\%$, $n=73$)). Similarly, irinotecan containing regimens performed better than others (irinotecan + cisplatin 58% (95%CI 51-65%, I^2 84.5%, $n=22$) and platinum + etoposide/irinotecan 80% (95%CI 70-88%, I^2 75.5%, $n=5$)). Studies including worse PS and older individuals had lower 1-year survival (PS 0-4 49% (95% CI 38-60%, I^2 93.3%, $n=24$) ≥ 70 years 50% (95% CI 40-60%, I^2 84.9%, $n=20$)).

LD-SCLC survival was 73% (95% CI 70-75%, I^2 74.0% $n=91$). This was lower with carboplatin + etoposide (66% (95% CI 59-73%, I^2 73.8%, $n=18$)). Early thoracic radiotherapy and PCI augmented survival (77% (95% CI 73-80%, I^2 68.0%, $n=40$) and 75% (95% CI 72-77%, I^2 74.1%, $n=69$) respectively).

One-year survival for ED-SCLC was lower at 38% (95% CI 35-40%, I^2 74.9%, $n=80$). This improved with time (2010-2015 55% (95% CI 43-68%, I^2 83.9%, $n=7$) vs 1980-1989 28% (95% CI 24-33%, I^2 45.4%, $n=15$)). There were no differences in survival by addition of thoracic radiotherapy or PCI.

Table 5.6: Pooled 1-year survival															
	Overall					Limited stage					Extensive stage				
	1-year Observations=n	1-year Survival %	95% CI	I ² %	P	1-year Observations=n	1-year Survival %	95% CI	I ² %	P	1-year Observations=n	1-year Survival %	95% CI	I ² %	P
All	189	54	51-57	93.3		91	73	70-75	74.0		80	38	35-40	74.9	
Quality															
Moderate (10-14)	22	50	40-59	90.1	0.60	10	68	61-76	59.8	0.27	10	40	31-51	82.5	0.58
Good (15-19)	111	54	48-60	94.2		56	75	71-78	72.9		46	37	34-39	64.6	
Very good (20-25)	56	53	47-59	91.3		25	71	66-76	78.4		24	39	33-45	81.4	
Design															
RCT	82	49	45-54	95.2	0.01	26	73	96-77	83.1	0.48	35	37	34-40	77.0	0.56
Cohort	107	58	53-62	88.6		65	72	69-76	67.7		45	38	34-43	70.0	
Chemotherapy															
Cisplatin+etoposide	96	55	51-60	93.9	<0.01	48	75	72-77	59.8	0.05	37	35	33-38	63.9	<0.01
Carboplatin+etoposide	39	46	39-53	89.9		18	66	59-73	73.8		15	33	28-38	57.9	
Irinotecan+cisplatin	22	58	51-65	84.5		7	77	66-86	62.6		15	49	43-54	70.6	
Topotecan+cisplatin	6	35	30-39	35.3		-	-	-	-		6	36	18-55	92.4	
Platinum+etoposide	21	58	46-69	92.8		14	70	61-79	82.9		6	35	30-39	35.3	
Platinum+etoposide/irinotecan	5	80	70-88	75.5		4	82	71-90	74.1		1	70	56-81	-	
Year of study															
1980-1989	39	50	43-58	91.0	0.22	19	71	66-76	55.6	0.17	15	28	24-33	45.4	<0.01
1990-1999	61	51	45-57	92.9		32	70	66-74	64.6		21	35	30-39	65.2	
2000-2009	79	57	52-62	94.7		37	76	72-80	81.5		37	39	37-42	72.1	
2010-2015	10	59	48-70	81.4		3	71	60-82	-		7	55	43-68	83.9	
Radiotherapy															
Early <3 rd cycle	41	76	73-79	67.8	<0.01	40	77	73-80	68.0	<0.01	-	-	-	-	0.23
Late > 3 rd cycle	34	63	56-70	89.6		27	71	66-76	67.7		-	-	-	-	
Yes/Timing not stated	42	48	41-56	94.0		19	68	62-75	82.7		20	35	29-41	83.9	
No/Not stated	72	38	36-41	69.3		5	56	45-67	-		60	39	36-41	70.1	
Region															
Europe	63	46	41-51	89.9	<0.01	30	66	61-70	62.9	<0.01	23	30	26-34	64.2	<0.01
North America	36	54	47-61	95.3		18	73	69-77	67.8		16	36	33-39	48.5	
Asia	73	62	57-67	88.6		37	79	75-82	60.9		31	47	42-52	72.9	
International	12	44	33-56	97.3		2	80	77-84	-		9	36	33-39	48.5	
Africa	2	74	61-85	-		2	74	61-85	-		-	-	-	-	
Australasia	3	44	19-70	-		2	55	44-66	-		1	23	14-36	-	
PCI															
Yes	103	62	58-66	93.5	<0.01	69	75	72-77	74.1	0.01	25	35	31-40	76.5	0.29
No	26	46	38-54	87.7		10	67	58-74	57.1		13	37	29-45	81.1	
Not stated	60	42	39-46	80.0		12	63	54-72	61.8		42	39	36-42	71.9	
Included performance status															
0-1	15	61	49-73	96.0	0.02	9	79	72-86	59.0	0.05	6	39	37-42	16.7	0.10
0-2	102	58	53-62	93.6		50	75	73-77	53.1		42	32	22-44	76.1	
0-3	31	45	39-53	85.5		13	65	55-75	77.8		17	33	29-38	46.0	
0-4	24	49	38-60	93.3		11	71	61-80	77.7		9	40	37-43	85.2	
Not stated	17	45	32-58	94.0		8	61	46-76	88.4		6	34	18-51	88.3	
Median age of study participants															
50-59	40	59	53-66	91.6	0.02	20	74	69-79	61.7	0.14	19	42	36-48	82.3	0.02
60-69	106	55	51-60	94.5		52	74	71-77	76.0		43	37	34-40	75.2	
≥70	20	50	40-60	84.9		10	70	62-77	40.2		7	43	34-52	53.0	
Not stated	23	40	30-51	92.0		9	59	41-75	87.5		11	31	27-36	33.2	
P= Between group heterogeneity test															

P= Between group heterogeneity test

Table 5.7: Pooled 2-year survival															
	Overall					Limited stage					Extensive stage				
	2-year Observations=n	2-year survival %	95% CI	I ² %	P	2-year Observations=n	2-year Survival %	95% CI	I ² %	P	2-year Observations=n	2-year Survival %	95% CI	I ² %	P
All	163	23	20-26	94.4		85	41	38-44	78.9		66	9	7-10	67.5	
Quality															
Moderate (10-14)	16	25	16-36	92.2		9	40	31-49	73.0		7	11	4-22	88.9	
Good (15-19)	99	23	19-28	95.1		52	43	40-47	74.1		40	8	7-9	61.6	
Very good (20-25)	48	21	16-27	93.0	0.67	24	37	30-44	85.7	0.28	19	8	6-10	37.7	0.76
Design															
RCT	74	18	14-23	96.2		26	41	36-47	88.6		41	8	7-9	57.1	
Cohort	89	28	24-32	88.6	<0.01	59	41	36-44	66.8	0.86	25	9	6-13	73.9	0.28
Chemotherapy															
Cisplatin+etoposide	86	22	18-27	95.2		44	42	39-45	69.8		34	7	6-8	32.5	
Carboplatin+etoposide	26	20	13-27	90.9		15	35	28-41	70.9		8	5	2-9	61.8	
Irinotecan+cisplatin	20	25	18-33	88.0		7	45	32-59	74.1		13	14	10-18	66.6	
Topotecan+cisplatin	4	7	6-9	-		-	-	-	-		6	10	2-24	91.0	
Platinum+etoposide	22	29	20-39	91.7		15	41	31-50	84.0		4	7	6-9	-	
Platinum+etoposide/irinotecan	5	39	18-62	94.5	<0.01	4	48	30-66	89.8	0.32	1	10	4-22	-	0.01
Year of study															
1980-1989	31	18	11-25	93.2		15	37	30-45	76.8		11	4	3-6	-	
1990-1999	51	21	16-26	93.6		31	36	31-40	71.4		17	7	4-10	69.2	
2000-2009	73	27	22-32	95.6		38	46	42-51	80.6		31	10	8-12	71.1	
2010-2015	8	20	9-32	83.7	0.07	1	58	41-74	-	<0.01	7	11	7-16	44.5	<0.01
Radiotherapy															
Early <3 rd cycle	41	45	40-49	77.0		40	45	41-49	77.2		-	-	-	-	
Late > 3 rd cycle	30	31	23-39	91.8		25	38	32-44	77.0		-	-	-	-	
Yes/Timing not stated	40	18	13-24	93.5		18	37	32-43	80.8		19	8	4-11	83.8	
No/Not stated	52	9	7-10	66.7	<0.01	2	37	25-50	-	0.10	47	9	7-10	47.7	0.63
Region															
Europe	51	19	14-23	91.4		27	34	30-39	73.3		18	6	4-8	46.8	
North America	32	21	15-28	96.3		17	42	38-45	37.7		13	8	6-9	52.9	
Asia	68	28	22-33	91.9		37	46	40-51	76.6		28	12	9-15	70.9	
International	9	17	7-31	98.2		2	54	49-58	-		7	9	7-12	58.3	
Africa	2	56	43-69	-		2	56	43-69	-		-	-	-	-	
Australasia	1	17	8-31	-	<0.01	1	17	8-31	-	<0.01	-	-	-	-	<0.01
PCI															
Yes	100	30	26-35	94.1		70	43	39-46	79.6		22	7	5-10	72.9	
No	22	15	9-22	89.4		8	31	23-41	67.8		11	11	6-17	84.0	
Not stated	41	11	9-14	94.4	<0.01	7	32	23-41	60.3	<0.02	33	8	7-9	37.5	0.46
Included performance status															
0-1	14	28	16-42	97.1		8	49	38-60	77.6		6	10	7-12	52.1	
0-2	91	26	21-30	94.9		50	43	39-46	71.8		35	9	7-11	58.5	
0-3	26	15	9-22	90.5		11	35	24-47	82.8		14	5	4-7	20.5	
0-4	20	18	11-27	91.8		9	34	24-44	79.0		7	8	2-16	85.8	
Not stated	12	25	14-36	92.6	0.09	7	35	24-47	83.6	0.14	4	14	3-30	88.2	0.05
Median age of study participants															
50-59	38	26	19-32	92.9		19	46	40-51	61.6		18	9	7-11	45.4	
60-69	94	24	20-28	95.5		51	42	38-46	82.3		35	9	7-11	69.6	
≥70	17	19	11-28	87.7		9	36	29-43	32.5		6	9	2-18	81.2	
Not stated	14	12	4-21	92.3	0.09	6	26	12-42	86.3	0.05	7	4	1-9	70.0	0.40

Survival at 5 years

There were 65 survival observations reported at 5 years. The results of the meta-analysis are summarised in *Table 5.8*. The majority of reports came from studies recruiting LD-SCLC (n=48 (73.9%)) the remaining were ED-SCLC and combined stage (n=14 (21.5%) and n=3 (4.6%) respectively). The pooled 5-year survival for LD-SCLC studies was 23% (95%CI 20-25%, I^2 72.3, n=48). Survival varied considerably by study design, chemotherapy, study year, region, PCI and PS (p values all ≤ 0.01). All studies gave radiotherapy except one, which did not specify this. Five-year survival was very poor in ED-SCLC studies (1% 95%CI 0-3%, I^2 76.3, n=14) and there was statistically significant variation by study factors (quality, design, chemo, radiotherapy, region, PS and participant age) but the absolute percentage differences in survival were very small.

Table 5.8: Pooled 5-year survival

	Overall					Limited stage					Extensive stage				
	5-year Observations=n	5-year survival %	95% CI	I ² %	P	5-year Observations=n	5-year Survival %	95% CI	I ² %	P	5-year Observations=n	5-year Survival %	95% CI	I ² %	P
	65	15	11-19	94.6		48	23	20-25	72.3		14	1	0-3	76.3	
All															
Quality															
Moderate (10-14)	11	9	4-16	83.5		6	17	10-24	72.8		5	4	1-8	69.7	
Good (15-19)	43	15	10-20	95.4		33	23	19-26	68.0		9	1	0-2	33.9	
Very good (20-25)	11	21	13-31	90.9	0.09	9	28	23-33	48.9	0.04	-	-	-	-	<0.01
Design															
RCT	27	15	11-19	96.9		19	23	18-27	75.3		6	0	0-1	69.8	
Cohort	38	16	11-21	88.9	<0.01	29	23	20-27	70.8	<0.01	8	2	1-5	55.1	<0.01
Chemotherapy															
Cisplatin+etoposide	35	15	11-21	95.0		28	22	19-25	70.4		6	1	0-2	70.1	
Carboplatin+etoposide	8	18	6-34	94.5		6	27	16-40	83.2		2	1	0-3	-	
Irinotecan+cisplatin	2	0	0-1	-		1	46	31-62	-		1	0	0-1	-	
Platinum+etoposide	19	11	6-17	84.8		12	20	15-26	53.0		5	4	1-8	33.9	
Platinum+etoposide/irinotecan	1	34	29-40	-	<0.01	1	34	29-40	-	<0.01	-	-	-	-	<0.01
Year of study															
1980-1989	9	11	5-21	94.6		6	20	13-27	74.6		3	1	0-4	-	
1990-1999	23	13	8-19	89.6		19	18	15-22	60.3		2	0	0-3	-	
2000-2009	33	17	11-24	96.2	0.52	23	28	24-31	63.1	<0.01	9	1	0-4	83.4	0.83
Radiotherapy															
Yes	56	18	15-22	90.0		47	23	20-26	72.5		6	3	1-6	49.9	
Not stated	7	1	0-4	89.2		1	17	10-27	-		8	1	0-2	74.5	
No	2	2	1-5	-	<0.01	-	-	-	-	0.19	-	-	-	-	0.04
Region															
Europe	22	9	4-16	92.8		15	17	12-23	80.1		5	0	0-1	-	
North America	16	10	5-18	96.5		10	21	18-23	29.4		6	1	0-3	80.0	
Asia	24	22	17-28	84.0		20	27	23-31	49.4		3	6	4-10	-	
International	2	32	29-37	-		2	32	29-37	-		-	-	-	-	
Australasia	1	17	8-31	-	<0.01	1	17	8-31	-	<0.01	-	-	-	-	<0.01
PCI															
Yes	48	20	15-24	92.4		41	24	21-27	70.8		5	2	0-5	69.4	
No	11	7	2-12	80.7		6	13	8-20	60.3		4	3	0-7	37.3	
Not stated	6	1	0-5	90.9	<0.01	1	17	10-27	-	0.01	5	0	0-2	73.4	0.06
Included performance status															
0-1	8	18	3-40	98.1		6	33	27-38	12.4		2	0	0-0	-	
0-2	29	23	19-27	82.5		28	24	21-27	70.3		1	1	0-5	-	
0-3	9	6	1-13	91.1		5	14	6-25	78.3		4	0	0-3	66.5	
0-4	12	6	2-12	87.7		6	15	9-21	63.5		5	2	1-5	41.4	
Not stated	7	10	2-23	95.0	<0.01	3	25	20-30	-	<0.01	2	6	2-11	-	<0.01
Median age of study participants															
50-59	16	19	12-26	86.1		14	22	17-28	67.3		2	1	0-4	-	
60-69	33	15	10-22	96.6		23	25	22-29	76.5		8	1	0-2	77.6	
≥70	10	11	5-19	81.6		7	17	12-22	12.9		2	5	3-9	-	
Not stated	6	6	0-20	89.0	0.36	4	12	2-28	82.5	0.09	2	0	0-3	-	0.02

P= Between group heterogeneity test

5.3.5 Median survival

The full results of median survival are shown in *Table 5.9*. Overall median survival was 13.0 months (95% CI 12.4-13.7, I^2 95.1%, n =233). In LD-SCLC and ED-SCLC it was 18.0 months (95% CI 17.0-19.1, I^2 77.3%, n =110) and 9.6 months (95% CI 8.9-10.3, I^2 95.2%, n =103) respectively. Overall, good PS, thoracic radiotherapy, PCI, Asian and modern studies had longer median survival.

These results showed significant heterogeneity and this did not change when the sensitivity analysis was conducted (removing studies where 95% CIs were estimated, as shown in *Table 5.10*). Indeed, after these outcomes were excluded there were 90 survival observations remaining, which is considerably less than in the original analysis. Nevertheless, the median survival estimates remained similar, with the overall survival tending to be 1 month longer. The trend in median survival by study factors remained similar, however, as the sensitivity analysis consisted of fewer studies the confidence intervals of the results widened. This translated into some factors losing statistically significant variation, these factors were study year, radiotherapy, PCI and PS.

The majority of studies had normally distributed 95% CIs (where 95% CIs were reported). This was calculated by subtracting the difference in the lower CI from the median from the difference in the upper CI from the median. The majority of studies had values of 0, demonstrating equal variation (this is shown in *Figure 5.3*). Therefore, it is reasonable to conclude that this method of estimating the 95% CIs (which assumes normal distribution of variance around the median (standard error)) was valid.

	Both stages					Limited stage					Extensive stage				
	Observations =n	Median survival (months)	95% CI	I ² %	P	Observations =n	Median survival (months)	95% CI	I ² %	P	Observations =n	Median survival (months)	95% CI	I ² %	P
All	233	13.0	12.4-13.7	95.1		110	18.0	17.0-19.1	77.3		103	9.6	8.9-10.3	95.2	
Quality															
Poor (0-9)	3	9.92	3.0-16.8	88.0		1	19.5	10.8-28.2	-		2	6.6	1.4-11.7	82.0	
Moderate (10-14)	35	12.9	11.5-14.2	89.5		15	18.4	15.7-21.0	67.7		13	9.2	7.5-10.9	81.5	
Good (15-19)	132	13.1	12.3-13.9	92.8		65	18.2	16.7-19.7	79.6		59	9.5	8.7-10.4	92.2	
Very good (20-25)	63	13.1	11.7-14.5	96.3	0.86	29	17.9	16.0-19.7	77.1	0.54	29	10.1	8.5-11.7	96.8	0.08
Design															
RCT	94	12.5	11.9-13.2	89.7		35	19.1	17.3-21.0	85.2		52	9.9	9.4-10.3	73.1	
Cohort	139	13.3	12.3-14.3	95.2	0.79	75	17.3	16.0-18.6	69.9	0.20	51	9.3	8.3-10.4	93.0	0.12
Chemotherapy															
Cisplatin+etoposide	120	13.3	12.6-14.0	88.7		60	18.5	17.1-19.9	77.3		50	9.4	9.0-9.9	64.0	
Carboplatin+etoposide	52	11.6	10.1-13.1	95.8		24	15.7	14.0-17.5	67.1		22	8.8	7.3-10.3	93.6	
Irinotecan+cisplatin	22	12.6	11.4-13.7	69.0		6	18.5	14.5-22.5	45.1		16	11.5	10.6-12.5	55.1	
Platinum+etoposide	25	13.9	11.1-16.8	97.1		16	18.4	14.4-22.5	82.1		8	8.1	4.4-11.7	93.9	
Topotecan+cisplatin	6	9.7	8.8-10.5	41.6		-	-	-	-		6	9.7	8.8-10.5	41.6	
Platinum+etoposide/irinotecan	8	18.6	14.5-22.7	89.4	0.32	4	24.5	15.0-34.1	86.6	0.19	1	15.4	13.9-16.9	-	0.59
Year of study															
1980-1989	48	11.4	9.9-12.9	89.6		22	15.7	13.5-18.0	54.8		21	8.3	6.9-9.7	83.7	
1990-1999	82	12.0	11.2-12.9	89.6		42	16.5	15.2-17.8	69.6		31	8.6	7.8-9.5	81.1	
2000-2010	93	14.4	13.4-15.4	94.7		43	20.6	18.6-22.6	83.9		44	10.3	9.2-11.3	94.4	
2010-2015	10	14.7	12.1-17.3	88.3	<0.01	3	21.9	17.6-26.1	-	<0.01	7	13.1	10.5-15.7	89.3	<0.01
Radiotherapy															
Yes	144	15.5	14.4-16.5	94.2		100	18.4	17.3-19.5	78.4		28	8.9	7.3-10.4	94.9	
No/ Not stated	89	10.1	9.3-10.8	94.6	<0.01	10	11.7	9.1-14.3	-	<0.01	75	10.0	9.1-10.8	95.3	0.07
Region															
Europe	76	11.8	10.7-13.0	95.6		38	15.7	14.5-16.9	62.7		29	8.5	7.3-9.7	94.6	
North America	47	12.7	11.7-13.6	87.0		22	18.7	17.0-20.3	43.7		22	9.5	9.2-9.8	-	
Africa	2	21.9	14.7-29.1	-		2	21.9	14.0-29.1	-		-	-	-	-	
Asia	83	14.8	13.7-15.8	84.5		40	20.2	17.8-22.5	78.7		38	11.3	10.4-12.2	69.1	
International	13	11.3	10.0-12.6	88.9		2	27.5	22.6-32.4	47.9		9	9.6	9.2-10.0	-	
Australasia	8	11.2	7.8-14.5	90.5		4	16.0	12.7-19.2	-		3	7.1	3.6-10.6	93.1	
South America	3	5.9	0.50-11.2	94.7		1	7.4	5.1-9.7	-		2	5.2	-2.9-13.3	92.9	
Not reported	1	22.7	17.6-27.8	-	0.02	1	22.7	17.6-27.8	-	0.13	-	-	-	-	<0.01
PCI															
Yes	125	15.4	14.5-16.3	89.7		78	19.7	18.5-21.0	75.7		33	9.4	9.0-9.8	12.7	
No	35	10.8	8.8-12.8	95.0		15	13.	10.5-16.6	81.1		18	9.1	6.7-11.6	96.3	
Not stated	73	10.6	9.6-11.5	95.7	<0.01	17	14.2	13.1-15.2	0.0	<0.01	52	9.9	8.9-10.3	96.5	0.45
Included participant performance status															
0-1	18	15.1	13.3-17.0	92.2		11	22.5	18.7-26.1	72.4		7	9.7	9.3-10.2	-	
0-2	120	14.1	13.1-15.0	96.3		57	19.1	17.8-20.4	74.0		54	10.3	9.3-11.3	96.3	
0-3	40	10.2	9.3-11.2	48.2		17	13.7	11.3-16.1	45.5		21	9.2	8.4-10.0	28.4	
0-4	29	11.6	9.1-14.1	93.9		13	15.3	11.5-19.1	77.9		11	7.9	4.7-11.1	94.3	
Not stated	26	11.6	10.1-13.0	89.9	<0.01	12	16.1	13.5-18.6	63.7	<0.01	10	8.3	6.6-10.0	81.8	<0.01
Participants median age															
50-59	51	13.6	12.7-14.5	88.5		24	18.0	15.6-20.4	68.7		24	10.3	9.3-11.3	86.5	
60-69	128	13.6	12.6-14.5	96.3		63	18.6	17.2-20.0	82.5		56	9.7	8.7-10.6	96.4	
>70	23	11.9	10.5-13.3	57.2		12	15.9	12.9-18.9	43.2		9	10.3	9.0-11.6	5.5	
Not stated	31	10.9	9.4-12.4	86.4	0.05	11	16.1	12.6-19.7	64.4	0.31	14	8.3	6.6-9.9	83.0	0.06
P= P value of difference between subgroups from metaregression															

P= P value of difference between subgroups from metaregression

Table 5.10 Pooled median survival of studies where 95% confidence intervals were included															
	Both stages					Limited stage					Extensive stage				
	Observations =n	Median survival (months)	95% CI	I ² %	P	Observations =n	Median survival (months)	95% CI	I ² %	P	Observations =n	Median survival (months)	95% CI	I ² %	P
All	90	14.1	13.11-15.08	97.6		40	19.80	18.16-21.45	87.0		43	10.13	9.08-11.19	97.9	
Quality															
Moderate (10-14)	9	12.60	10.14-15.06	94.6		2	17.33	10.90-23.76	86.5		2	8.34	4.72-11.97	96.5	
Good (15-19)	53	13.92	12.71-15.13	96.5		25	20.18	17.78-22.57	88.6		26	9.72	8.54-10.90	96.5	
Very good (20-25)	28	14.86	12.68-17.03	98.2	0.43	13	19.81	17.19-22.43	82.0	0.06	15	11.10	8.77-13.42	98.4	0.43
Design															
RCT	48	12.98	12.17-13.79	93.1		15	21.98	19.09-24.87	90.5		30	10.26	9.74-10.78	82.1	
Cohort	42	14.90	13.06-16.74	97.7	0.46	25	18.20	16.19-20.21	83.4	0.05	13	9.26	7.34-11.18	97.7	0.13
Chemotherapy															
Cisplatin+etoposide	49	14.34	13.31-15.36	93.7		24	20.82	18.66-22.97	86.4		21	9.71	9.10-10.33	82.6	
Carboplatin+etoposide	15	13.01	10.12-15.90	98.6		7	17.65	15.93-19.37	60.5		7	9.15	6.31-11.98	97.7	
Irinotecan+cisplatin	15	12.69	11.39-13.98	74.2		5	18.71	13.87-23.54	55.0		10	11.57	10.56-12.58	61.6	
Platinum+etoposide	3	5.53	-0.54-11.60	93.1		2	12.86	-3.79-29.51	58.2		1	1.32	0.73-1.91	-	
Topotecan+cisplatin	3	9.84	8.84-10.84	70.8		-	-	-	-		3	9.84	8.84-10.84	70.8	
Platinum+etoposide/irinotecan	5	19.54	14.41-24.67	90.4	0.71	2	26.27	9.91-42.63	95.5	0.69	1	15.40	13.90-16.90	-	0.61
Year of study															
1980-1989	4	8.76	5.23-12.29	96.1		-	-	-	-		3	7.77	4.12-11.43	96.4	
1990-1999	28	13.46	12.12-14.81	93.7		15	17.33	15.57-19.10	79.5		10	9.44	8.42-10.45	86.2	
2000-2010	52	14.93	13.59-16.28	96.7		24	21.87	19.16-24.59	88.2		25	10.13	8.82-11.44	96.8	
2010-2014	6	12.98	10.40-15.56	91.1	0.20	1	15.5	11.45-19.55	-	0.12	5	12.59	9.79-15.40	92.6	0.01
Radiotherapy															
Yes	52	17.65	15.65-19.66	97.4		39	19.88	18.21-21.54	87.3		8	8.46	5.46-11.46	98.5	
No	7	10.05	8.88-11.21	64.2		-	-	-	-		7	10.05	8.88-11.21	64.2	
Not stated	31	10.55	9.29-11.81	97.9	<0.01	1	15.90	6.85-24.95	-	0.56	28	10.45	9.14-11.77	98.1	0.20
Region															
Europe	27	13.18	11.29-15.08	98.3		15	16.87	15.29-18.44	75.5		10	8.78	6.83-10.73	98.0	
North America	13	11.4	10.18-12.62	89.1		3	19.12	17.31-20.92	-		9	9.55	9.19-9.90	-	
Africa	1	20.2	11.75-28.65	-		1	20.2	11.75-28.65	-		-	-	-	-	
Asia	35	16.73	15.18-18.28	91.6		16	23.38	20.37-26.39	79.9		16	12.04	10.93-13.15	82.1	
International	8	12.13	10.43-13.84	93.4		2	27.5	22.6-32.4	47.9		6	9.68	9.18-10.18	34.2	
Australasia	4	12.01	8.32-15.70	75.4		2	15.41	11.42-19.41	-		1	8.9	7.55-10.25	-	
South America	2	4.24	-1.69-10.16	96.0	0.09	1	7.37	5.07-9.67	-	<0.01	1	1.32	0.73-1.91	-	0.02
PCI															
Yes	50	17.11	15.59-18.63	93.8		33	20.82	19.10-22.55	82.7		12	9.45	8.88-10.03	42.1	
No	10	12.44	8.50-16.38	98.5		4	15.90	8.73-23.07	95.6		6	10.06	5.45-14.67	98.8	
Not stated	30	10.80	9.49-12.11	98.1	<0.01	3	14.55	13.24-15.86	-	0.13	25	10.41	9.03-11.80	98.2	0.34
Included participant performance status															
0-1	14	15.25	13.27-17.22	93.8		8	23.11	18.83-27.40	80.2		6	9.74	9.32-10.16	-	
0-2	55	14.73	13.42-16.05	98.0		26	19.91	18.25-21.57	81.2		28	10.60	9.26-11.94	98.0	
0-3	7	10.43	8.91-11.95	64.6		1	15.90	6.85-24.95	-		6	10.27	8.77-11.78	67.0	
0-4	7	11.47	5.58-17.35	96.3		2	12.86	-3.79-29.51	58.2		1	1.32	0.68-1.86	-	
Not stated	7	11.77	9.70-13.85	90.4	0.03	3	15.96	11.40-20.53	82.3	0.01	2	8.29	7.34-9.25	26.5	0.07
Participants median age															
50-59	24	13.62	12.19-15.05	93.5		10	19.58	16.36-22.80	76.1		12	10.57	9.28-11.86	93.1	
60-69	55	14.54	13.20-15.88	98.1		28	19.74	17.74-21.73	89.4		26	9.89	8.49-11.28	98.2	
>70	3	13.57	8.70-18.44	80.5		1	24.10	16.15-32.05	-		2	10.87	8.95-12.79	-	
Not stated	8	10.51	9.52-11.51	39.7	0.25	1	26.00	2.50-49.50	-	0.67	3	9.75	8.81-10.69	-	0.74

P= P value of difference between subgroups from metaregression

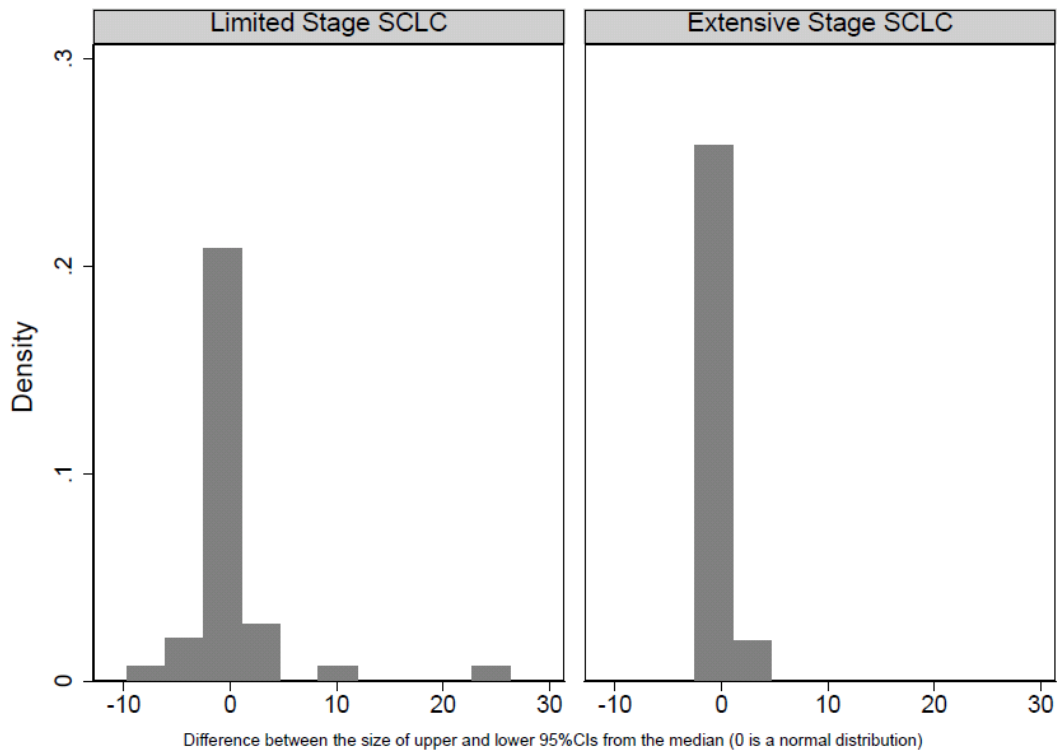


Figure 5-3 Histogram of the difference in variance of 95% confidence intervals from the median survival

5.4 Discussion

5.4.1 Main Findings

The overall survival at 30 and 90-days was 98% and 95% respectively. The majority of 30-day deaths were attributed to neutropenic sepsis. Early survival was equal across all ages but this changed beyond 1-year, where the elderly were less likely to be alive, which is most likely a result of attrition bias. The overall median survival was 13.1 months. Late survival was better with early thoracic radiotherapy, PCI, good PS as well as Asian and modern research. Studies administering irinotecan performed the best although the majority were in Asian cohorts. Reporting of 5-year survival was almost exclusive to LD-SCLC studies.

5.4.2 Strengths

To my knowledge, this is the largest systematic review conducted in SCLC that comprehensively examines survival. By investigating early and late survival this study was able to directly compare the early mortality risks of treatment vs the long term survival gains. This knowledge is important if the process of patient selection is to be augmented. Including a large number of studies means the results are less likely to be subject to publication bias unlike other systematic reviews in SCLC which are smaller.⁵⁰

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5.4.3 Limitations

Some factors in the meta-analysis, such as PCI and radiotherapy, do not consist of all individuals who received these treatments due to grouping by study protocol. This broad grouping was made as there was significant heterogeneity in study design and reporting. This can cause aggregation bias, however, the results are mostly consistent with other literature. These findings are not fully representative of survival in the “real world” as many patients who receive chemotherapy in clinical practice do not meet experimental trial inclusion criteria. However, by including observational studies in this analysis it is able to examine survival from far less selected populations than if RCTs alone were included. Therefore, within the constraints of a systematic review, these results are as reflective as possible of real world outcomes. Many of the studies included in the pooled median survival analysis did not include 95% CIs and hence these were estimated. However, the statistical rigor of this estimation method has been tested by performing a sensitivity analysis, which yielded similar results. In addition, the distribution of the 95% confidence intervals in the studies where they

were known were examined and these matched the assumptions made in order to generate the estimated confidence intervals.

5.4.4 Comparisons with other research

Early survival

The evidence base for early mortality and its causes following chemotherapy is limited. The proportion of treatment related deaths, defined as death related to and within 4 weeks of completion of chemotherapy, was found to be 2.95% in a systematic review of phase III SCLC trials.¹⁰⁷ Neutropenic sepsis was found to be the leading cause of these. Conversely, observational research from England found that 30-day mortality for palliative and curative intent chemotherapy in SCLC was 12% and 4% respectively.¹⁰⁵ This study's findings sit in between these two manuscripts, most likely as clinical trials and observational studies were included.

Chemotherapy

Irinotecan + cisplatin tended to have better long term survival than cisplatin/carboplatin + etoposide. A systematic review of 6 randomized control trials concluded that irinotecan containing regimens permitted a survival benefit of 1-2 months compared to standard platinum + etoposide.³⁰⁵ Many trials administering irinotecan + cisplatin are conducted in Asia, hence *Lara et al* compared survival in a Caucasian cohort and found no differences between etoposide and irinotecan containing chemotherapy.³⁰⁷ Indeed the survival gains of irinotecan seen in this systematic review may reflect the differing aetiology of SCLC in Asian and Caucasian groups as the incidence of SCLC in never-smokers is greater in Asia due to increased rates of passive smoke inhalation, indoor cooking and air pollution.^{43 308}. Another

important factor that may explain why irinotecan has more favourable survival in Asian groups than Caucasians may relate to its metabolism and excretion. Irinotecan is a prodrug to SN-38 which is estimated to be 1000 times more active than irinotecan and is dependent on numerous enzyme pathways one of which is UDP-glucuronosyltransferase 1 polypeptide A1 (UGT1-A1).³⁰⁹ Approximately 10% of Caucasians have a variant of the UGT1A1 enzyme which leads to poor SN-38 metabolism and increased concentrations resulting in toxicity and hence poorer outcomes.³¹⁰ Studies that gave carboplatin + etoposide had lower 1-year survival in LD-SCLC, however this finding is biased by these studies including more elderly and individuals with worse PS.

Region

Survival was better in Asian studies. In NSCLC, mutations of the epidermal growth factor receptor (EGFR) were found to be more common in Asian, female, non-smokers and hence they responded better to EGFR inhibitors.³¹¹⁻³¹³ It is possible that undiscovered oncogene driver mutations may underpin the findings in this meta-analysis as research in this area is limited in SCLC. Indeed, as I have discussed previously the aetiological exposures of SCLC differ in Asian populations and it has been proposed that SCLC in never-smokers could be treated as a separate disease to SCLC in smokers.⁴³ Unfortunately smoking status was not routinely recorded in studies as it would be interesting to examine this hypothesis and stratify survival by smoking. Other factors that were included in my analysis and are confounders to the augmented survival in Asian cohorts include the study design and patient selection criteria.

Study year

Survival was shorter in older studies and on closer inspection many included people with worse PS.^{158 161 174 178 273 295 296} Likewise there have been advances in healthcare over time, such as, better awareness for infection control; which is important as neutropenic sepsis is a common cause of death.³¹⁴

Thoracic radiotherapy

In-keeping with treatment recommendations, early radiotherapy in LD-SCLC augmented survival. A seminal meta-analysis of 7 RCTs demonstrated improvement in 2 and 3 year survival with thoracic radiotherapy if given within 9 weeks of chemotherapy.⁶⁷ Other meta-analyses have found that early radiotherapy increases survival at the risk of causing side effects e.g. severe oesophagitis.^{66 315}

Prophylactic cranial irradiation

The findings in this study align with an important systematic review by *Aupérin et al* showing PCI prolongs survival in LD-SCLC.⁷⁹ An area that remains unclear is whether the timing of PCI influences survival.⁴⁸ In the analysis PCI timing was not clear in half the studies that gave it. The remaining gave it equally before and after the sixth chemotherapy cycle.

5.4.5 Relevance to practice and guidelines

The recommended treatments in SCLC have remained unchanged for years in comparison to NSCLC. This has likely increased the nihilistic connotations for patients and clinicians. This study has shown that survival has improved over time in SCLC despite few new therapies; a finding which can raise optimism in clinical practice.

Table 5.11 compares the findings of this meta-analysis with current ESMO recommendations and generally supports these. In particular, early thoracic radiotherapy, PCI in LS-SCLC and cautious use of chemo-radiotherapy in people with worse PS. In contrast increasing age, which is currently cited as a criterion for selecting cisplatin + etoposide, was not found to result in poorer short or long term survival, especially in ED-SCLC. Consequently, this guideline statement may inadvertently lead to patients being denied appropriate chemotherapy. Similarly, current recommendations have minimal patient selection criteria for chemotherapy in order to encourage its use. However, this may inadvertently cause variations in the likelihood of receiving chemotherapy as individual physician judgement of a patient's fitness may differ. By quantifying 30-day survival and the cause of these deaths this study provides useful information that could, if incorporated into guidance, reduce variation and maintain the permissive approach to chemotherapy administration by allowing better shared decision making, based on the patient's early mortality risk.

As well as relating to current recommendations this research can inform future guideline decision making as it provides a reference for survival following present treatments which novel therapies will need to surpass if they are to be approved.

Table 5.11: This study's findings in comparison to ESMO guidelines

	European Society of Medical Oncology recommendation	Systematic review finding
Thoracic radiotherapy	All patients with T1-4, N0-3, M0 tumours who are a good performance status should be treated with concurrent chemotherapy and thoracic radiotherapy.	Early thoracic radiotherapy augments long term survival in LD-SCLC.
	Twice daily 1.5Gy in 30 fractions.	Radiotherapy dosing and fractionation were not evaluated.
	The routine use of thoracic irradiation in patients with metastatic SCLC is not recommended.	Receipt of thoracic radiotherapy was not stated in many ED-SCLC studies. Thoracic radiotherapy did not augment survival in ED-SCLC.
Prophylactic cranial irradiation	All SCLC patients responding to first-line treatment should be evaluated for prophylactic cranial irradiation.	PCI (mostly given to chemotherapy responders) improved one year survival in LD-SCLC. The survival benefit of PCI was less clear in ED-SCLC.
Chemotherapy regimen	Four to six cycles of etoposide plus cisplatin or carboplatin are recommended.	Many studies gave 4-6 cycles of chemotherapy. There were disparities in long term survival by regimen. Cisplatin + etoposide and cisplatin + irinotecan had better long term survival in LD-SCLC. However Irinotecan may favour survival in Asian cohorts rather than Caucasian.
	Irinotecan + cisplatin, gemcitabine + carboplatin (in poor prognosis patients only) and I.V or oral topotecan + cisplatin are alternative options if etoposide is contraindicated.	Cisplatin + irinotecan combinations had better long term survival in ED-SCLC compared to other regimens. However, this likely relates to the underlying cohort ethnicity. Studies using gemcitabine + carboplatin did not meet all of the inclusion criteria and were therefore not assessed. Six studies administered topotecan + cisplatin, all were in ED-SCLC patients. Survival was similar to cisplatin + etoposide.
Age and performance status	In young patients cisplatin and etoposide is recommended.	Across all ages long term survival was lower with carboplatin + etoposide when compared to cisplatin + etoposide/ irinotecan. Elderly people had poorer long term survival in LD-SCLC. Whereas, in ED-SCLC, survival was equally poor across all ages. Elderly patients did not have an increased risk of death within 90-days of chemotherapy.
	PS is not listed in chemotherapy administration criteria except for use of concurrent chemo-radiotherapy.	Individuals with worse PS were less likely to survive in the short and long term regardless of age.

5.5 Conclusions

This is the largest systematic review and meta-analysis of survival in SCLC. The findings support European guideline recommendations, in particular, early thoracic radiotherapy, PCI and cautious use of chemotherapy in people with worse PS. Despite cisplatin and carboplatin doublet regimens being the preferred treatments there were significant disparities in their long-term survival. This may be attributed to the country where research was conducted as survival was better in Asia. The survival disparities between ethnic groups can be partly attributed to the different aetiological exposures of lung cancer and the metabolism of chemotherapy. Further research to gain a better understanding of the biologic characteristics of these subtypes of patients and in particular how this relates to smoking status, may give new insights for novel targeted genetic driver mutation treatments to be developed.

At present, early mortality risk is not included in the criteria for chemotherapy administration but is a metric that can inform patient selection. Early mortality risk does not increase in the elderly and caution should be taken citing age in selection criteria as this may unfairly deny individuals of appropriate chemotherapy. There is optimism going forward into the era of immunotherapy as new treatments are desperately needed to improve outcomes for SCLC. Importantly, this research sets a reference point for survival following current treatments to which the success of immunotherapies can be measured

Chapter 6 Conclusions and future research

This chapter summarises the findings from this thesis, discusses the clinical implications, draws conclusions and explores future directions of research.

6.1 Summary of findings

The aims of this thesis were to:

1. Determine the factors associated with receipt of chemotherapy in SCLC and how these are related to early mortality.
2. Examine how the access to chemotherapy, radiotherapy and PCI vary by geographic location.
3. Determine what patient, tumour, treatment and hospital factors are associated with early and late survival for SCLC.
4. Establish early and late survival benchmarks following platinum based chemotherapy for SCLC.

To my knowledge this is the first time these national audit data have been linked to provide an in-depth perspective of care for SCLC and importantly how treatment factors, such as radiotherapy dose, PCI and chemotherapy regimen influence survival. In addition, this thesis contributes one of the largest systematic reviews and meta-analyses that has ever been carried out for SCLC. The findings from this work can be summarised into 4 parts relating to receipt of chemotherapy, early survival, late survival and median survival.

6.1.1 Receipt of treatment

After case-mix adjustment there was significant variation in the odds of receiving chemotherapy, radiotherapy and PCI by the different lung cancer networks in the NLCA data. Approximately 60-62% of people diagnosed with SCLC received chemotherapy which is below the NLCA standard of 70%.³⁶ Increasing age, worse PS and more comorbidities (score ≥ 4) were independently associated with less chance of

receiving chemotherapy, however, there was no association with stage. Carboplatin+etoposide was the favoured regimen ahead of cisplatin+etoposide however there remained a minority of patients who received single platinum chemotherapy and other “off guidance” treatment. Some of these treatment and patient factors were also associated with survival.

6.1.2 Early mortality and survival

When all the stages of SCLC were combined in the NLCA data 30-day mortality following chemotherapy was roughly 7.8%, however this varied significantly by lung cancer network. The odds of early death were considerably higher for individuals with ED-SCLC and worse PS.

The meta-analysis of other SCLC studies, which generally had very selected cohorts, revealed a much lower 30-day mortality of approximately 2.0%. This showed little variation by sub-factors, such as the study design, chemotherapy and study year. Neutropenic sepsis and disease progression were the predominant causes of early death. Survival at 90 days was approximately 95% and was better in Asian cohorts, modern studies and following receipt of early radiotherapy.

6.1.3 Late survival

The 1-year survival following chemotherapy in the national audit data was roughly 40%, however, this was markedly different for LD-SCLC and ED-SCLC (approximately 62% and 26% respectively). Individuals who had better PS, were younger and female were more likely to survive 1-year after receiving chemotherapy. Additional radiotherapy with a total dose above 30Gy and 40Gy augmented the odds of survival

for ED-SCLC and LD-SCLC respectively as did receiving PCI. Indeed, the network that had better 1-year survival was more likely to offer these treatments.

The pooled 1-year survival from the meta-analysis was greater at 73% and 53% respectively. Survival variation by PS and ethnicity were present across both stages of cancer, whereas survival differences by radiotherapy and PCI administration was only observed in LD-SCLC cohorts. Two and 5-year survival were almost exclusive to LD-SCLC studies.

6.1.4 Median survival

The median survival for individuals who received chemotherapy was poor in the national audit data. The pooled meta-analysis revealed a similar median survival of roughly 9-10 months for ED-SCLC but a longer survival of 18 months for LD-SCLC.

In comparison to the extensively cited work by *Zelen et al* the research in this thesis found the median survival for individuals who did not receive chemotherapy in the NLCA to be longer than previously estimated for LD-SCLC and markedly shorter for ED-SCLC at 251 and 32 days respectively.¹⁰⁰

6.2 Clinical implications

6.2.1 National healthcare delivery

The variation in early mortality observed between lung cancer networks is concerning and is likely to be multifactorial, as previously discussed. Since highlighting this inequality I have advised both PHE and the NLCA in order for them to investigate the reasons behind this and help the trusts that are underperforming by means of examining their data submissions and clinical practices. The variation in receiving

treatment by cancer network highlights that successive governments have been unable to meet their objectives of reducing and eliminating healthcare inequalities in England. This will likely continue to be a challenge in the future.

6.2.2 Guideline recommendations

The treatment landscape in SCLC looks set to change with the results of the IMPOWER-133 study showing the immunotherapy agent atezolizumab, in combination with chemotherapy, can improve survival in ED-SCLC. However, many other immunotherapy agents are still in the experimental stage and much of the initial enthusiasm has been dampened by the announcement of several recent clinic trials showing no improvement of survival (Checkmate 451 and 331). This thesis provides robust evidence of survival following the chemotherapy currently administered and can be used by national bodies to compare new treatments against, thus accelerating the evaluation and approval process.

This research has illustrated that 1-year survival following 4 or 6 cycles of chemotherapy does not differ considerably. Administering 4 cycles reduces the side effect burden to patients in addition to improving quality of life, hence, recommendations should be reviewed and updated as the duration of chemotherapy is currently ambiguous.

6.2.3 Patient selection

One of the ethical principles doctors must abide to is non-maleficence, which is defined as not harming or inflicting the least harm possible to reach a beneficial outcome. In order to abide by this principle and reduce the risk of early death from chemotherapy clinicians must be able to make a balanced judgment using the best

available evidence. This research provides that evidence by quantifying early mortality risk and assists clinicians and patients in making better informed treatment choices, ultimately improving patient selection. Better selection should translate into fewer early deaths.

This thesis has highlighted that some individuals received single platinum chemotherapy, which is not in accordance with NICE recommendations. People who received this treatment were less likely to survive 1-year, in comparison to someone who had received carboplatin+etoposide, and were more likely to die within 30 days (narrowly missing statistical significance adjusted OR 1.71 95%CI 0.99-2.95). This finding highlights these individuals, where full doublet treatment is considered too toxic, as the group that will benefit the most from better informed shared decision making as the risk of early death from treatment is increased relative to the long-term survival gain.

Individuals who were female and from Asian backgrounds had better survival following chemotherapy for SCLC. It is possible that there are undiscovered germline and somatic oncogene mutations that could be responsible for this observation and that these mutations are more prevalent in never smokers (who are predominantly Asian females). Indeed, a similar example of this is in NSCLC and mutations of the gene coding for EGFR. Somatic mutations in the EGFR gene are more prevalent in female, Asian, never-smokers than in Caucasians. Hence, these people are more likely to respond to tyrosine kinase inhibitors and have better survival.³¹⁶ Somatic and germline mutations can also shorten survival as some cause treatment resistance e.g. the T790M mutation in EGFR.³¹⁷ In order to better understand this concept in SCLC it is

clear that further research examining ethnic variation in mutation prevalence and how this relates to different aetiological exposures and survival is needed. This research could then provide a pathway for novel treatment strategies to be developed.

6.3 Future research

The research in this thesis has answered important questions but has also generated others that merit further research. I have outlined these research ideas and briefly discussed a methodology as follows.

6.3.1 *Quality of life for patients undergoing chemotherapy for SCLC*

Survival is poor even for individuals who receive treatment, hence, quality of life has an important role in treatment decisions but the evidence in this area is sparse. *Zikos et al* conducted a systematic review to assess the adequacy of reporting health related quality of life scores in chemotherapy RCTs for SCLC. They concluded that overall reporting of quality of life scores was acceptable however the authors did not summarise these.³¹⁸ Hence, a further systematic review and meta-analysis to summarise quality of life outcomes is needed.

6.3.2 *Factors predicting receipt of second-line chemotherapy for SCLC and survival*

NICE recommends second-line treatment of CAV, platinum doublet or topotecan for relapsed SCLC. To my knowledge the current proportion of individuals receiving second-line treatment and the drugs used in the UK is unknown. Understanding what treatments are administered and their subsequent survival is important in determining the efficacy of these therapies and can be used by clinicians to inform patients of the

positive and negative consequences of committing to further chemotherapy. This study could utilise NLCA and SACT records to identify these individuals and the chemotherapy they receive.

6.3.3 Quantifying factors that influence receipt of immunotherapy and early mortality following treatment

Immunotherapy (atezolizumab), in combination with chemotherapy, will likely become a new standard treatment for SCLC. Other immunotherapy agents have had negative clinical trial results. The factors influencing its receipt will likely differ in comparison to chemotherapy as immunotherapy can have more favourable side effects. In addition there is increasing evidence that a subgroup of patients acquire disease hyper-progression as a result of immunotherapy and death occurs shortly after treatment.³¹⁹ To date, the factors associated with hyper-progression have not been identified, although, linked NLCA and SACT data may be able to determine these. Presently, immunotherapy administration is recorded within the SACT data for NSCLC patients but not SCLC, as it is not approved. Hence, it will not be conducive to start this analysis until several years' time when immunotherapy is likely to be routinely used.

6.3.4 Validation of an early mortality risk score

Stage and PS were identified as factors that are independently associated with early mortality and this risk has been quantified in the dataset available to me. In order to develop a mortality risk score further work is needed to validate the ability of these factors to predict early death in a larger cohort. Subsequent years of NLCA data, or another large cancer dataset that contains these metrics, could be used to achieve this.

6.3.5 Survival following surgery for individuals with SCLC

Surgical resection is an option for treating very early stage SCLC. Previous research by *Luchtenborg et al* quantified survival following surgery for SCLC patients using NLCA data. However, there were two major limitations to their work. These were: high levels of missing data relating to stage and no record of other treatment given following surgery e.g. adjuvant chemotherapy/radiotherapy. Now, with the improved acquisition of cancer stage in the NLCA and the ability to link radiotherapy and chemotherapy data these limitations could be addressed and the analysis repeated to provide more accurate results.

6.3.6 Quantifying the timing of PCI after chemotherapy and its association with survival

This thesis has illustrated that receiving PCI augments the odds of 1-year survival for SCLC patients. Current recommendations state PCI should be offered to patients who have responded to first-line chemotherapy and hence it is usually given after 4 or 6 cycles. The treatment guidelines of the American College of Chest Physicians' acknowledge that the optimal timing for PCI is unknown.⁴⁸ It would be possible to use NLCA, SACT and RTDS to establish the timing of PCI in relation to chemotherapy and investigate whether this is associated with overall survival. The limitation of using these data will be that they are not able to describe the rate of recurrence from brain metastases, which is an important outcome measure following this treatment.

6.3.7 Organisational factors that determine receipt of treatments and survival for individuals with SCLC

There was significant variation in receipt of treatment and 30-day mortality by lung cancer network. I have speculated that the variation could be attributed to local expertise and resources, however there is limited evidence to support this statement. The NLCA research group have, in the past, conducted an organisational audit in order to quantify access to diagnostics and treatment for lung cancer in England.³²⁰ This audit primarily focused on access to thoracic surgery and not chemotherapy or radiotherapy. A future study could gather and use hospital organisational data, such as the number and working hours of members of the lung cancer MDT, and link these with NLCA and SACT data. These data could be used to develop a multiple logistic regression model to test the association of these factors in relation to receiving treatment and survival which will help explain the variation previously seen.

6.4 Conclusion

Many decisions in clinical practice are made on past experience and the “gut” instinct of the patient and clinician. This research has provided the lung cancer community with a means to logically explain the risks and benefits of treatment to patients and improve the selection and consent process. New treatments are desperately needed for SCLC and immunotherapies show promise. This research is a comprehensive summary of survival and provides national commissioning bodies with an important benchmark that can be used to help ensure the survival gains of novel therapies are true and are economically viable. In addition to new therapies survival can be augmented by ensuring more equitable access to the existing treatments, an issue that has been highlighted by this work. Furthermore, these studies demonstrate the

richness of the routinely collected cancer data in England. In an increasingly digitalised healthcare system it may soon be possible to link and explore other datasets in order to answer questions raised by this research and investigate other factors that may influence survival.

Appendices

Appendix A: Abstracts of work within this thesis presented at conferences

Chemotherapy prescriptions for small cell lung cancer in England; An analysis of the National lung cancer audit, systemic anti-cancer therapies and hospital episode statistics databases

Poster presentation at British Thoracic Oncology Group conference, January 2018

G S Jones¹, A Khakwani¹, T McKeever¹, D R Baldwin¹, R B Hubbard¹

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Introduction

We describe what first line chemotherapy regimens are being used to treat histologically confirmed SCLC in England.

Methods

We used data from the National lung cancer audit between 1/4/2014 - 31/12/2015 to identify people with SCLC and linked these records with the systemic anti-cancer therapies and hospital episode statistics datasets to gain information about the chemotherapy given and patient comorbidity.

Results

There were 6,725 people diagnosed with SCLC. The median age was 70 years (IQR 63-76). Approximately 5,074 people (75.5%) had extensive stage.

In total 3,979 (59.2%) people received chemotherapy. The median time from histological diagnosis to first dose of chemotherapy was 13 days (IQR 7-22). Chemotherapy was given to 2,081 (52.3%) people with a performance status (PS) of 0-1, 717 (18%) people with PS 2 and 268 (6.7%) people with PS 3-4. Nearly 66% (2,614) of people who received chemotherapy had little or no comorbidity (Charlson comorbidity index (CI) of 0-1). Approximately 75% (2,972) of the chemotherapy prescribed was carboplatin + etoposide, followed by 9.8% (391) for cisplatin + etoposide and 6.9% (274) for single agent platinum. Combinations of gemcitabine + carboplatin or cyclophosphamide, doxorubicin + vincristine (CAV) were used to treat 0.4% (15) and 1% (38) of people respectively. Chemotherapy regimens varied by lung cancer network however carboplatin + etoposide remained the most commonly prescribed.

Conclusion

NICE guidance (CG121) recommends cisplatin based chemotherapy in the treatment of SCLC and to consider substituting cisplatin for carboplatin in patients with poor performance status or significant comorbidity. These observational data demonstrate that, in England, carboplatin + etoposide is the preferred combination of chemotherapy to treat SCLC even in a population of which 66% had minimal comorbidity. This choice is perhaps influenced by carboplatin's toxicity profile compared to cisplatin. Other chemotherapy regimens, which are not recommended by NICE, are also being prescribed.

What factors are associated with early mortality following the first dose of chemotherapy in small cell lung cancer?

Oral and poster presentation at British Thoracic Oncology Group conference January 2018

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Introduction

National guidelines are permissive in offering chemotherapy to people with small cell lung cancer (SCLC) who have medical comorbidities or borderline performance status (PS). In these people the risks and benefits of chemotherapy are less clearly understood.

Methods

We calculated the proportion of people with SCLC who died within 30 days of receiving the first dose, in their first cycle, of chemotherapy and investigated the patient, tumour and hospital factors that influence this using linked data from the National lung cancer audit, systemic anti-cancer therapies and Hospital episode statistics datasets.

Results

There were 6,725 people diagnosed with SCLC from 1/4/2014 to 31/12/2015 in England.

In total 3,979 (59.2%) people received chemotherapy. The observed 30-day mortality was 7.54% (300) in people who received chemotherapy compared to 14.5% (399) in those who did not.

30-day mortality after chemotherapy was nearly 18% in people with a PS of 3-4 compared to 3% with PS 0 (adjusted OR 5.13 95%CI 3.43-7.68). A Charlson comorbidity index ≥ 4 compared to 0 was also associated with early death (adjusted OR 1.21 95% CI 1.0-1.46). Approximately 8.9% (257) of people with extensive stage died within 30 days compared to 3.6% with limited stage (adjusted OR 2.06 95% CI 1.58-2.68). There was significant variation in 30-day mortality by lung cancer network (p value <0.01 LR test) and the chemotherapy regimen prescribed (cisplatin + etoposide vs carboplatin + etoposide adjusted OR 0.5 95%CI 0.32-0.77).

Age, sex and social deprivation were not associated with early mortality.

Conclusion

There is significant variation in early mortality across lung cancer networks, perhaps due to different institutional practices and resources. After adjusting for comorbidity and performance status, cisplatin + etoposide is associated with a lower risk of early mortality compared to carboplatin + etoposide even though it is generally perceived to have greater toxicity.

What factors are associated with early mortality following the first dose of chemotherapy in small cell lung cancer?

Oral and poster presentation at *Cancer Services, Data and Outcomes Conference June 2018*

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Introduction

NICE guidelines (CG121) recommend the use of chemotherapy to treat individuals with small cell lung cancer (SCLC), even if they have poor performance status (PS>2) or significant comorbidity. This poses a significant chance of early death following treatment. The department of health have suggested that deaths within 30 days of chemotherapy should be used as an indicator for harm as they indicate toxicity or futility of treatment. Until now, little research exists quantifying 30-day mortality in SCLC.

Methods

We calculated the proportion of people with SCLC who died within 30 days of receiving the first dose of chemotherapy and investigated what patient, tumour and geographical factors influence this by linking English National Lung Cancer Audit, Systemic Anti-Cancer Therapies and Hospital Episode Statistics data.

Results

In total 2,238 (60.2%) people received chemotherapy for SCLC in England during 2015. The overall 30-day mortality was 7.8% (n=174).

Importantly age, sex, social deprivation, comorbidity (Charlson index) and the chemotherapy received were not independently associated with early death.

Individuals with a PS of 3-4 were more likely to die within 30 days of chemotherapy than those with PS 0 adjusted OR 6.92 (95% CI 3.02-15.86). Extensive stage cancer was also associated with an increased risk of death compared to limited stage adjusted OR 1.68 (95% CI 1.03-2.74).

After adjusting for all our measured factors we found significant variation in the proportion of early death between lung cancer networks (p <0.01).

Conclusion

PS and disease extent were independently associated with 30-day mortality. Early death varied significantly by lung cancer network. These findings can be used to quantify and better inform patients of the risks of early death following treatment by their PS and stage. This may ease decision making for clinicians and guide patient selection for chemotherapy in the future.

Factors associated with early mortality following chemotherapy in small cell lung cancer: An analysis of national audit data.

Sue Watson PhD prize oral presentation, University of Nottingham, May **2018**

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Introduction

Small cell lung cancer (SCLC) is an aggressive tumour that carries a poor prognosis if left untreated. Fortunately it is very responsive to first line chemotherapy. Hence, National treatment guidelines recommend offering chemotherapy to individuals even if they have significant medical comorbidities and poor fitness. Treating frail patients increases the risk of early death from toxicity and this makes the decision of whether to treat difficult. Thirty-day mortality following anti-cancer treatment is a recognised metric of sub-optimal patient selection and until now has not been quantified in SCLC. We aim to increase the evidence in this area so that patient selection for anti-cancer treatment can be improved.

Methods

We calculated the proportion of people with SCLC who died within 30 days of receiving the first dose of chemotherapy and investigated what factors influence this by linking three national healthcare datasets from 2015: the National Lung Cancer Audit, Systemic Anti-Cancer Therapies and Hospital Episode Statistics.

Results

There were 3,718 people diagnosed with SCLC in England. In total 2,238 (60.2%) people received chemotherapy. The overall 30-day mortality following the first chemotherapy dose was 7.8% (n=174).

Performance status (a measure of an individual's wellbeing) was independently associated with 30-day mortality (PS4 (unable to carry out self-care) vs. PS0 (asymptomatic) adjusted OR 6.92 (95%CI 3.02-15.86)). Stage was independently associated with death within 30 days (extensive vs. limited stage adjusted OR 1.68 (95%CI 1.03-2.74)). Allowing for case mix adjustment, there was significant variation in 30-day mortality by geographical region (p-value <0.01 LR test). There was a signal, though not significant, that patients who received chemotherapy not in keeping with national recommendations were at an increased risk of early death (single platinum chemotherapy vs. Carboplatin+etoposide adjusted OR 1.71 (95% CI 0.99-2.95)). Age, sex, social deprivation and comorbidity were not independently associated with 30-day mortality.

Discussion / Conclusions

Performance status and the extent of cancer were independently associated with 30-day mortality. Early death varied significantly by geographical region, which suggests inequalities in lung cancer care across England.

Relevance to patients/public, other scientists:

Our research can be used to quantify and better inform patients of the risks of early death following treatment by the two associated factors, performance status and stage. This knowledge allows better shared decision making, ultimately improving the patient selection process for chemotherapy and will help standardise care. It also raises awareness to clinicians of individuals most at risk of early death so that appropriate referrals for enhanced supportive palliative care can be made.

A systematic review and meta-analysis of early and late survival following anti-cancer therapies for small cell lung cancer

Poster presentation world conference on lung cancer, Toronto, September 2018

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Background

Treatments for small cell lung cancer (SCLC) have not changed significantly in contrast to non-small cell, where this is more individually tailored. Current guidelines generally have a one size fits all approach to chemotherapy. We conducted the largest systematic review and meta-analysis in SCLC to evaluate early and median survival by different study factors

Methods

We searched EMBASE and MEDLINE for randomized controlled trials and observational cohort studies which reported survival following platinum doublet chemotherapy for SCLC. We calculated overall survival at 30 and 90 days along with the median survival.

Results

We identified 10,487 titles, 161 were included. Cisplatin + etoposide (n=87 (49.4%)), carboplatin + etoposide (n=36 (20.5%)) and cisplatin + irinotecan (n=23 (13.1%)) were predominantly reported. The commonly reported cause of death within 30 days was neutropaenic sepsis (n=27), disease progression (n=11) and cardiovascular (n=8). Across both stages 30-day survival was 98% (95% CI 98-99%) whilst 90-day was 95% (95% CI 94-96%). Thirty and 90-day survival showed similar patterns to study factors as median survival.

Limited stage median survival was 18.1 months (95% CI 17.0-19.1). Studies that administered thoracic radiotherapy and PCI had better survival than those that did not. Studies giving carboplatin + etoposide or included poorer PS (0-3) individuals had inferior survival. PCI timing did not show survival differences.

Extensive stage median survival was 9.6 months (95% CI 8.9-10.3). This was augmented in studies that gave irinotecan + cisplatin and were conducted in Asia. There were no survival differences by cisplatin/carboplatin or median participant age.

Conclusion

Neutropenic sepsis accounts for the majority of 30-day deaths and was mostly reported with cisplatin + etoposide. Our findings broadly support guideline recommendations but suggest certain sub-populations e.g. Asian individuals, benefit from targeted treatment with irinotecan + cisplatin. Age should be re-considered as a treatment-deciding factor in extensive stage.

A systematic review and meta-analysis of early and late survival following anti-cancer therapies for small cell lung cancer

Oral presentation East midlands thoracic society conference, Loughborough, October 2018

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Background

We conducted a systematic review and meta-analysis of survival in SCLC following treatment recommended by the European Society of Medical Oncology in order to benchmark survival for novel therapies to be compared with.

Methods

Randomized controlled trials and observational studies reporting overall survival following chemotherapy for SCLC were included. We calculated survival at 30 and 90-days along with 1-year, 2-year and median.

Results

We identified 10,487 titles and included 160. There were minimal 30-day deaths. Survival at 90-days was 95% (95% CI 94-96%, I²=81.7% n=167) and this was equal across all ages. The median survival in limited stage was 18.1 months (95% CI 17.0-19.1, I²=77.3 n=110) and early thoracic radiotherapy, prophylactic cranial irradiation and better performance status augmented this. In extensive stage the median survival was 9.6 months (95% CI 8.9-10.3) and this improved where irinotecan + cisplatin was used. Long term survival in all stages was better in modern and Asian studies and poorer where carboplatin + etoposide was used.

Conclusion

This detailed survival summary supports early thoracic radiotherapy, prophylactic cranial irradiation and cautious use of chemotherapy in poor performance status individuals. Novel therapies will need to out-perform these survival benchmarks if they are to be successful.

Appendix B: Work published or presented at conferences extra to this PhD

Recent advances in the management of lung cancer

Authors: Gavin S Jones^A and David R Baldwin^{B,C}

ABSTRACT

Historically, the prognosis for individuals diagnosed with lung cancer has been bleak. However, the past 10 years have seen important advances in treatment and diagnosis which have translated into the first improvements seen in lung cancer survival. This review highlights the major advances in treatments with curative intent, systemic targeted therapies, palliative care and early diagnosis in lung cancer. We discuss the pivotal research that underpins these new technologies/strategies and their current position in clinical practice.

KEYWORDS: Lung cancer, curative treatment, targeted therapies, early diagnosis, lung cancer management

Introduction

For several decades lung cancer has been the most common cancer in the world.¹ In 2014 there were 46,403 new cases of lung cancer diagnosed in the UK.² It is the third most common cancer after breast and prostate, but has the largest proportion of all cancer-related deaths (22%).² The overall age standardised incidence has declined slightly over the past 40 years, which is a combination of a marked decline among men and an increase for women (Fig 1). Approximately 62% of people have advanced stage disease at diagnosis.³ When combining all stages of lung cancer in England, 1-year survival has improved from 24.5% in 1995–9 to 36.7% currently.⁴ Much of this improvement has occurred since 2010 and is attributed to developments in lung cancer care.

Staging

It is important to accurately stage patients with lung cancer as this contributes to treatment options and prognosis. Better access to positron emission tomography with computed tomography (PET-CT) scanning and endobronchial ultrasound (EBUS) for mediastinal lymph node sampling have increased the accuracy of staging for lung cancer.

The American joint committee on cancer adopted the 8th edition of the International Association for the Study of Lung Cancer's (IASLC) staging project⁵ in January 2017. This replaced the previous edition that was originally published in 2009. The 8th edition is derived from the IASLC database of 77,156 evaluable cases of histologically confirmed NSCLC diagnosed between 1999 and 2010 from 35 sources in 16 countries. The stage groupings are summarised in Fig 2 and are based on the new TNM ('tumour, nodes and metastases') classification which is as follows.

Tumour

Primary tumour classification is now subdivided into: T1a ≤1 cm, T1b >1 to 2 cm, T1c >2 to 3 cm, T2a >3 to 4 cm, T2b >4 to 5 cm, T3 >5 to 7 cm and T4 >7 cm. Tis and T1mi were introduced for adenocarcinoma *in situ* and minimally invasive adenocarcinoma.

Endobronchial tumours located <2 cm from the main carina were found to have a better prognosis so have been reclassified as T2 rather than T3. Similarly, total lung atelectasis / pneumonitis is now classed as T2. Diaphragmatic invasion has been upstaged to T4. Mediastinal pleural invasion is no longer used as a descriptor.

Node

Nodal station descriptors have not changed: N1 ipsilateral hilar node, N2 ipsilateral mediastinal or subcarinal node, N3 contralateral mediastinal or supraclavicular/scalene node.

Metastases

M1a, for intrathoracic metastases, remains unchanged.

Extrathoracic metastases have been reclassified into M1b; single extra-thoracic metastasis in a single organ or M1c; multiple extrathoracic metastases in a single organ or multiple organs.

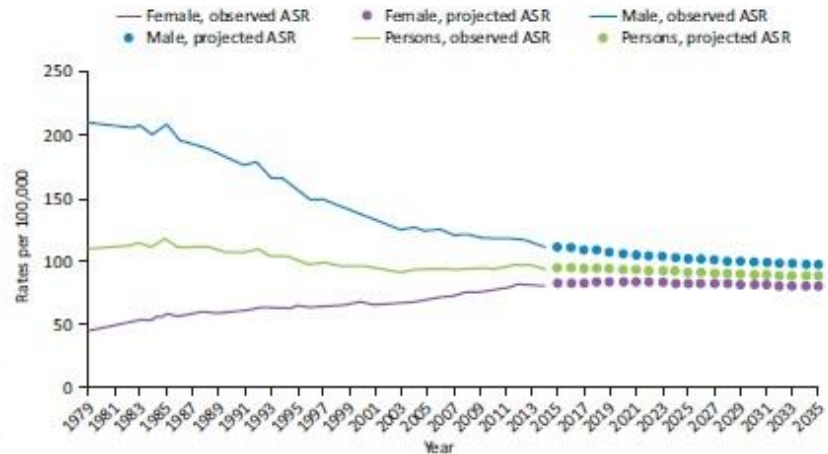
Previously curative treatments were generally reserved for stages I–IIIA; however, the treatment of oligometastatic disease (broadly defined as less than 5 metastases in a single organ⁶) is an area of growing research interest. When oligometastatic lung cancer is treated aggressively with ablative radiotherapy or resection, several observational studies have estimated 1-year survival to be 35–56%.^{6–8} This is a significant improvement if one considers that the overall 1-year survival for people with stage IV lung cancer in the UK is 14%.⁹

Thoracic surgery

Thoracic surgery is considered the standard of care for people with early stage lung cancer who are deemed fit enough. Modern

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Fig 1. Age standardised ratios of lung cancer in the UK since 1979. Reproduced with permission. Web content: Cancer Research UK, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence> ASR = age standardised ratio



surgical techniques have been developed, including less invasive video-assisted thoracoscopic surgery (VATS) for lung resections (Fig 3), that are changing the boundaries of surgical fitness. Perioperative mortality and long-term survival following VATS lobectomy has been shown to be better than open surgery in some studies. A large European retrospective cohort study found in-hospital mortality following VATS lobectomy to be 1% vs 1.9% for open lobectomy.¹⁰ Similarly, a systematic review and meta-analysis found 5-year survival following VATS lobectomy for early stage lung cancer to be 80.1% vs 65.6% for open lobectomy.¹¹ Video-assisted thoracoscopic surgery lobectomy also has a lower risk of total complications (29.1% VATS vs 31.7% open¹⁰) and a shorter hospital stay (8.3 days VATS vs 13.3 days open¹¹).

Over the past 10 years, surgical resection rates have increased from 9% to nearly 17%³ and surgeons are now more likely to operate on people who are older than 70 years¹² (the median age of lung cancer diagnosis is 73 years). The use of lung-sparing surgery has also increased which has resulted in the incidence of pneumonectomy decreasing, an operation which carries an approximate 11% mortality risk within 90 days.¹³ Laparoscopic

robotic surgery is being developed but it is not currently recommended in the UK.

There are inequalities in access to thoracic surgery across the UK. The 2016 National Lung Cancer Audit reported that the range of patients with non-small cell lung cancer (NSCLC) who received surgical treatment varied from 5% to 36% across different trusts.³ Previous studies have also demonstrated that a person can be up to 51% more likely to receive thoracic surgery for lung cancer if they are first diagnosed in a thoracic surgical centre,^{14,15} and this effect is most pronounced in surgical centres with the largest lung cancer populations.¹⁵

Radical radiotherapy

Radiotherapy continues to evolve and there are different techniques now being used to treat lung cancer with curative

	N0	N1	N2	N3	M1a	M1b	M1c
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

Fig 2. International Association for the Study of Lung Cancer (IASLC) 8th edition lung cancer stage groupings. International Association for the Study of Lung cancer 2015.

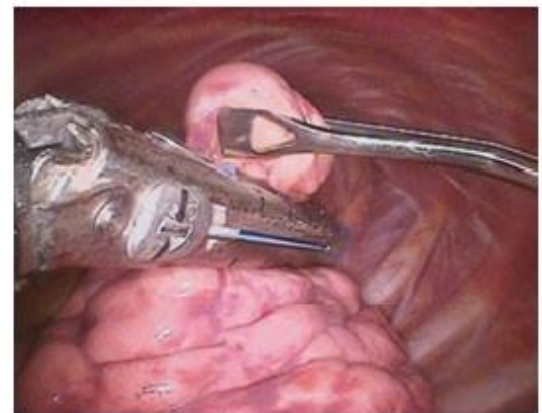


Fig 3. Video-assisted thoracoscopic surgery (VATS). Reproduced with permission of the © ERS 2018: *The European Lung White Book Respiratory Health and Disease in Europe, 2nd Ed.* European Respiratory Society, Sheffield, UK, 2013. Print ISBN: 978-1-84984-042-2, Online ISBN: 978-1-84984-043-9.

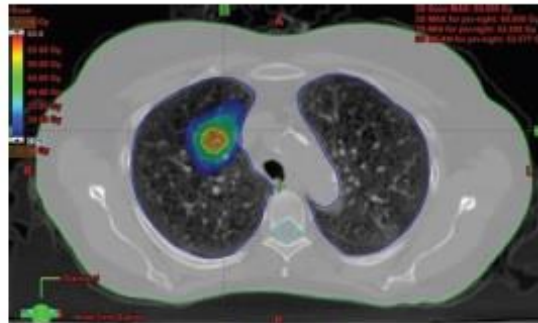


Fig 4. A planning CT thorax for Stereotactic Ablative Radiotherapy (SABR). Reproduced and adapted with permission from *Frontiers in oncology*: www.frontiersin.org/articles/10.3389/fonc.2015.00213/full CT = computed tomography

intent. Stereotactic ablative radiotherapy (SABR), which has been developed for use in lung cancer since the early 2000s, but not widely used in the UK until the late 2000s, is able to deliver large doses of radiation with a high precision of 1–2 mm to small lesions of $<1 \text{ cm}^3$ using an external 3D coordinated system that is linked with movements during the respiratory cycle (Fig 4). It has primarily been reserved for people with early stage cancer who have been unable/unwilling to undergo surgical resection due to medical comorbidities. A meta-analysis of observational studies has demonstrated that SABR has a survival benefit over conventional curative intent radiotherapy (2-year survival 70% with SABR vs 53% for conventional radiotherapy).¹⁶ A phase II prospective cohort study also found 3-year survival to be 55.8% with SABR in T1–2 N0 M0 lung cancers.¹⁷ As well as improved overall survival, SABR also has better rates of local disease control compared to conventional radiotherapy at 3 years (87.2% SABR vs 43% conventional radiotherapy).^{17,18}

Given its success in treating inoperable patients, research is now focused on its use in patients who would be medically fit for surgery. Research evidence has so far been restricted to propensity matching and the two best studies show conflicting results, one favouring SABR¹⁹ and the other surgery for early stage lung cancer.²⁰ There have been attempts to run randomised controlled trials but these have failed to recruit adequately. Three further trials are underway.

Radiofrequency / microwave ablation

Originally used for the treatment of primary or secondary hepatic tumours, percutaneous radiofrequency ablation (RFA) for lung tumours was first described in 2000 by Dupuy *et al.*²¹ It is used for early stage peripherally based lung tumours or metastases in medically inoperable patients. Under CT guidance, an expandable needle which contains multiple electrodes is inserted percutaneously into the lung lesion (Fig 5). A sinusoidal current is then passed through the electrodes causing thermal destruction of cells and coagulation necrosis. Alternatively, a microwave probe can be used to achieve the same ablative effect. The commonest complication reported is pneumothorax; however, only 4–16% of patients require chest drain insertion.²² There are no studies comparing outcomes from RFA with surgical resection; although, cases series report 75% overall survival in stage I inoperable lung cancer.²³



Fig 5. CT scan demonstrating multiple radiofrequency ablation probes being deployed within a peripheral tumour. Reproduced with permission from the Global Resource for Advancing Cancer Education (www.cancerGRACE.org) CT = computed tomography

Systemic therapies

In contrast to treatments for small cell, chemotherapy for NSCLC has revolutionised over recent years and is becoming increasingly more targeted and individually tailored to each patient based on identification of driver genetic mutations; epidermal growth factor receptor (EGFR), epidermal growth factor receptor *thr790met* (EGFR T790M), anaplastic lymphoma kinase (ALK) and ROS proto oncogene 1 (ROS-1). It has therefore become more important than ever to obtain a histological diagnosis in those physically fit enough to have treatment, particularly as these newer treatments are better tolerated by patients than standard chemotherapy.

The notion of targeted treatments based on lung cancer histological subtype first became apparent as people with adenocarcinoma were found to have superior survival with cisplatin/pemetrexed chemotherapy compared to cisplatin/gemcitabine, whereas the opposite was true for those with squamous cell histological type.²⁴

The first genetically targeted treatment for NSCLC was gefitinib. This is an orally administered treatment which effects the EGFR through tyrosine kinase inhibition. The EGFR is a transmembrane surface protein that is activated by the binding of epidermal growth factor. Once bound, an intracellular tyrosine kinase domain causes a cascade of events, primarily DNA synthesis and cellular proliferation. In approximately 15% of people with NSCLC, control of the tyrosine kinase domain in the EGFR is lost due to a mutation in the EGFR gene leading to uncontrolled proliferation. When initially given to all patients with NSCLC, gefitinib was found to have a response in a certain subgroup of patients, predominantly Asian, female, adenocarcinomas and never-smokers.²⁵ This prompted researchers to investigate for mutations in the EGFR gene which proved to be overexpressed in those who responded to gefitinib.²⁶ A further randomised control trial by Maemondo *et al* was pivotal as all patients with NSCLC harbouring EGFR mutations were randomised to receive either gefitinib or standard

chemotherapy (paclitaxel and carboplatin). The gefitinib group had a significantly longer progression free survival of 10.8 months vs 6.4 months in the chemotherapy group.²⁷ There are now several approved treatments by The National Institute for Health and Care Excellence (NICE) for use in people with EGFR mutation positive NSCLC: erlotinib, afatinib and gefitinib. Other targeted treatments which have been approved by NICE are crizotinib for ALK / ROS-1 mutation positive NSCLC and osimertinib for EGFR T790M mutation positive NSCLC.

The newest class of systemic treatments are immune checkpoint inhibitors: pembrolizumab, nivolumab and atezolizumab. They act through the programmed death-ligand 1/2 (PD-L1 and PD-L2) and programmed death 1 (PD-1) receptor pathway. PD-L1 and PD-L2 are proteins which are thought to suppress the immune system by binding with the PD-1 receptor on activated T cells (which are responsible for causing cytotoxic death of cancer cells when activated by tumour antigens). Some cancer cells have been found to express PD-L1 and PD-L2 on their cell membrane, effectively providing a cloak of protection from the immune system. These immunotherapies block the PD-L1/2 and PD-1 receptor pathway, thereby removing the brakes on the immune system, allowing cancer cells to be identified and undergo cytotoxic T cell mediated death. PD-L1 testing was developed as part of the KEYNOTE-001 trial and is carried out via immunohistochemistry staining of tumour cells and calculating the proportion of cells stained. The KEYNOTE-010 trial demonstrated that pembrolizumab at two different doses significantly improved overall survival compared to standard chemotherapy (docetaxel) in people with previously treated NSCLC who had >1% expression of PD-L1 tumour cells.²⁸ Similar findings have also been found with nivolumab compared to docetaxel in patients with >1% PD-L1 expression.²⁹ CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) is another molecule present on lymphocytes that down regulates the immune system for which inhibitors are available. Ipilimumab, a CTLA-4 inhibitor, has shown promising results³⁰ and phase III trials of this drug in combination with other systemic anticancer therapies to treat NSCLC, such as the checkmate 227 trial, are currently in progress.

These treatments are expensive and it is estimated the cost per quality-adjusted life year (QALY) of pembrolizumab is approximately £50,000. Despite its significant cost, pembrolizumab has been approved by NICE for use within the cancer drugs fund, as first-line treatment for PDL-1 positive (>50% tumour staining) advanced stage NSCLC. Similarly, nivolumab as well as pembrolizumab have both been recommended by NICE to treat previously treated advanced stage PDL-1 positive NSCLC.

Supportive and palliative care

Specialist palliative care also has a vital role in lung cancer care and much work has been carried out to optimise its use and improve patient outcomes. Temel *et al* examined the effect of early specialist palliative care support compared with standard care in ambulatory patients with metastatic NSCLC referred to the medical oncology outpatient department.³¹ They found a significant difference in median survival with the early supportive care group, 11.6 months, compared to 8.9 months in the standard care group. These patients also had a better quality of life score and fewer depressive symptoms (based on questionnaire results) and were less likely to require aggressive end-of-life care support. The finding is supported by another trial, which found an improvement in 1-year survival in patients who received early supportive care.³²

Integrating early enhanced supportive care for people with advanced cancer into standard oncology care has been recommended by the American Society of Clinical Oncology, which, after conducting a systematic review of clinical trials concluded there is strong evidence that early palliative care improves quality of life, reduces depression and improves satisfaction with care; however, there was less evidence to show that it improves survival.³³ Integrated palliative care and oncology services vary by hospital in the UK as no national guidance exists. This integration is arguably a more cost-efficient use of resources than approving use of some of the systemic targeted treatments as not a single trial of enhanced supportive care has demonstrated a cost increase over routine care.³³

Early detection

A significant shift in the outcomes of lung cancer may lie with improved early detection. Broadly, this can be augmented by introducing screening initiatives, improving awareness and recognition of lung cancer and clearer referral pathways.

Screening for lung cancer using low dose CT scanning is currently under consideration by the UK National Screening Committee. It has been shown as an effective way to detect early stage lung cancers and improve mortality compared to chest X-ray. The largest trial, the National Lung Cancer Screening Trial (NLST),³⁴ was conducted in the USA. It randomised 53,454 people who were 55–74 years old and were current or ex-smokers in the past 15 years, with a 30 or more pack year history, to receive either a CT chest or plain chest X-ray. The authors found a 20% reduction in lung cancer specific mortality rate and a reduction of 6.7% in overall mortality rate in the CT group. A similar pilot trial has been conducted in the UK, the UK Lung Cancer Screening Trial (UKLS),³⁵ and has used a more selective method of identifying patients for CT screening by sending a questionnaire to identify high-risk individuals (defined as ≥5% 5-year lung cancer risk) using the Liverpool Lung Project risk score. Those identified were then randomised to CT or no intervention. The lung cancer detection rate was 2.1%, the majority of which (86%) were stage I and II. The resection rate was 83% with 10% of resections being done for benign disease (less than half that in other screening trials). The incremental cost-effectiveness ratio was estimated to be £8,466 (£5,542–£12,569) per QALY. Other European trials have been conducted with mixed results, partly due to inadequate study design. The Dutch-Belgian trial, NELSON, is due to report on mortality outcomes in the near future and the results may influence the decision of whether to implement lung cancer screening in the UK.

Before screening can be implemented many questions remain and much research has been focused to address the concerns of cost effectiveness, screening intervals, selection criteria, participation rates, optimal diagnostic workup and minimising harm as well as incorporating effective smoking cessation. Although there is no national screening programme there have been many localised CT screening pilots set up throughout the UK as part of the 'Accelerate, coordinate and evaluate' project by Cancer Research UK and through other funding sources, these are still ongoing.

Increasing awareness through national media campaigns such as 'Be Clear on Cancer', implemented in 2012, have been used to augment early diagnosis. When evaluated the campaign was estimated to have led to 700 additional lung cancers being diagnosed compared to the previous year, with approximately 400 more people having an earlier stage at diagnosis.³⁶ Improving

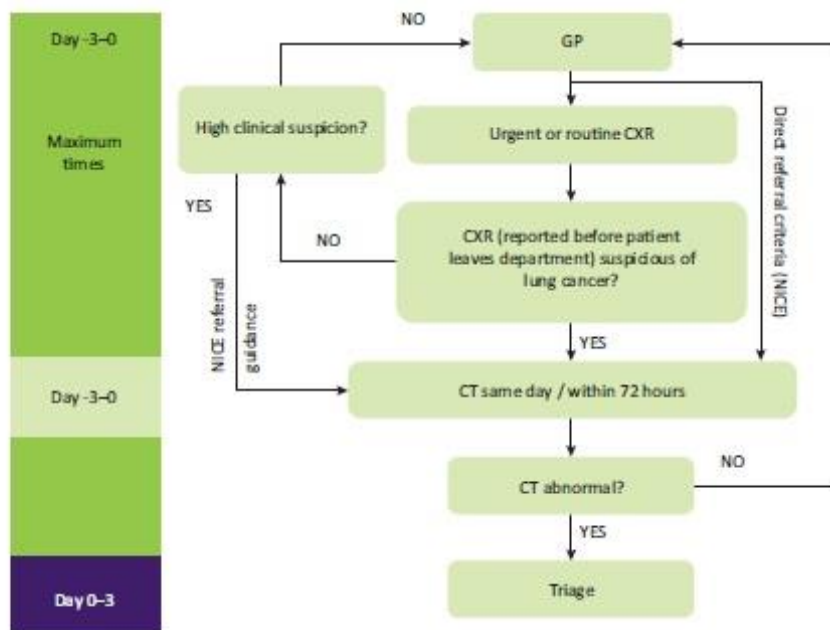


Fig 6. First stage of the optimum lung cancer pathway. 0 on the maximum waiting times bar corresponds to the date of referral onto the cancer pathway. CXR = chest X-ray; CT = computed tomography; NICE = National Institute for Health and Care Excellence

awareness among healthcare professionals as well as patients is also needed. Research has suggested that people who die within 90 days of a lung cancer diagnosis have more interactions with their GP prior to diagnosis than those who lived longer, suggesting that earlier opportunities to capture the diagnosis are being missed perhaps due to lack of awareness.³⁷

Augmenting early detection also requires clear and efficient referral pathways. The Clinical Expert Group for lung cancer, NHS England, has produced guidance to assist commissioners in allocating resources to balance the hub and spoke inequalities in lung cancer care. It has also developed a National Optimum Lung Cancer Pathway. Part of this new pathway recommends that the chest X-ray is reported while the patient is within the radiology department and if it is abnormal the patient undergoes a CT chest the same day or within 72 hours (Fig 6). The new pathway would also allow primary care direct access to CT scanning. These changes could reduce referral times by weeks as they bypass the inherent delays of the report reaching the GP and the subsequent GP referral / further secondary care CT scan. This may also decrease emergency presentations as patients are captured earlier. In order to best select patients for referral from primary care several lung cancer risk scores have been developed; however, they all need to be compared head-to-head to assess which performs best so that radiology services are not overwhelmed by chest X-ray and CT scan requests once the pathway is introduced.

Conclusion

Many technical, pharmacological and service developments have been made in the staging and treatment of lung cancer over the past 10 years but questions still remain about how to best implement these and their cost effectiveness. Further research is

needed to ascertain whether newer radiotherapy techniques, such as SABR, are equivalent to surgery for early stage lung cancers. Much discussion still surrounds the newer targeted agents' cost effectiveness and whether improving early supportive care might be a good use of resources.

Although new treatments are available there are inequalities in access to them and further consideration in commissioning of resources is needed to tackle the hub and spoke effect. Arguably the most effective development that has been made in improving the outcomes for lung cancer is CT screening; however, it still remains to be introduced in the UK despite good evidence for effectiveness. ■

Conflicts of interest

DRB has received an educational grant to support the Cambridge chest meeting from AGFA, Boehringer Ingelheim, Irwin Mitchell and Roche. Travel support was received from Oncimmune Ltd.

GSI's current employment is funded by Roy Castle Lung Cancer foundation and University of Nottingham. He previously received a travel grant from Actelion Pharmaceuticals to attend a pulmonary hypertension preceptorship.

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Themes that influence lung cancer diagnosed through an emergency presentation

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The University of
Nottingham

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Introduction

The National lung cancer audit for 2015 found that 62% of people were diagnosed with advanced stage (III or IV) lung cancer, meaning they were not suitable for curative treatment. Many of these people with advanced stage lung cancer will have been diagnosed through an emergency admission, as shown in previous studies [CADIAS & Wilson *et al*]. This study aims to describe the themes that contribute to an emergency admission diagnosis of lung cancer.

Methods

Nine hospitals within the East Midlands lung cancer network participated. Each was asked to identify people who had been diagnosed with lung cancer through an emergency admission to hospital between September 2014 and February 2015. Each institute wrote to the identified patients' GPs practices and asked them to complete a cancer significant event analysis report (SEA). Secondary care also completed SEA reports for the patients identified. The anonymised reports were then forwarded to the study authors and a descriptive and thematic analysis was performed. The study results were presented at a regional lung cancer care workshop where primary and secondary care attended. The workshop included a brainstorming session of ideas to tackle the issues raised and how to implement them locally.

Results

A total of 120 SEAs, corresponding to 105 people, were reviewed. Of these, 64 were from primary care and 56 from secondary care. Fifteen were identical patients in primary and secondary care. The median age was 72 years (IQR 66-91). A total of 80 (70%) people had died at the time of analysis.

Of the secondary care cases, 30 (54%) people were referred by their GP. Most entered the hospital through Accident and Emergency 45 (80%). Forty one (73%) had stage 4 cancer. Eight (14%) patients had a histological diagnosis of small cell and 21 (38%) had a clinical diagnosis of lung cancer. Thirty one (56%) had a performance status of greater than 3. Shortness of breath, cough and pain were the commonest symptoms affecting 32 (57%), 17 (30%) and 36 (62%) people respectively.

An infographic was produced summarizing the thematic analysis results (Figure 1).

Turnour them

Vague, atypical symptoms which consisted of weight loss, reduced mobility and pain, either locally or at a distant site from bony metastases, were seen. Many symptoms were attributed to exacerbations of pre-existing lung disease, most commonly COPD.

Person themes

Patients had anxious personality types. There was a reluctance to present to the GP practice, or to have investigations, often because symptoms were attributed to another benign problem. Other patients concealed or denied symptoms.

System themes

There was less vigilance for lung cancer in people who were not current smokers. Lack of continuity in primary care was evident as many people saw different GPs as well as non-GP health professionals.

System themes continued

Patients were sometimes admitted whilst on the 2 week wait referral pathway for lung cancer. GP practices did not have an investigation recall service so patients had to re-initiate contact after tests. There was less attention to repeat attenders with respiratory co-morbidity. People were referred under the gastrointestinal malignancy pathway due to symptoms of weight loss and anaemia.

Diagnostic themes

A chest X-ray was often not considered in time and there was a false assurance that a normal chest X-ray excluded lung cancer. On reflection many GPs found the lack of direct access to CT scanning contributed to a delay in the diagnosis.

Figure 1: Aiken's map summarizing the small findings that were used at a regional lung cancer workshop.



Conclusion

GPs need to have an increased awareness that lung cancer can present with vague and atypical symptoms. Redesigning safety netting measures, considering a chest X-ray earlier and allowing direct access to CT scanning for GPs could be feasible solutions to preventing fewer emergency presentations of lung cancer. The results of this audit have helped spread awareness within the East midlands and have assisted with service development in primary care.

The incidence and association of thrombocytosis in people referred to the suspected lung cancer clinic

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UNITED KINGDOM - CHINA - MALAYSIA

Introduction

Secondary thrombocytosis in malignancy is thought to be driven by cytokine and interleukin production by cancer cells. Platelets also have been implicated in assisting haematogenous spread of cancer cells. Two studies have estimated the incidence of thrombocytosis ($>400 \times 10^9/l$) in people admitted to hospital with lung cancer as 53% (Petersen LM, Milmon M) and 26% in patients whose serum sample was taken in primary care (Hamilton et al). These two studies underpin NICE guidance, NG12, which recommends considering an urgent chest X-ray to assess for lung cancer in people aged 40 and over with thrombocytosis. This study adds further evidence towards this guideline statement.

Methods

People who were first seen in the suspected lung cancer clinic at Nottingham University Hospitals between 1st January and 31st December 2014 were identified and data were extracted from patient records. We examined the most recent blood sample up to and including the date the person was first assessed in the lung cancer clinic as the reference value. The incidence of thrombocytosis, defined locally as $>450 \times 10^9/l$, in people who were subsequently diagnosed with lung cancer and those who were not were calculated. The odds of being diagnosed with lung cancer in all comers were calculated using multivariable logistic regression accounting for factors; age, sex, platelet count, haemoglobin, leucocyte count and plasma sodium. In the population subsequently diagnosed with lung cancer we assessed for factors associated with thrombocytosis; age, sex, stage, histology and haemoglobin.

Results

We identified 704 people, 396 (56%) were male, who were referred to the suspected lung cancer clinic. A total of 194 (28%) people had a diagnosis of lung cancer. The median age of people diagnosed with lung cancer was 70 years (IQR 65-77). The predominant histological type was adenocarcinoma 74 (38%), followed by squamous cell 63 (32%), radiological diagnosis 22 (11%), small cell 21 (11%) and other 14 (7%). The majority 91 (47%) had stage IIB and IV disease.

The median time the serum sample was taken before the clinic was 0 days (IQR 0-20). Thrombocytosis was seen in 40 (21%) of the lung cancer cases and 31 (6%) of the non-lung cancer cases. Thrombocytosis and leucocytosis were associated with a diagnosis of lung cancer in all comers adjusted OR 3.32 95% CI 1.87-5.89 and adjusted OR 2.33 95% CI 1.52-3.57 respectively (Table 1).

In people diagnosed with lung cancer thrombocytosis was associated with stage IIB/IV disease compared to IA-IIA (adjusted OR 4.25 95% CI 1.69-10.9) and squamous cell carcinoma compared to adenocarcinoma (adjusted OR 3.31 95% CI 1.23- 8.95). Being anaemic was also associated with thrombocytosis (adjusted OR 4.05 95% CI 1.60-10.28) (Table 2)

Table 1: Factors associated with a diagnosis of lung cancer.

Factor	Univariate odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P value (bilateral test)
Age			
<50 years	0.21 (0.09-0.51)	0.18 (0.07-0.45)	
50-59 years	0.45 (0.25-0.79)	0.44 (0.24-0.82)	
60-69 years	0.94 (0.62-1.42)	0.90 (0.58-1.40)	
70-79 years	1	1	
≥80 years	0.78 (0.48-1.34)	0.70 (0.42-1.16)	<0.001
Sex			
Female	1	1	
Male	0.74 (0.52-1.05)	0.66 (0.45-0.96)	<0.01
Platelets			
<450 x10 ⁹ /l	1	1	
≥450 x10 ⁹ /l	4.01 (2.43-6.64)	3.92 (2.37-6.39)	<0.001
Haemoglobin			
Anaemic	1.16 (0.8-1.68)	1.09 (0.66-1.59)	
Normal	1	1	
Polycythaemic	0.88 (0.3-0.45)	0.86 (0.04-8.17)	0.6
Leucocyte count			
Low	2.21 (0.87-5.63)	1.16 (0.18-7.7)	
Normal	1	1	
Elevated	2.69 (1.83-3.95)	2.33 (1.52-3.57)	<0.001
Sodium			
<135mmol/l	0.98 (0.6-1.6)	0.61 (0.35-1.07)	
135-145mmol/l	1	1	
>145mmol/l	0.52 (0.25-0.88)	0.46 (0.26-0.82)	<0.001

Table 2: Factors associated with thrombocytosis in people with lung cancer.

Factor	Univariate odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P value (bilateral test)
Age			
<50 years	5.27 (0.94-29.6)	6.4 (0.86-46.5)	
50-59 years	1.05 (0.26-4.26)	0.94 (0.22-4.14)	
60-69 years	1.54 (0.64-3.7)	1.79 (0.68-4.71)	
70-79 years	1	1	
≥80 years	1.64 (0.61-4.39)	0.94 (0.28-3.19)	0.9
Sex			
Female	1	1	
Male	0.75 (0.47-1.5)	0.45 (0.19-1.07)	0.07
Stage			
IA-IIA	1	1	
IIB-IV	2.8 (1.25-6.27)	4.25 (1.69-10.7)	
Small cell all stages	1.15 (0.29-4.62)	2.46 (0.49-12.45)	
Not staged	3.45 (0.29-41.62)	8.95 (0.50-160.5)	<0.01
Histology			
Adenocarcinoma	1	1	
Squamous cell	1.73 (0.75-4.0)	3.31 (1.23-8.95)	
Small cell	0.84 (0.22-3.33)	1	
Other	0.85 (0.17-4.3)	0.65 (0.1-4.38)	
Radiological	2.47 (0.8-7.1)	2.61 (0.71-9.62)	0.05
Haemoglobin			
Anaemic	2.48 (1.2-5.1)	4.05 (1.60-10.28)	
Normal	1	1	
Polycythaemic	1	1	<0.001

Conclusion

Thrombocytosis and leucocytosis are associated with a diagnosis of lung cancer in electively referred patients. They are unlikely to be useful as standalone tests to encourage early diagnosis in primary care, as the lung cancer incidence will be less in the population seen by GPs. However they could be incorporated into multifactorial risk prediction.

Abstract of a study presented at the East Midlands thoracic society conference
October 2016

Treatment and survival in people with advanced stage Non-small cell lung cancer: An analysis of the UK National Lung Cancer Audit

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Abstract

Introduction

This study aims to quantify treatment patterns and outcomes for people with metastatic non-small cell lung cancer presenting in England and Wales.

Methods

People with Stage IIIB and IV NSCLC first seen in 2011 were identified from the National Lung Cancer Audit (NLCA) database for England and Wales. The impact of age, sex, histology, performance status and socioeconomic status (based on the Townsend index of deprivation) on the odds of receiving systemic anti-cancer therapies (chemotherapy) were estimated and a survival analysis was performed.

Results

Of the 14,591 people identified, a total of 4,574 (31%) people received chemotherapy. There was variation in the use of chemotherapy by individual hospital trust with the median proportion of people treated in each trust being 31% (IQR 25%-37%). After adjusting for confounders, patients were less likely to receive chemotherapy with increasing age (75-79 years vs 70-74 years adjusted OR 0.62 95% CI 0.54- 0.72), highest levels of deprivation (adjusted OR 0.82 95% CI 0.71-0.95) and stage IV cancer (adjusted OR 0.66 95% CI 0.59- 0.74).

People who received chemotherapy were less likely to die than those who did not (adjusted HR 0.48 95% CI 0.46-0.50,).

Conclusion

In the UK older age and socioeconomic disadvantage are associated with lower use of chemotherapy. The use of palliative chemotherapy was associated with a lower risk of death.

Appendix C: Data sharing agreement

Data Sharing Contract



Public Health
England

Part 1: Front Sheet

ODR Reference	ODR1516_497
Title	An analysis of treatment choices and outcomes in the UK National Lung Cancer Audit - an analysis of cancer registry and linked clinical datasets

1 Parties

This Contract is made between:

1.1 Public Health England, an Executive agency of the Department of Health ("PHE"),

of Wellington House, 133-155 Waterloo Road, London SE1 8UG, United Kingdom; and

1.2 The party whose details are set out below ("**Data Recipient**"):

Name:	Prof Richard Hubbard on behalf of:
Organisation or Company (including company number if	University of Nottingham
Department	Epidemiology and Public Health
Address:	City Hospital NG5 1PB

2 Term of this Contract

2.1 This Contract shall commence on the Start Date specified in the table below and shall

continue, unless terminated earlier in accordance with the terms of this Contract (Section 13) until the End Date in the table below.

Start Date	12/07/2016	End Date	31/12/2018
Term:	As above		

3 Status of this Contract

3.1 This Data Sharing Contract (**Contract**) comprises this Part 1 (Front Sheet), Part 2

(Terms and Conditions) and Part 3 (Purpose – including objectives for processing, Special Conditions, Approved Project Documentation, Data Specification and where applicable Permitted Users). It sets out the terms on which the PHE agrees to share the Data with the Data Recipient.

3.2 The purpose of this Contract is to:

3.2.1 clarify the responsibilities and commitments of the parties in relation to the Data;

3.2.2 impose confidentiality requirements on the Data Recipient;

3.2.3 outline the data security principles and requirements with which the Data Recipient must comply

3.2.4 set out the audit rights of PHE; and

3.2.5 include arrangements for termination of this Contract.

By signing this Part 1, the parties agree to be bound by the terms of this Contract.

Signed for and on behalf of the Data Recipient:	
Organisation Name:	University of Nottingham
Signature:	G Jones
Name:	Gavin Jones
Position in organisation:	Clinical research fellow
Date:	19/7/16

Part 2: Terms and Conditions

1 Interpretation

1.1. Capitalised words and expressions used in this Contract shall bear the meanings given to them in SCHEDULE 1. The rules of interpretation set out in SCHEDULE 1 shall apply to this Contract.

2 PHE responsibilities

2.1 The PHE will transfer the Data to the Data Recipient (or, if specified in the ODR request form, the Data Processor authorised by PHE) using the data transfer method as set out in Part 3 of this contract.

2.2 PHE will be a Data Controller for the Data insofar as the Data constitutes Personal

Data.

3 Licence and Intellectual Property

3.1 PHE grants to the Data Recipient a non-exclusive, revocable licence to use the Data in the Territory for the duration of the term of this Contract solely for the Purpose and only in accordance with this Contract.

3.2 The Data Recipient shall not be entitled to sub-license the Data

3.3 Nothing in this Contract shall affect the ownership of any intellectual property rights or know-how exclusively owned by a party or existing prior to this Contract. No right or license under any intellectual property owned by the PHE or the Data Recipient is granted or implied under this Contract. The Data Recipient must acknowledge the contribution of PHE in any such publication resulting from the Data shared in this contract.

3.4 The Data Recipient shall ensure that any data processing involving Data provided by PHE must have regard for the Code of Practice on confidential information. This Contract will require the Data Recipient to have regard to the Code

3.4.1 Code of Practice on Confidential Information:

<http://systems.hscic.gov.uk/infogov/codes/cop>

3.5 The Data Recipient shall ensure that any publication derived from the Data by any party complies with the following guidance (as may be updated or superseded from time to time):

3.5.1 Anonymisation Standard for Publishing Health and Social Care Data:

<http://www.isb.nhs.uk/library/standard/128; and>

3.5.2 Anonymisation: managing data protection risk code of practice:

http://ico.org.uk/for_organisations/data_protection/topic_guides/anonymisati_on.

3.6 Where the Data derives from the Office for National Statistics, the Data Recipient must also comply with the following guidance (as may be updated or superseded from time to time):

3.6.1 ONS Guidance for Health Statistics:

<http://www.ons.gov.uk/ons/guide->

[method/best-practice/disclosure-control-of-health-statistics/index.html](http://www.ons.gov.uk/ons/guide-method/best-practice/disclosure-control-of-health-statistics/index.html); and

3.6.2 ONS policy on protecting confidentiality within birth and death statistics and

the Code of Practice for Official Statistics:

<http://www.ons.gov.uk/ons/guide-method/best-practice/disclosure-control-policy-for-birth-and-death-statistics/index.html>.

4 Data Recipient responsibilities

4.1 Where the Data Recipient obtains Data from PHE:

4.1.1 if the Data constitutes Personal Data, the Data Recipient shall hold the Data as Data Controller, unless otherwise specified in this Contract; or

4.1.2 if the Data constitutes Non-Identifiable Data, but then the Data becomes Personal Data in the hands of the Data Recipient, the Data Recipient shall be a Data Controller and shall be responsible for compliance with the DPA.

4.2 The Data Recipient shall:

4.2.1 use the Data only in accordance with the Purpose as stated in this Contract;

4.2.2 process the Data only in accordance with the terms of this Contract, including any Special Conditions contained in this Contract;

4.2.3 not share the Data with any third party without the prior written consent of PHE;

4.2.4 ensure that staff processing the Data are suitably trained and made aware of their responsibilities in handling the Data;

4.2.5 subject to Clause 13, on termination of this Contract or earlier if use of the Data is completed, permanently destroy/delete or erase the Data, together with all hard or soft copies of the same and certify such destruction to the PHE;

4.2.6 notify any Data Breach to the PHE Office for Data Release as soon as the Data Recipient discovers such Data Breach and:

(a) where the Data Recipient is obliged to complete the IG Toolkit, the Data Recipient shall assess whether a Serious Incident Requiring Investigation (as defined in the IG Toolkit) report needs to be made; or

(b) where the Data Recipient is not obliged to comply with

the IG Toolkit, the Data Recipient shall assess whether to notify the Information Commissioner's Office of the Data Breach, in accordance with the Information Commissioner's guidance on breach notification; and

4.2.7 immediately notify PHE if it no longer has a legal basis on which to process the Data.

4.3 Unless specified in the Purpose or otherwise authorised by PHE, the Data Recipient must not combine the Data with any other data held by the Data Recipient and must not use or manipulate the Data in any way that re-identifies any individual from the Data.

4.4 If the Data Recipient is obliged to respond to requests under the Freedom of Information Act 2000 (FOIA) and a request is received regarding the Data, the Data Recipient must consult with PHE prior to any release of the Data.

4.5 The Data Recipient shall comply at all times with:

4.5.1 the Data Security Requirements set out in SCHEDULE 2; and

4.5.2 the DPA (to the extent that the Data includes Personal Data or becomes Personal Data in the hands of the Data Recipient), the common law duty of confidentiality and all other Applicable Law and Department of Health directives covering issues of data sharing, including but not limited to those listed in SCHEDULE 3.

4.6 Before undertaking any publishing activity using the Data or any derived information, the Data Recipient must undertake an organisational risk assessment exercise to ensure compliance with the terms of this Contract. The Data Recipient must conduct the risk assessment in accordance with the standards set out in the Anonymisation Standard for Publishing Health and Social Care Data.

4.7 Without prejudice to its rights under Clause 13 of this Contract, PHE shall be entitled

to suspend the supply or use of Data to the Data Recipient under this Contract without incurring any liability to the Data Recipient if, in the reasonable opinion of PHE, the Data Recipient may be in breach of any of its obligations under this Contract.

5 Data protection

5.1 To the extent that any of the Data constitutes Personal Data, the Data Recipient shall

hold and process such Data at all times:

5.1.1 in accordance with the DPA; and

5.1.2 using appropriate technical and organisational security measures against

unauthorised or unlawful processing of Data and against accidental loss or destruction of, or damage to, the Data.

5.2 The Data Recipient shall not transfer Personal Data to another territory outside the European Economic Area except with the express prior written consent of PHE and only in circumstances when such transfer is permitted under, and complies with the requirements of the DPA.

5.3 Where the Data includes Personal Data, the Data Recipient shall:

5.3.1 store and process the Data securely, and permanently destroy/delete or erase it when it is no longer needed for the Purpose;

5.3.2 maintain good information governance standards and practices, meeting or exceeding the IG Toolkit standards required of its organisation type;

5.3.3 not disseminate the Data, or a subset of the Data, to any third party without prior written consent from PHE;

5.3.4 take reasonable steps to ensure the reliability of each of its Personnel who have access to the Personal Data;

5.3.5 inform PHE immediately if it receives any communication from the Information Commissioner's Office which relates to the Personal Data; and

5.3.6 ensure access to the Data is managed, auditable and restricted to those needing to process the Data.

5.4 The Data Recipient must not contact any individual that could be identified from the Data, except where the individual concerned has already consented in writing to such contact and with the prior written consent of PHE. In determining whether to grant such consent, PHE will consider if there is statutory authority to release the Data, and if doing so would be in the public interest, having regard to guidance published by the Department of Health, NHS England, PHE or Health Research Authority.

5.5 In the event of any change in data protection or other applicable laws or regulations subsequent to the date of signature of this Contract, the Data Recipient shall take such steps (including, agreeing to additional obligations and/or executing additional documents) as may be requested by P H E to ensure that the transfer to the Data Recipient, and the processing by the Data Recipient, of the Personal Data complies with such data protection laws.

5.6 The Data Recipient may only appoint a Data Processor to process the Data on behalf of the Data Recipient with the prior written consent of PHE. A Data Processor can only act on the instructions of the relevant data controller or controllers.

5.7 The Data Recipient may only amend the Data Processor with the prior written consent of PHE.

6 Confidentiality

6.1 The Data Recipient shall be responsible for any unauthorised disclosure or use of the Data made by any of its Personnel and shall take all reasonable precautions to prevent such unauthorised disclosure or use.

6.2 The confidentiality obligations contained in this Clause 6 shall continue indefinitely following termination or expiry of this Contract.

7 Audit and specific rights

7.1 PHE shall be entitled at any time during the term of this Contract to audit the Data Recipient's use of the Data (including making unannounced visits and carrying out spot checks of the Data Recipient's sites should PHE have any concerns that the terms of this Contract are not being adhered to).

7.2 PHE shall be entitled at any time during the period of twelve months after the termination or expiry of this Contract to audit the Data Recipient's compliance with the requirements of this Contract.

7.3 The Data Recipient shall, for the purpose of any audit carried out under this Clause 7, provide or procure the access to the Data Recipient's sites, systems, procedures, documents and staff as may be necessary or desirable in connection with the audit and shall permit PHE to take copies of relevant documents and data pursuant to such audit.

7.4 The Data Recipient shall provide such information as PHE reasonably requests in order to verify its compliance with the terms of this Contract.

7.5 The cost of any audit carried out under this Clause 7 shall be borne by PHE unless the audit reveals that the Data Recipient either has not complied, or is not complying, with any of its obligations under this Contract, in which case the Data Recipient shall promptly reimburse PHE for all reasonable costs of the audit.

8 Data Release Register

8.1 On release of the Data, PHE shall be entitled to publish details of Data Recipient's use of the Data in the PHE Data Release Register.

9 Warranties

9.1 The Data Recipient warrants that:

9.1.1 it has the full right and authority to enter into this Contract;

9.1.2 it shall use the Data in accordance with all Applicable Laws.

9.2 The Data is provided to the Data Recipient by PHE on an 'as is' basis and PHE does not warrant the accuracy or completeness of the Data, nor that the Data does not infringe the Intellectual Property Rights of any third party, nor does it undertake that the Data will meet the requirements of, or be fit for any purpose of, the Data Recipient.

10 Charges

10.1 In consideration of the provision of the Data by PHE, the Data Recipient agrees to pay the Charges (if any) as set in the table below

10.2 PHE operates on a cost recovery basis, where the costs of data provision under this Contract are not fully covered by those statutory duties which are covered by its central organisational funding. PHE does not seek to make an operating profit from providing services under Contract.

10.3 The following charges shall be recouped via the Service Production Fee specified in the table below;

10.3.1 all design or implementation specific services required to generate bespoke

datasets or extracts; and

10.3.2 all administration services associated with providing access to the same.

10.4	Type of Charge	Amount	Time
	NIL	NIL	NIL

The Charges set out in this Contract are payable by the Data Recipient thirty (30) days from the date of receipt of the Data (the **Due Date**).

10.5 All Charges (or appropriate portions thereof) shall be paid by the Data Recipient to PHE to its nominated bank account by the Due Date(s), in cleared funds, without withholding, set-off or deduction.

10.6 All Charges payable shall be paid in pounds (£) sterling and are exclusive of VAT, which shall be paid in addition at the appropriate rate, where VAT applies.

10.7 Where the Data Recipient fails to make payment, PHE shall be entitled (but shall not be obliged) to charge the Data Recipient interest on all sums overdue at the rate of 4% above Barclays Bank plc base rate (from time to time in force) calculated on a daily basis from the relevant Due Date until payment is made in full by the Data Recipient.

10.8 In addition to its right to charge interest on late payment as set out in Clause 10.9, and without prejudice to its other rights under this Contract, where the Data Recipient fails to make payment within a further fourteen (14) days from the first date that any sums are overdue, PHE shall be entitled (but shall not be obliged) to terminate the applicable Contract.

11 Liability

11.1 This Clause 11 sets out the entire liability of PHE to the Data Recipient arising from or in connection with this Contract, regardless of form of action and whether in contract, tort (including negligence or breach of statutory duty) or otherwise.

11.2 Subject to Clause 11.5, PHE shall in no circumstances be liable to the Data Recipient for:

11.2.1 any loss of profits, revenue, opportunity, contracts, sales, turnover,

anticipated savings, goodwill, reputation, business opportunity, production, or loss to or corruption of data (regardless of whether any of these losses or damages are direct, indirect or consequential); and

11.2.2 any indirect or consequential loss or damage whatsoever

(including where such loss or damage is of the type specified in Clause 11.2.1).

11.3 Other than any warranties expressly set out in this Contract, all warranties, conditions or other terms, whether express or implied by statute, common law, trade usage or otherwise are excluded except to the extent the exclusion is prohibited by law.

11.4 Subject to Clause 11.5, PHE's total aggregate liability for any and all claims arising under or in connection with this Contract regardless of form of action and whether in contract, tort (including negligence and breach of statutory duty) or otherwise is limited to the total Charges paid by the Data Recipient to PHE in the twelve months prior to which the event or events giving rise to liability occurred under the Contract under which the event or events giving rise to the liability occurred.

11.5 Nothing in this Contract shall limit PHE's liability to the Data Recipient for:

11.5.1 death or personal injury resulting from the negligence of PHE, its employees, agents or subcontractors;

11.5.2 fraud or fraudulent misrepresentation; or

11.5.3 any other liability that cannot be excluded or limited as a matter of law.

12 Indemnity

12.1 The Data Recipient shall indemnify PHE in full for any liabilities, losses, demands, claims, damages, amounts agreed in settlement, costs and expenses incurred which arise from or in connection with:

12.1.1 any loss of the Data by the Data Recipient;

12.1.2 unauthorised or unlawful use of the Data beyond the Purpose by the Data Recipient;

12.1.3 any breach of this Contract by the Data Recipient, whether arising in

negligence, contract or otherwise; and

12.1.4 any monetary penalty notice imposed on P H E by the Information Commissioner under Section 55 of the DPA as a result of the Data Recipient's breach of this Contract.

13 Term and termination

13.1 This Contract shall, subject to prior termination in accordance with this Clause 13, continue for the period set out in Part 1.

13.2 If the Data Recipient wishes to retain the Data beyond the expiration date of this Contract, it must contact PHE not less than one month prior to the expiration date to seek an extension to this Contract. Under no circumstances shall the Data Recipient retain the Data without an extant Contract in place which relates to that Data.

13.3 PHE may terminate this Contract by giving to the Data Recipient not less than one month's prior written notice.

13.4 On or at any time after the occurrence of an event specified in Clause 13.5, PHE shall be entitled to terminate this Contract, with immediate effect by written notice to the Data Recipient.

13.5 PHE may terminate this Contract if:

13.5.1 the Data Recipient is in material breach of this Contract and that breach cannot be remedied;

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13.5.2 the Data Recipient is in material breach of this Contract which can be remedied but the Data Recipient fails to do so within 30 days starting on the day after receipt of written notice from PHE;

13.5.3 in respect of Personal Data, the Data Recipient no longer has the legal basis to process this Data;

13.5.4 the Data Recipient stops payment of its debts or is unable to pay its debts as they fall due;

13.5.5 the Data Recipient is dissolved;

13.5.6 the Data Recipient becomes or is declared insolvent or a resolution is passed for the winding up of the Data Recipient, or the Data Recipient convenes a meeting of its creditors or makes or proposes to make any arrangement or composition with its creditors or a liquidator, an administrative receiver, a receiver, manager, trustee or administrator or analogous officer is appointed in respect of all or any part of its property, undertaking or assets, or the Data Recipient becomes subject to any bankruptcy procedure or analogous insolvency procedure in any jurisdiction, or any person files a notice of intention to appoint an administrator or a notice of appointment of an administrator or applies to court for an administration order in respect of the Data Recipient;

13.5.7 it becomes unlawful for the Data Recipient to perform all or any of its obligations under this Contract;

13.5.8 there is a change in Applicable Law which materially affects PHE's powers to provide Data to the Data Recipient; or

13.5.9 the Data Recipient (being a natural person) shall die or become mentally incapacitated.

13.6 Without prejudice to PHE's rights under Clauses 13.3 and 13.4, where the Data Recipient either (i) commits any breach of this Contract, or (ii) an event specified in Clause 13.5 occurs, PHE shall be entitled to suspend this Contract without incurring any liability to the Data Recipient, with immediate effect by written notice to the Data Recipient.

13.7 The Data Recipient may terminate this Contract at any time by notifying PHE in writing.

14 Consequences of termination

14.1 On termination or expiry of this Contract for any reason, the Data Recipient must ensure that:

14.1.1 all Data is securely and permanently destroyed/deleted or erased promptly and in any event within ten (10) working days of the date of termination or expiry of this Contract; and

14.1.2 confirmation of the secure and permanent destruction is provided to PHE in the form of a Certificate of Destruction.

15 Assignment

The Data Recipient shall not assign, novate, transfer, charge, dispose of or deal in any other manner with this Contract, or any of its rights or beneficial interests under it, or purport to do any of the same, nor sub-contract any or all of its obligations under this Contract, without the prior written consent of PHE. PHE may assign, transfer, charge, dispose of or deal in any manner with its rights and obligations under this Contract. Where it does so, PHE shall notify the Data Recipient of such change.

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16 Notices

16.1 Except where any provision of this Contract states otherwise, all notices and communications sent pursuant to this Contract shall be in writing and shall be deemed to have been duly given:

16.1.1 when delivered, if delivered by hand;

16.1.2 if sent by email, when the sender receives a reply email confirming delivery;

or

16.1.3 on the second working day after mailing, first class postage pre-paid.

16.2 Notices shall be addressed to the addresses provided in Part 1 of this Contract or to

such other address as the parties may notify in writing from time to time. Each party shall notify the other party in accordance with this Clause 16 if the address specified in Part 1 of this Contract is no longer an appropriate address for the service of notices and communications.

17 Miscellaneous

17.1 Nothing in this Contract or any arrangement contemplated by it shall constitute either party a partner, agent, fiduciary or employee of the other party.

17.2 No amendment or variation of the terms of this Contract shall be effective unless made or confirmed in writing and signed by the parties to this Contract.

17.3 If any provision of this Contract shall be found by any court or body or authority of competent jurisdiction to be invalid or unenforceable, such provision shall be severed from the remainder of this Contract which shall remain in full force and effect to the extent permitted by law.

17.4 The rights and remedies provided by this Contract are cumulative and (unless otherwise provided in this Contract) are not exclusive of any rights or remedies provided by law.

17.5 The Parties shall attempt to resolve any dispute arising from this Contract informally and promptly by officers who have day-to-day responsibility for the operation of this Contract. If the dispute cannot be resolved within 60 days of it arising, the matter shall be referred to the Chief Executive (or the corresponding individuals) of the Parties.

17.6 This Contract does not create, confer or purport to create or confer any benefit or right enforceable by any person not a party to it (except that a person who is a permitted successor to or assignee of the rights of a party to this Contract shall be deemed to be a party to this Contract).

17.7 PHE shall not be liable to the Data Recipient for any delays in performance, non-performance or breach of any of its obligations under this Contract caused by matters beyond its reasonable control. Such matters shall include (without limitation) industrial disputes, acts of God, insurrection or civil disorder, war or military operations, national or local emergency, acts of government or acts or omissions of third parties.

18 Governing law and jurisdiction

18.1 This Contract and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with English law.

18.2 Each party irrevocably agrees that, subject to Clause 18.3, the courts of England and Wales shall have exclusive jurisdiction to hear and determine any suit, action or

proceedings, and to settle any disputes or claims (including non-contractual disputes or claims) which may arise out of or in connection with this Contract, its subject matter or formation.

18.3 Nothing in this Clause 18 shall limit the right of PHE to take proceedings against the Data Recipient in any other court of competent jurisdiction, nor shall the taking of proceedings in any one or more jurisdictions preclude the taking of proceedings in any other jurisdictions, whether concurrently or not, to the extent permitted by the law of such other jurisdiction.

19 Entire agreement

19.1 This Contract constitutes the entire agreement and understanding of the parties and supersedes any previous agreement between the parties relating to the subject matter of this Contract but without prejudice to the rights and liabilities of the parties accrued before the date of this Contract.

19.2 Nothing in this Clause 19 shall operate to limit or exclude any liability for fraud.

Part 3: Purpose

20 Objectives for Processing

The Data Recipient agrees to process the Data only for the purposes agreed with PHE.

Processing Activities:

The overall aim of this proposal is to provide evidence to drive improvements in access to active treatments for people with lung cancer in the UK (including mesothelioma) and thereby to improve outcomes for these people. We plan to do this by conducting a programme of research using the National Lung Cancer Audit and additional linked clinical datasets. Questions that we will answer include:

1. What proportion of people with lung cancer receive active anti-cancer treatments including surgery with curative intent, radiotherapy and/or chemotherapy?
2. What are the individual patient and tumour level features that are associated with these treatment choices?
3. What are the trust level features that are associated with these treatment choices?
4. What is the survival of people treated with specific types chemotherapy and biological therapy for lung cancer and what patient and trust level factors influence this?
5. What is the hospital admission rate of patients treated with specific chemotherapy and biological therapy and what patient and trust level factors influence this?
6. What is the survival of people treated with surgery for lung cancer and what patient and trust level factors influence this?
7. What is the hospital admission rate of patients treated with surgery and what patient and trust level factors influence this?
8. What is the survival of people treated with radiotherapy for lung cancer and what patient and trust level factors influence this?
9. What is the hospital admission rate of patients treated with radiotherapy and what patient and trust level factors influence this?

PROTOCOL Treatment choices an			
Specific outputs expected:			
Internal meeting	☐	External meeting	☒
Internal report	☒	External report	☐
Conference	☒	Publication	☒
Other (please specify)			

21 Legal gateway

Direct care	☐
Informed patient consent	☐
Regulation 3, Health Service (Control of Patient Information) Regulations 2002	☐

Regulation 5, Health Service (Control of Patient Information) Regulations 2002	☐	CAG Reference:
Other (please specify): Regulation 2, anonymised in contract	☒	
ONS Data		
Direct care ☐	SRSA ☐	Consent ☐

22 Data specification

PHE will provide the nominated Data Recipient with pseudonymised (project specific), patient-level data in accordance with the specifications below.

Data in Table 1 will be disclosed for all patients diagnosed or treated in England, from 2005 to 2014 with lung cancer or mesothelioma, as defined by the following diagnostic codes:

1. Malignant neoplasm of trachea (C33.*)
2. Malignant neoplasm of bronchus and lung (C34.*)
3. Malignant neoplasm of thymus (C37.*)
4. Malignant neoplasm of heart, mediastinum and pleura (C38.*)
5. Malig neoplasm of sites in the resp sys and intrathorac organs (C39.*)
6. Mesothelioma (C45.*)

Table 1: LUCADA historical dataset

Pseudo ID (PATIENTID)	OrganisationProvider
Sex	
mber	TNMClassificationVNu
AgeDiagnosis	SourceReferral

Data Sharing Contract

DateDecisionRefer DateFirstSeen OrganisationFirstSeen DateReferredSpecialist
DateDiagnosis OrganisationDiagnosis PrimaryDiagnosis

Laterality

BasisDiagnosis

TStage

NStage

MStage

TCertainty NCertainty MCertainty TNMStage Histology
StagingClassification MDTDiscussion

DateMDT DateCarePlan

CarePlanIntent

CoMorbidity

DateCoMorbidity

COPD

DementiaCerebrovascular Cardiovascular

RenalFailure OtherMalignancy SevereWeightLoss OtherCoMorbidity FEV1Amount
FEV1Percentage PerformanceStatus OrganisationSurgery DateDecisionSurgery
DateSurgery PrimaryProcedure MediastinoscopyMediastinoto my

ExcisionMargin

pTStage

pNStage

pMStage

pTCertainty pNCertainty pMCertainty pTNMStage OrganisationDrug
DateDecisionDrug

DateDrug DrugTreatmentIntent ReceivePCI
OrganisationTeletherapyDateDecisionTeletherapy TeletherapyTreatmentIntent
TeletherapySite DateTeletherapy OrganisationBrachytherapy
DateDecisionBrachytherapy DateBrachytherapy OrganisationPalliativeCare
DateDecisionPalliativeCare DatePalliativeCare OrganisationMonitoring
DateDecisionMonitoring ResultDate

pHistology

pStagingClassification TrialStatus

DateDeath DeathRelatedTreatment TreatmentMorbidity ReceivedPCI
RadiotherapyTreatmentGiven ChemotherapyTreatmentGive n

TreatmentPlanType SuggestedTreatmentPlan OriginalPlanCarriedOut
PlanFailureReason ReasonNotFirstChoice CTScan

DateCTScan

PETScan

DatePETScan

Bronchoscopy

DateBronchoscopy Biopsy

DateBiopsy

CTBiopsy

DateCTBiopsy

PalliativeProviderType CommunityProviderType InterventionalTxGiven

DateInterventionalTxGiven StagingProcedure StagingMediastinoscopyMedi
astinotomy

StagingFNA

OtherStaging

UnknownStaging AssessedCNS DateAssessedCNS HowAssessedCNS

WhenAssessedCNS CNSPresentDiagnosis

Data in Tables 2 – 7 will be disclosed for all patients diagnosed or treated in England, from 1st January 2014 to 31 December 2020 as defined by the following diagnostic codes:

1. Malignant neoplasm of trachea (C33.*)
2. Malignant neoplasm of bronchus and lung (C34.*)
3. Malignant neoplasm of thymus (C37.*)
4. Malignant neoplasm of heart, mediastinum and pleura (C38.*)
5. Malignant neoplasm of sites in the respiratory systems and intrathoracic organs (C39.*)
6. Mesothelioma (C45.*)

Table 2: AV Patient

Pseudo ID (PATIENTID)

SEX

ETHNICITY

ET

HN

ICI

TY

NA

ME

VIT

AL

ST

AT
US
DEATHDATEBEST

Table 3: AV Tumour

Pseudo
ID
(PATIENTID)
Pseudo
ID
(TUMOURID)
AGE

DIAGNOSISDATEBEST
DIAGNOSISYEAR

BASISOFDIAGNOSIS
DCO

SITE_ICD10_O2

SITE_ICD10_O2_3
CHARACTER_CODING_SYSTEM

CODING_SYSTEM_DESC
MORPH_ICD10_O2
BEHAVIOUR_ICD10_O2
HISTOLOGY_CODED
HISTOLOGY_CODED_DESC

NODESEXCISED
NODESINVOLVED
LATERALITY
T_IMG
N_IMG

M_IMG
STAGE_IMG
STAGE
_IMG_S
YSTEM
T_PATH
N_PATH
M_PATH
STAGE_PATH
STAGE_PATH_SYSTEM
STAGE_PATH_PRETREATED

15

T_BEST N_BEST M_BEST STAGE_BEST STAGE_BEST_SYSTEM
EXCISIONMARGIN DATE_FIRST_EVENT TRUSTCODE_FIRST_EVENT
TRUSTNAME_FIRST_EVENT DATE_FIRST_SURGERY
TRUSTCODE_FIRST_SURGERY TRUSTNAME_FIRST_SURGERY SCN_CODE
SCN NAME

Table 4: AV Treatment

Pseudo ID (EVENTID)

Pseudo ID (TUMOUR ID)

Pseudo ID (PATIENTID) EVENTCODE EVENTDESC EVENTDATE
EVENTYEAR PROVIDERCODE PROVIDERDESC

TRUST_CODE TRUST_NAME PRACTITIONERCODE PRACTITIONERDESC
CREG_CODE WITHIN_SIX_MONTHS_FLAG SIX_MONTHS_AFTER_FLAG
OPCS4_CODE OPCS4_NAME RADIOCODE RADIODESC IMAGINGCODE
IMAGINGDESC IMAGINGSITE LESIONSIZE CHEMO DRUG

Table 6: SACT

Pseudo ID (PATIENTID)

ORGANISATION CODE (CODE OF PROVIDER)

PRIMARY DIAGNOSIS (ICD AT START SYSTEMIC ANTI-CANCER
THERAPY)

MORPHOLOGY (ICD-O AT START SYSTEMIC ANTI-CANCER
THERAPY)

ANALYSIS_GROUP

BENCHMARK_GROUP

PERFORMANCE STATUS FOR (ADULT)

PERFORMANCE STATUS CODE (YOUNG PERSON)

START DATE ANTI- CANCER DRUG REGIMEN

ANTI-CANCER DRUG CYCLE IDENTIFIER

Table 7: Radiotherapy

Pseudo ID
(PATIENTI
D) Pseudo
ID
(TUMOUR
ID)
PRIMARY
_DIAG_IC
D
APPT_DA
TE_MIN

RT_TREATMENT_MODALITY
TREATMENT_INTENT
RT_TREATMENT_REGION
ANATOMICAL_TREATMENT_SITE_RT
RT_ACTUAL_DOSE

Table 8: Core fields – Cancer Outcomes and Services Dataset

Pseudo ID (PATIENTID)

PERSON STATED GENDER CODE
ADULT COMORBIDITY EVALUATION - 27 SCORE
ANATOMICAL SIDE (IMAGING)*
BRACHYTHERAPY TYPE
CANCER CARE PLAN INTENT
CANCER IMAGING MODALITY*
CANCER OR SYMPTOMATIC BREAST REFERRAL PATIENT STATUS
CANCER TREATMENT EVENT TYPE
CANCER TREATMENT INTENT
CANCER TREATMENT MODALITY
CLINICAL NURSE SPECIALIST INDICATION CODE
CONSULTANT CODE (TREATMENT)
DATE FIRST SEEN (CANCER SPECIALIST)
DATE FIRST SEEN
DISCHARGE DATE (HOSPITAL PROVIDER SPELL)
DISCHARGE DESTINATION (HOSPITAL PROVIDER SPELL)
ETHNIC CATEGORY
HOSPITAL SITE CODE OF MULTIDISCIPLINARY TEAM MEETING
IMAGING ANATOMICAL SITE*
IMAGING CODE (NICIP)*
IMAGING CODE (SNOMED CT)*
MULTIDISCIPLINARY TEAM DISCUSSION DATE (CANCER)
MULTIDISCIPLINARY TEAM DISCUSSION INDICATOR
MULTIDISCIPLINARY TEAM MEETING TYPE
MULTIDISCIPLINARY TEAM MEETING DATE

NO CANCER TREATMENT REASON

NUMBER OF NODES POSITIVE

ORGANISATION SITE CODE (PROVIDER FIRST CANCER SPECIALIST)

ORGANISATION SITE CODE (PROVIDER FIRST SEEN)

ORGANISATION SITE CODE (PROVIDER TREATMENT START DATE (CANCER))

PERFORMANCE STATUS (ADULT)

PLANNED CANCER TREATMENT TYPE

PRIMARY PROCEDURE (OPCS)

PRIMARY PROCEDURE (SNOMED CT)

PROCEDURE (OPCS)

PROCEDURE (SNOMED CT)

PROCEDURE DATE (CANCER IMAGING)

PROCEDURE DATE

REFERRAL TO TREATMENT PERIOD START DATE

SITE CODE (OF IMAGING)

SOURCE OF REFERRAL FOR OUT-PATIENTS

TREATMENT START DATE (CANCER)

Table 9: Site specific fields – Cancer Outcomes and Services Dataset

Pseudo ID (PATIENTID)

PROCEDURE DATE (CT SCAN)

SCAN PERFORMED INDICATOR (CT)

PROCEDURE DATE (PET SCAN)

SCAN PERFORMED INDICATOR (PET)

FORCED EXPIRATORY VOLUME IN 1 SECOND (PERCENTAGE)

FORCED EXPIRATORY VOLUME IN 1 SECOND (ABSOLUTE AMOUNT)

SMOKING STATUS CODE

MEDIASTINAL SAMPLING INDICATOR

PROCEDURE DATE (BRONCHOSCOPY)

BRONCHOSCOPY PERFORMED INDICATOR

EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONAL STATUS

INVESTIGATION RESULT DATE
SERVICE REPORT IDENTIFIER
TUMOUR PROXIMITY TO CARINA
EXTENT OF ATELECTASIS
EXTENT OF PLEURAL INVASION
TUMOUR INVASION INDICATOR (PERICARDIUM)
TUMOUR INVASION INDICATOR (DIAPHRAGM)
TUMOUR INVASION INDICATOR (GREAT VESSELS)
TUMOUR INVASION INDICATOR (HEART)
MALIGNANT PLEURAL EFFUSION INDICATOR
SATELLITE TUMOUR NODULES LOCATION

23 Method of data transfer

The Data is categorised as restricted and will be transferred to the Data Recipient by PHE in accordance with the [“Guidelines on Use of Encryption to Protect Person Identifiable and Sensitive Information.”](#)

Data Transfer Procedure:

1. All Data will be encrypted to AES 256 standard
2. All Data will be transferred by electronic transfer (if possible) or removable media (if

necessary)

3. Decryption password will be communicated by alternative method to data transfer, i.e. telephone.

24 Special Conditions (legal basis, S251 renewal, consent and dissent notification,

publications restrictions, Authorship)

ONS Mortality Data

24.1 ONS mortality data, where they relate to patients referred for treatment or diagnosis of neoplasia, are released in accordance with the Health Service (Control of Patient Information) Regulations 2002 for the purposes set out in clause 20 only. The Statistics and Registration Service Act 2007 (SRSA), section 39, requires that personal information must not be disclosed by any 'person who has received the personal information directly or indirectly' from the ONS, unless directly authorised by the ONS. Disclosures of information that contravene section 39 of the SRSA will be an offence and may carry penalties, as specified in section 39(9) of the SRSA.

Authorship

24.2 In accordance with the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals¹, the Data Recipient must acknowledge intellectual, scientific and professional contribution of PHE employees through co-authorship on any publication arising from the Data;

24.2.1 Co-authorship is mandatory where any substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work is made.

24.2.2 Where contributions do not justify authorship, non-author collaborators should be acknowledged individually or together as a group under a single heading and their contributions should be specified.

24.2.3 In addition to the responsibilities determined in clause 24.2.1, for all releases of Cancer Registration data, the Data Recipient must acknowledge the role of PHE as a non-author collaborator by including:

"Data for this study is based on information collected and quality assured by the PHE National Cancer Registration and Analysis Service. Access to the data was facilitated by the PHE Office for Data Release"

Data Sharing Contract

International Committee of Medical Journal Editors, 2013.

"Applicable Law"	all laws, regulations, orders, guidance (including codes of practice and guidance issued by the Information Commissioner), directions or determinations that are applicable to the obligations of the Data Recipient under this Contract;
"Certificate of Destruction"	a certificate signed by an authorized representative of the Data Recipient or specialist third party engaged to securely destroy the Data, which certifies that the Data and all hard and soft copies thereof held by the Data Recipient have been securely and permanently destroyed;
"Charges"	the charges payable, if any, for the provision of the Data as set out in the Contract and the cost of audit where applicable;
"Data"	any data that is provided by PHE to the Data Recipient under a Contract;
"Data Breach"	a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to Data;
"Data Controller"	a data controller as defined in Section 1(1) of the DPA;
"Data Processor"	a data processor as defined in Section 1(1) of the DPA;
"Data Recipient"	A data recipient, in relation to this contract means an employee or agent of the data controller to whom the data are disclosed.
"DPA"	the Data Protection Act 1998. In the event that the DPA is superseded by another data protection law, the term "DPA" shall be construed to mean the new data protection law, and terms used in this Contract shall be given the corresponding meaning under the new data protection law;
"FOIA"	means the Freedom of Information Act 2000;

Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. ICMJE

February 2016 Version 1.6

SCHEDULE 1 Interpretation

1. In this Contract the following expressions have the following meanings:

Data Sharing Contract

"IG Toolkit"	the Department of Health's information governance toolkit, which includes the policies and standards required by the Department of Health, and which can be accessed from
"Intellectual Property Rights" or "IPR"	all intellectual property rights including copyright, database rights, trademarks and trade names, patents, topography rights, design rights, trade secrets, know-how and all rights of a similar nature or having similar effect which subsist anywhere in the world, whether or
"Non-Identifiable Data"	information that does not relate to people including information about organisations, companies, resources, projects or information about people that has been aggregated to a level that is not about individuals but that could become Personal Data when merged with other data sets held or acquired by the Data Recipient;
"Personal Data"	personal data as defined in Section 1(1) of the DPA;
"Personnel"	all employees, agents and contractors of the Data Recipient who may have access to the Data;
"process" and "processing"	have the meaning set out in section 1(1) of the DPA;
"Publish(ing)"	to make available to third parties in any form, including the production of hard copy materials, soft and/or electronic copies, e-mails and posting online;
"Purpose"	the purpose(s) for which the Data Recipient is permitted to use the Data, as set out in the relevant Contract;
"Special Conditions"	the special conditions for processing the Data as set out in the Contract; and
"Territory"	the territory specified in the relevant Contract.

2 In this Contract:

2.1 any gender includes any other gender and the singular includes the plural and vice versa;

2.2 references to persons include bodies corporate, unincorporated associations, governments, states, partnerships and trusts (in each case, whether or not having separate legal personality);

2.3 the Schedules and ODR Data Request form, form part of this Contract and the expression "this Contract" includes the Schedules and Form;

2.4 any reference to a statutory provision includes a reference to any modification, consolidation or re-enactment of the provision from time to time

in force and all subordinate instruments, orders or regulations made under it. any reference to codes of practice, policies and guidance is a reference to such codes of practice, policies and guidance as amended or extended from time to time

SCHEDULE 2

Data Security Requirements

Section A

1. Without prejudice to the Data Recipient's other obligations in respect of information security, the Data Recipient shall:

1.1 having regard to the state of technological development, provide a level of security (including appropriate technical and organisational measures) appropriate to:

1.2.1 the harm that might result from unauthorised or unlawful processing of Data or accidental loss, destruction or damage of such Data; and

1.2.2 the nature of the Data;

1.2 ensure that access to the Data is limited to those Personnel who need access to the Data to meet the Data Recipient's obligations under this Contract;

1.3 take reasonable steps to ensure the reliability of the Data Recipient's Personnel who have access to the Data which shall include:

1.3.1 ensuring all such Personnel understand the confidential nature of the Data and the issues which arise if proper care is not taken in the processing of the Data;

1.3.2 ensuring all such Personnel are properly trained in data protection and to ensure that all such Personnel have completed such training prior to their use of the Data. Where requested to do so the Data Recipient shall provide examples of training materials used, together with methodologies used to demonstrate that Personnel have understood the training. Training shall be repeated at regular intervals to take account of developments in law on good data protection practice and in any event on an annual basis; and

1.3.3 ensuring all such Personnel are properly vetted, both during the initial recruitment process and throughout their engagement in their processing of the Data, including through the use of procedures to identify changes in personal circumstances which may affect an individual's ability to process the Data in accordance with the terms of this Contract;

1.4 provide PHE with such information, assistance and co-operation as PHE may require from time to time to establish PHE's and/or the Data Recipient's compliance with the DPA;

1.5 inform PHE as soon as reasonably practicable of any particular risk to the security of the Data of which it becomes aware, and of the categories of Data and individuals which may be affected;

2 The Data Recipient shall promptly, and in any event not later than reasonably required in order to enable PHE to fulfil its duties under the Contract:

2.1 pass on to PHE any enquiries or communication (including subject access requests) relating to any Personal Data or its processing; and

2.2 provide such information as may be required for the purpose of responding to any such data subjects or otherwise to comply with its or PHE's duties under the DPA.

3 The Data Recipient shall implement and maintain security standards, facilities, controls and procedures appropriate to the nature of the Data held by it and the harm that would be caused by its loss or disclosure including a comprehensive and up-to-date data protection policy. The Data Recipient shall ensure that all its Personnel who have access to the Data shall comply with the obligations upon them contained in the data protection policy.

4 The Data Recipient shall ensure:

4.1 that it has properly configured access rights for its Personnel including a well-defined joiners and leavers process to ensure access rights to the Data are properly managed;

4.2 that it has proper controls in place to make sure that complex alphanumeric passwords are required for access to the Data and that training is provided in relation to the need to keep such passwords secure;

4.3 it has in place procedures to identify wrongful use of Data, including the monitoring of wrongful access to Data;

4.4 suitable and effective authentication processes are established and used to protect Data;

4.5 Data is backed up on a regular basis and that all back up data is subject to such vigorous security procedures as are necessary in order to protect data integrity, such security measures being commensurate to the nature of the data. The Data Recipient shall take particular care when transporting backup data and other personal information and shall ensure such backup data and other personal information is transported in a safe and secure manner;

4.6 Data transferred electronically is encrypted;

4.7 Information stored on laptops or other portable media is encrypted and that the Data Recipient maintains an accurate, up to date asset register, including all such portable media used to process the Data;

4.8 that Personnel are not able to access the Data from home or via their own electronic device other than through a secure electronic network and that Data may not be stored in such devices;

4.9 that suitable physical security measures are established commensurate to the harm that could result from the unlawful disclosure of the Data. Such physical security measures shall be as identified in the Data Recipient's data protection policy;

4.10 without prejudice to the Data Recipient's obligations to PHE in relation to the disposal of Data, all Data which is disposed of must be disposed of pursuant to the Data Recipient's policy for the disposal of Data identified in the data protection policy, including the disposal of assets containing personal data, a copy of which policy shall be provided, on request, to PHE; and

254.11 that the Data Recipient establishes and maintains adequate data security compliance policies and audits its use of personal data in compliance with its data security policies on a regular basis and in any event annually.

5 The Data Recipient shall nominate in writing an individual to take responsibility and be accountable for compliance with the DPA, and shall provide to PHE the name of that

Section B

1 Without prejudice to the Data Recipient's general obligations under this Contract, the

Data Recipient understands and accepts that:

1.1 it becomes a Data Controller for Personal Data received from PHE. As such the Data Recipient is responsible for processing the Data in accordance with the DPA and maintaining good information governance standards and practices; and

1.2 it shall be responsible for the security and protection of Non-Identifiable Data received from PHE. The Data Recipient shall process such Non- Identifiable Data in accordance with all Applicable Laws.

2 To provide assurance that good information governance practices are being maintained, the Data Recipient must demonstrate, and will allow PHE to audit, that it:

2.1. Meets or exceeds the **IG Toolkit** standards required for their organisation type
2.2. Is certified against international security standard **ISO 27001** or

2.3. Has **other assurance** in place

3 In cases where the Data Recipient does not complete an IG Toolkit assessment and where the Data Recipient is not ISO 27001 certified, in addition to the information provided in the ODR Request Form, the Data Recipient must ensure that it meets the requirements set out in paragraph 4 of this section B of Schedule 2, which PHE reserves the right to audit.

4 Where the Data Recipient has indicated that **other assurance** is in place, and without prejudice to the Data Recipient's general obligations under this Contract, the Data Recipient shall:

4.1 process Personal Data only for purposes described in this Contract, and which are consistent with the purposes recorded in the Data Recipient's data protection registration with the Information Commissioner's Office;

4.2 request and process the minimum data necessary (e.g. using age range rather than age if sufficient);

4.3 deploy secure processes, procedures, practice and technology for storage and access, commensurate with the Personal Data being processed;

4.4 ensure the rights of individuals are met, such as satisfying subject access requests received, ensuring data accuracy and correcting errors, and handling objections and complaints;

4.5 permanently destroy/delete or erase the Data once it is no longer required for the purpose for which it was collected and confirm destruction to PHE;

4.6 ensures all Personnel with access to Personal Data provide a written undertaking that they understand and will act in accordance with the DPA, will not share passwords, and will protect the confidentiality of the Personal Data;

4.7 report immediately to PHE any security incidents relating to the Data, and any instances of breach of any of the terms of this Contract; and

4.8 comply with any specific legislation in relation to the Data (such as the Statistics and Registration Services Act 2007).

SCHEDULE 3

List of relevant legislation and standards

- The Data Protection Act 1998
- British (International) Standard ISO 27001
- The Caldicott Report 1997
- Information: To share or not to share? The Information Governance Review March 2013
- The Freedom of Information Act 2000
- Section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001)
- Confidentiality: NHS Code of Practice 2003
- NHS Records Management Code of Practice (Part 1, 2006 & Part 2, 2009)
- Health and Social Care Act 2012
- The NHS Information Security Management Code of Practice 2007
- The Computer Misuse Act 1990
- The Electronic Communications Act 2000
- The Regulation of Investigatory Powers Act 2000
- The Copyright, Designs and Patents Act 1988
- The Human Rights Act 1998
- The NHS Care Record Guarantee 2011 (Version 5)
- The Social Care Record Guarantee 2009
- Anonymisation Standard for Publishing Health and Social Care Data
- Anonymisation: managing data protection risk code of practice (ICO 2012)
- A guide to confidentiality in health and social care (HSCIC 2013)
 - Code of Practice on confidential information²⁸

Appendix D: Study protocol

**An analysis of treatment choices and outcomes in the
UK
National Lung Cancer Audit - an analysis of cancer
registry
and linked clinical datasets**

Final 1.0

02/03/2016

Short title: Treatment choices and outcomes in the UK
National Lung Cancer Audit.

IRAS Project ID: **201523**

Study Sponsor: University of Nottingham

Sponsor reference: *16029*

Funding Source: University of Nottingham John Turland fund
and

Roy Castle Lung Cancer foundation

Number of participants	~460,000 people. The data we initially have access to will be from 2006/09/2015. This historical data will include ~ 340,000 people. Roughly 40,000 people are diagnosed with lung cancer in the U.K each year ^[1] . If we include these people over the 3 years our research is carried out we would expect to have data on 460,000
Eligibility criteria	People who have a diagnosis of lung cancer whose data has been logged into the national lung cancer audit database.
Description of interventions	None, this is a study of a clinical dataset
Duration of study	The project will complete in February 2020
Methods of analysis	All data management and analysis will be carried out using STATA software. We will initially perform a descriptive analysis of the population and its demographics. We will summarise people in terms of their clinical and tumour related features including ethnicity, performance status, disease stage, disease site, histological diagnosis, comorbidity and lung function. Comorbidity will be assessed using data linked from HES and a Charlson score will be calculated. We will then quantify anti-cancer treatment use and the impact of demographic, clinical and tumour features on the likelihood of receiving that treatment using multivariate logistic regression. For our analyses of outcome we will study survival and hospital admission after each of the anti-cancer treatments. We will quantify the impact of demographic, clinical, tumour and trust related features on survival using multivariate cox regression models to generate hazard ratios. In addition we will quantify the influence these variables have on early survival, defined as mortality in hospital or at 30 or 90 days after anticancer treatment using the multivariate logistical regression model. In this analysis we will consider the following as confounders and effect modifiers- age, sex, ethnicity, histological diagnosis, stage, performance status, site of cancer, comorbidity (including lung function), and trust features.

STUDY BACKGROUND INFORMATION AND RATIONALE

For several decades lung cancer has been the most common cancer in the world. In 2012 there were estimated to be 1.8 million new diagnoses worldwide^[2] 44,000 of which were cases within the United Kingdom^[1]. Lung cancer is the second most common cancer in the United Kingdom after breast cancer in terms of disease incidence, but it is by some distance the most important cause of cancer deaths in the UK. It is also a disease strongly associated with smoking and hence it is most common in people from poorer socioeconomic groups. As a result of smoking, many people also have significant smoking related comorbidities such as COPD and heart disease, and the presence of these can restrict investigations and treatment. The United Kingdom has one of the poorest survival outcomes for lung cancer in Europe. Five year survival has been estimated to be around 10%^[3]. Much of this is thought to be due to high mortality within the first year as 1 year survival is quoted to be around 30%^[3]. One explanation for this is that people present with advanced stage cancer at diagnosis. Inequalities in cancer care resources throughout the country and an increasingly elderly population also contribute to this figure. These factors combine and result in a significant burden to the National Health Service (NHS). Further research is needed in the above areas if outcomes are to improve.

The National Lung Cancer Audit (NLCA) was developed in response to the findings in the late 1990s that outcomes for lung cancer patients in the UK lag behind those in western countries, and vary considerably between hospital trusts in the UK. The NLCA began collecting data nationally in 2005, has become an exemplar of national cancer audit and currently forms part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP) managed by the Healthcare Quality Improvement Partnership (HQIP). The 2015 National lung cancer audit analysis found that only 58%^[4] of people with lung cancer received anti-cancer treatment – and this is below the national target. The last 7 years of results from the NLCA have been widely used in abstracts at national/international meetings and in peer reviewed publications in scientific journals. It has also been used at local trust level to help drive service improvement. The data help to underpin NICE guidelines and to inform research protocols, it assists in guiding national service developments. The NLCA is now a major factor in improving care for people with lung cancer in the U.K.

Treatment for lung cancer consists of surgery, chemotherapy, radiotherapy and palliative/supportive care. Surgical resection is the standard of care for treatment with curative intent in those who are fit enough because overall it offers the best chance of cure from the disease. The proportion of people with lung cancer who receive an operation varies across the UK, and these differences are not explained by patient level features such as age and performance status. Patients who are first seen at a centre that performs lung cancer surgery (around 30% of patients) are more likely to have an operation than those seen in peripheral centres^[5] although survival is equally good wherever patients are first seen suggesting that peripheral patients are missing out on potentially beneficial treatments. There is a pressing need to understand better why variations in access occur and to ensure that all patients have access to potentially curative treatment.

An operation for lung cancer surgery represents a major operation and is not without risk. We have previously shown in an analysis of the National Lung Cancer audit that 30 day mortality after surgery is 3% and 90 mortality is 6%. Over recent years

advancements have been made in surgical techniques, in particular the advent of video assisted thoroscopic surgery (VATS) for lung resections. This type of surgery offers a less invasive method of resection than open thoracotomy and has been shown to be as effective as open surgery for lung cancer survival. As the shift in surgical procedures occurs there is a pressing need to develop predictive models to help surgeons to select who might best benefit from surgery. Recent analyses [6, 7] suggest that neither of the best current scores performs well and so this is an area in need of further research. The NLCA is one of the largest and most detailed datasets currently available for such research.

Radiotherapy can also be used for treatment with curative intent. Established treatments such as Continuous Hyperfractionated Accelerated Radiotherapy (CHART) have been shown to increase survival over conventional radiotherapy^[8]. The recent advent of Stereotactic Ablative Radiotherapy (SABR) for radical treatment of early stage lung tumours has been found to be superior in reducing cancer related mortality compared with conventional radiotherapy and it has been suggested that it achieves similar outcomes to surgical resection^[9]. It is primarily used in people who decline surgery or who are not fit for surgical resection. Clinical trials are currently underway evaluating the effectiveness of SABR compared to surgery in those with an increased risk of mortality from surgery, SABRTooth (ISRCTN13029788). These treatments have limitations and further work is needed on developing novel techniques to help increase survival. At present there has been very little research on variations in access to these treatments across the UK. In addition there has been little research into early mortality after starting treatment and such data are needed to help guide treatment decisions to ensure the right person gets the right treatment.

At present the vast majority of chemotherapy for lung cancer is for palliative care rather than any attempts at curative treatment. The exception is when chemotherapy is combined with surgery and to a lesser extent when combined with radiotherapy for locally advanced disease. There has been a long established practice of using chemotherapy, sometimes in combination with radiotherapy, to treat people with small cell lung cancer and these treatments have remained unchanged for some time. People with small cell lung cancer will often respond well to treatment but the relapse rates are high although there is a considerable survival benefit compared with no active treatment. Survival for most patients is nevertheless limited to a few months. People with small cell lung cancer can often present with advanced and rapidly progressive disease and so there is a need to develop prediction models around early deaths after starting chemotherapy for small cell lung cancer to help drive treatment choices. In contrast to treatments for small cell lung cancer, chemotherapy for non-small cell lung cancer has revolutionized over recent years and is becoming increasingly more targeted and individually tailored to each patient. Genetic mutation testing for epidermal growth factor (EGFR) and anaplastic lymphoma kinase (ALK) is now common practice as targeted treatments to these mutations exist and improve progression free survival in advanced stage cancer. Targeted immunotherapies are emerging as another novel treatment strategy for lung cancer. These consist of immune checkpoint inhibitors, monoclonal antibodies and therapeutic vaccines, all of which are designed to augment an immune response to cancer cells. Some drugs such as Nivolumab and Pembrolizumab, which are PD1/PDL1 checkpoint inhibitors, were recently approved by the United States food and drug agency in 2015 for the treatment of relapsed non-small cell lung cancer. Other checkpoint inhibitors and monoclonal antibody treatments are being evaluated in phase III clinical trials around the world and are expected to be made available in the forthcoming years. These new drugs are at an early stage of use and so now is a good time to begin to quantify variations in access to these drugs and other treatments for non-small cell lung cancer and also to quantify the early mortality and later survival associated with the use of these drugs.

Unfortunately inequalities exist in the provision of lung cancer treatment in the United Kingdom^[10]. Work done by our research group has demonstrated this inequality in surgical

care for lung cancer. Patients who are first seen in thoracic centres are more likely to have surgery for appropriately staged lung cancer than those first seen in non-thoracic centres^[5]. It appears that this effect is most marked in thoracic centres with large catchment areas. This hub and spoke model for cancer care has also displayed inequalities in chemotherapy administration^[11]. In essence patients who were first seen in centres where clinical trials are undertaken were more likely to receive chemotherapy for small cell lung cancer than those who were not seen in a clinical trials centre. Palliative care provision is also varied throughout the country^[12]. Most people with lung cancer when asked say that they would prefer to die at home or in a hospice compared to an acute hospital yet it has been found that the proportion of people dying in a hospital ranged from 28% to 48% across different NHS trusts. The trust variation appeared most marked in availability of hospice care where as low as 9% and as high as 33% died in a hospice.

The aim of this programme of research is to use the National Lung Cancer Audit to help to identify variations in access to treatment for people with lung cancer and to estimate the impact that these variations may have on outcomes for people with lung cancer in the UK. To do this we will use the new lung cancer audit which is now collected as part of the Cancer registry dataset, but will also compare our results to historical data.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to provide evidence to drive improvements in access to active treatments for people with lung cancer in the U.K. Understanding these inequalities will assist with distribution of resources resulting in better access to these treatments which will improve lung cancer survival.

PRIMARY OBJECTIVE

To understand and quantify the effect that demographic, clinical, tumour and trust related factors influence distribution of anti-cancer treatment and survival following anti-cancer treatment.

SECONDARY OBJECTIVES

- ☐ Develop risk prediction model for early death following chemotherapy.
- ☐ Continue to develop a pre-existing thoracic surgical risk of death prediction model. Based on previous work done by this research group.
- ☐ Create a risk calculator for early death following radiotherapy for lung cancer.
- ☐ Investigate the long term survival for people who have received anti-cancer treatment for lung cancer.

STUDY DESIGN

STUDY CONFIGURATION

The analysis will be performed at a single centre in the University of Nottingham. The data will be extracted by the National Cancer Registry Service in the same way data is used for the National Lung Cancer Audit. The data is multi-centred and encompasses all people across all NHS trusts in the UK who have been diagnosed with lung cancer. We will analyse all the data and no randomisation will occur.

STUDY MANAGEMENT

The study will be carried out through the University of Nottingham. The Chief Investigator is Prof Richard Hubbard and he will have overall responsibility for the study and oversee all study management. Our department has completed the IG toolkit (Organisation code 8HQ47-EPH – score 100%). Date of death will be required to yield precise analysis of survival and surgical outcome. The data will be stored and backed up on a secure University server system protected by Fortigate Firewalls. The data will be accessed on a personal computer in a locked room with individual username and password login. The data will be encrypted using Bit locker set at 256 AES and will also be protected by Windows Firewall and Sophos anti-virus software. No data will be stored on laptops. Remote access to the data will be via Microsoft remote desktop protocol (RDP). To access the data remotely the researcher will use their university username and password, and access time and access IP address will be logged to a central log management service. The University of Nottingham's network is protected by dual enterprise class Fortigate 3140B firewalls. The named users of this dataset will be Dr Gavin Jones, Dr Aamir Khakwani, Prof Richard Hubbard, Dr Tricia McKeever, Dr Emma O'Dowd and Dr Paul Beckett.

The project will be managed by Dr Gavin Jones who will also be undertaking a PhD as part of this study. The PhD will be registered through the University of Nottingham and will finish in February 2020. Dr Gavin Jones will be the primary analyst of the data and author for publications. Dr Gavin Jones will attend weekly meetings with his supervisors, Prof Richard Hubbard, Prof David Baldwin and Dr Tricia McKeever. Here progress, queries and data management will be discussed.

Dr Gavin Jones will also present at a well-attended quarterly trial management meeting where our research will be discussed and presented to a regional academic audience. Patients and non-medical persons are also invited to attend on behalf of the Roy Castle lung foundation. This meeting creates discussion on the research topic areas and can generate ideas for future projects. It is chaired by Dr Johnathan Bennett (Consultant respiratory physician University Hospitals Leicester).

DURATION OF THE STUDY AND PARTICIPANT

INVOLVEMENT Study Duration:

When starting the study we will have retrospective data from January 2006 to September 2015. We will receive further data for subsequent years annually until February 2019. The study will be complete by February 2020. A year has been allowed after data acquisition has finished in order to complete further revisions to work or if further analysis of data is needed. Historical data from the National Lung Cancer Audit has been requested in order to provide comparison with more recent data.

Participant Duration:

End of the Study

The final retrospective patient data is expected to be from September 2018. This will be received for analysis in February 2019.

SELECTION AND WITHDRAWAL OF

PARTICIPANTS Recruitment

The patients recruited into our study will be those identified in the National Cancer Registry and those from historical data in the National Lung Cancer Audit. No “face to face” recruitment with patients will be carried out as part of this study.

We will analyse data on patients diagnosed with lung cancer and mesothelioma from 1st January 2006 to February 2019 as defined by the 10th edition of International Statistical Classification of Diseases and Related Health Problems (ICD10) diagnostic codes.

Eligibility criteria

Those eligible are people who have been diagnosed with lung cancer in the United Kingdom who have been coded with ICD 10 classification for lung cancer or mesothelioma. From 1st of January 2006- February 2019.

Inclusion criteria

Patients included will be those people identified in the National Cancer Registry who have been diagnosed with lung cancer or mesothelioma from January 2014- February 2019 and Patients who were previously included in the National Lung Cancer Audit data from 2006.

Exclusion criteria

All people who were not coded to have lung cancer/ mesothelioma as defined above.

All patients who have died and date of death is not recorded.

Participant Withdrawal

Participation cannot be withdrawn from this study as it is derived from national datasets. **Informed consent**

We have chosen not to seek informed consent for this study for several reasons;

Firstly before the data is provided to us by the National Cancer Registry all patient identifiable information is removed and so the data we receive is anonymised.

The second reason is that the data collected is routine hospital data. In order to gain individual patient consent to use these data we would have to consent all people

diagnosed with lung cancer at the time of their diagnosis. We do not believe this is practical or even advisable for two reasons. The first is that at present the ascertainment of data is close to 100% of cases of

lung cancer which equates to ~40,000 people a year– and this is a major strength of the data. It would be impossible for healthcare professionals to obtain informed consent for every person, particularly those who are extremely unwell or unable to consent due to their illness. If this group of people were missing from the data it would bias the data. In previous years data collection was non-mandatory and it was felt that this extra burden of seeking consent would have discouraged hospitals from taking part in the audit, which in turn would lead to an incomplete, biased dataset. This is not in the best interests of people with lung cancer or those health professionals looking after them.

The third reason is that approximately 5% of people with lung cancer have a death certificate only diagnosis of lung cancer and so cannot be consented anyway. To remove these people from the audit would represent the removal of a subset of people with poor prognosis from which there are important things to learn in improving the care for all patients with lung cancer.

STUDY REGIMEN

Criteria for terminating the study

Once we have acquired the data we plan to analyse it using STATA software. Statistical analysis will be conducted and results will be concluded based on these and published. The study will not be terminated prior to completion as we are analysing retrospective data. This is an observational study and we are not recruiting patients or administering an intervention/ drug which could cause serious harm to participants.

ANALYSES

Methods

The analysis will primarily be carried out by Dr Gavin Jones with assistance from Dr Aamir Khakwani, Dr Emma O'Dowd, Dr Paul Beckett, Dr Tricia McKeever, Prof David Baldwin and Prof Richard Hubbard. Dr Tricia McKeever will oversee any statistical analysis and ensure that the appropriate statistical analyses are applied to the data to yield accurate and truthful results. The data will be analysed using STATA software on University of Nottingham computers at the Clinical Sciences Building. These computers may also be accessed by staff via a secure Remote Desktop login. Data will be backed up 24 hours to a secure University of Nottingham server.

Our initial analyses will be descriptive to quantify how many cases of lung cancer are present and to summarise the demographic details of the cohort. We will then summarise people in terms of their clinical and tumour related features including performance status, ethnicity, disease stage, disease site, histological diagnosis, comorbidity and lung function. The comorbidity for each patient will be assessed using our established methods to calculate a Charlson Score on the basis of previous hospital admissions [7, 13].

We will then quantify the use of active anti-cancer treatments including surgery with curative intent, radiotherapy and chemotherapy. For each treatment we will quantify

the impact of demographic, clinical and tumour related features on the likelihood of receiving that treatment using multivariate logistic regression. We will then assess the impact of trust level features on this model – including whether or not the hospital first seen at was one of the 28 thoracic surgical centres and whether or not the centre was able to administer chemotherapy or radical radiotherapy. For our analyses of outcome we will study survival and hospital admission after each of the active treatments for lung cancer. We will quantify the impact of demographic, clinical, tumour and trust level features on survival in a series of multivariate Cox Regression models (proportional hazards assumptions will be checked). In addition we will quantify the influence of these variables on early survival, defined as mortality in hospital and at 30 or 90 days using a multivariate logistic regression model. For these analyses we will consider the following variables as both potential confounders and effect modifiers – age, sex, ethnicity, histological diagnosis, stage, performance status, site of cancer, comorbidity (including lung function), and trust features.

Sample size and justification

The validated^[14] dataset as used for the NLCA will be one of the largest and most detailed cancer datasets reflecting clinical care in the world. For this reason there is considerable statistical power associated with the analyses even when we are assessing subgroups of patients. When we begin we expect to have 340,000 cases of lung cancer. It is estimated based on previous years data that we should obtain data on ~40,000 cases of lung cancer every year the study is active.

Within this group of 340,000 patients we expect that approximately 34,000 people would have undergone surgery for their lung cancer. This is expected to lead to 850 deaths within 30 days and 1700 deaths within 90 days of the operation.

For the use of chemotherapy we expect the number of people with small cell lung cancer in this dataset to be approximately 34,000 and that approximately 24,000 will receive chemotherapy. This dataset will provide more than 90% power to detect a hazard ratio of 0.9 or less in relation to the use of chemotherapy. For the use of chemotherapy for advanced non-small lung cancer we expect the rates of use to be about 70% in people with good performance status and this will provide more cases than seen for small cell and hence more statistical power for the analyses. The same is likely to be true for the use of radical radiotherapy.

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

ETHICAL AND REGULATORY ASPECTS

A statement for ethical approval of this study has been submitted to the national Medical Research Ethics Committee (MREC). Our department has stored and managed large datasets in the past and has completed the IG toolkit (Organisation code 8HQ47-EPH – score 100%). In order to perform accurate analysis on survival we require date of death to be included as part of our dataset. We will not hold date of birth, NHS number, name or post-code of patients'. Without date of death we cannot accurately perform our analysis on survival. Similarly if the date of death were summarised to month and year this would also cause bias to our survival data as many patients with lung cancer present as an emergency and are diagnosed and die from lung cancer during a single brief hospital admission spanning a few days.

Our data is backed up on a secure server system at the University of Nottingham which is protected by dual enterprise class Fortigate 3140B firewalls. It is encrypted using Bit Locker set at 256 AES on a personal computer using Windows 7 enterprise, with windows firewall and Sophos anti-virus software. In the unlikely event that our data is accessed illegally it would be impossible to ascertain a patient's identity from it, the date of death. If a breach of information did occur it would be reported to the CI Richard Hubbard and escalated appropriately to the relevant departments in the University of Nottingham

We have not consented patients for this study as it is not practically possible due to the large numbers of patients involved, many of which would have died by the time the data is analysed. Consenting would also cause bias to our data as a significant amount of people diagnosed with lung cancer, particularly those in an emergency setting, are extremely unwell and are unable to consent and therefore would not be included. The data we receive is also anonymised.

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol has received approval from the Medical Research Ethics Committee (MREC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment has been reviewed and received approval from the REC and R&D departments. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

Informed consent will not be taken as part of this study as we will be analysing anonymised, retrospective, observational data. No patient identifiable information will be obtained and data is anonymised by the National Cancer Registry before it is transferred to us. Parameters such as name, Date of birth, postcode, and hospital/NHS numbers will be removed. Date of death is not classed as identifiable data and this is necessary in order to accurately analyse survival. Given the size of our dataset it would be impossible to identify a person based on their date of death. We also feel that it is not practical to consent every participant who has been enrolled in this study as:

- 1) It is routine data recorded by all U.K hospitals
- 2) The data is anonymised.
- 3) It will cause bias to the data as patients of different demographics will be missed from the dataset such as those who present extremely unwell to hospital and cannot consent.

RECORDS

Case Report Forms

We are conducting a database study and therefore we will not complete any case report forms. Any paper documents that are held relating to our study will be securely locked away in a filing cabinet which only Dr Gavin Jones and Prof Richard Hubbard will have access to via a set of keys. This will be located in the Clinical Sciences Building in a locked office which requires photographic swipe card access to gain entry the building. Any printed data held related to the dataset will be destroyed once the study is complete in February 2020. Any paper documents relating to the study protocol will be archived as per the section record retention and archiving.

Source documents

Any source document shall be filed in a locked filing cabinet and office in the Clinical Sciences Building with Professor Richard Hubbard. The building requires photographic swipe card entry. The documents stored here will include any paper records of our data, study records, notes and documents relating to study approval. Dr Gavin Jones and Prof Richard Hubbard will have direct access to these.

Direct access to source data / documents

The Dataset and documents relating to this shall be made available at all times for review by the Chief Investigator for inspection by relevant regulatory authorities.

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants data, and will adhere to the Data Protection Act, 1998. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and stored on a dedicated web server with the University of Nottingham. It is protected by dual enterprise class Fortigate 3140B firewalls. Access will be via desktop PCs and data will be encrypted using bit locker set at 256 AES. The desktop P.Cs are equipped with a windows firewall and Sophos antivirus software. These desktop PCs are stored in a locked office in the Clinical Sciences Building which requires a key and ID card access entry. Dr Gavin Jones and Prof Richard Hubbard will hold a key to this office.

Desktop P.Cs can be accessed remotely via Microsoft remote desktop protocol (RDP). To access the data remotely the researcher will use their University username and password. The access time and access IP address will be logged into a central log service and is traceable. Direct access will be restricted to Richard Hubbard, Gavin Jones, Aamir Khakwani, Emma O'Dowd and Tricia McKeever. Each shall access data via their unique user identifiers and passwords (encrypted using a one way encryption method). Data will be backed up to the University of Nottingham server every 24 hours.

The University of Nottingham has an information security policy (copy included with this application) in place which is reviewed annually. The security model for the University, in line with good practice, is one based on building multiple layers of security so that if an attack breaches or bypasses one layer of security other layers will stand in the way of further progress.

In addition, there are multiple network, operational, access and physical controls in place. The University is a member of the Joint Academic Network (JANET) which monitors network traffic across the JANET network and provides alerts about

malicious activity and assistance with security incidents. The University of Nottingham is covered by the Data Protection Act (ref Z5654762 – University of Nottingham)

The Data will be destroyed in February 2020 using either System Mechanic or Diskwipe (performs 7 complete overwrites).

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for clinical study participants and study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; adherence to data protection. Prof Richard Hubbard will hold these documents securely in a locked filing cabinet in a locked office in the Clinical Sciences Building which can only be accessed by photographic swipe card and a personal key. The department is subject to an annual systems audit and results are published.

STUDY DATA

Monitoring of study data shall include; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The overall officer responsible for data security is Prof Tony Avery who is Dean of the School of Medicine. Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief Investigator, Prof Richard Hubbard, will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected goals, for data protection or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

We aim to produce a minimum of three research papers by using this data. We aim to publish these in high quality medical journals related to lung cancer e.g. Thorax, BMJ, Lung cancer, British Journal of Cancer etc so that they can contribute to improving lung cancer care worldwide. All data is anonymised.

The studies will also be used to write a PhD thesis by Dr Gavin Jones. These published studies will not include any patient identifiable information.

Our research will also be presented at a regional steering group meeting and at national and international conferences such as the British Thoracic Society Meetings and the British Oncology Group meeting. All data presented at these events will be anonymised. Our studies may also be used and incorporated into national clinical excellence guidelines, such as NICE guidelines of the treatment of patients with lung cancer.

USER AND PUBLIC INVOLVEMENT

The study will be partly funded by Roy Castle Lung Cancer Foundation, which is a recognised charity reliant on public funding. Previous lung cancer research carried out by Dr Emma O'Dowd under the University of Nottingham has been funded by Roy Castle. Her research is freely available on the Roy castle website for patients with lung cancer to read and comment on. Our steering group meeting is also an opportunity for public input into our research programme and is attended by non- medical staff from the Roy Castle Lung Foundation.

STUDY FINANCES

Funding source

This study is funded by The University of Nottingham John Turland Fund and Roy Castle Lung Cancer Foundation.

Appendix E: Systematised Nomenclature for Medicine (SNOMED) codes and corresponding histology in the NLCA.

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SNoMed code	Description	NLCA histology category
M8010/2	Carcinoma in situ	NSCLC
M8041/3	Small cell carcinoma	SCLC
M8046/3	Non-small cell carcinoma (includes adenosquamous carcinoma)	NSCLC
M8070/3	Squamous cell carcinoma NOS	NSCLC
M8140/3	Adenocarcinoma NOS (without alveolar cell features)	NSCLC
M8250/3	Bronchio-alveolar cell carcinoma	NSCLC
M8012/3	Large cell carcinoma NOS	NSCLC
M8020/3	Large cell – undifferentiated	NSCLC
M8013/3	Large cell neuroendocrine	NSCLC
M8240/3	Carcinoid tumour NOS (includes atypical carcinoid)	Carcinoid
M8980/3	Carcinosarcoma NOS	NSCLC
M9050/3	Malignant mesothelioma NOS	Mesothelioma
M9052/3	Mesothelioma (epithelioid)	Mesothelioma
M9051/3	Mesothelioma (sarcomatoid)	Mesothelioma
M8940/3	Mixed tumour (malignant)	NSCLC
M9999/3	Other	NSCLC

Appendix F: RTDS Z codes

RTDS 4.0 – OPCS 4.6 Z & O codes recommended for Anatomical Treatment Site

Please note that the Anatomical Treatment site code is only required when the Treatment Region is coded M (metastases), A (Non-anatomical specific primary site) or O (prophylactic to non primary site).

OPCS4 Code	Description
Z01	Tissue of Brain
Z06	Spinal Cord
Z061	Cervical spinal cord
Z062	Thoracic spinal cord
Z063	Lumbar spinal cord
Z064	Meninges of spinal cord
Z15	Breast
Z19	Eye
Z20	Ear
Z22	Nose
Z246	Lung
Z247	Mediastinum
Z301	Liver
Z313	Spleen
Z41	Kidney
Z47	Skin of Face
Z48	Skin of Other Part of Head Or Neck
Z491	Skin of Breast
Z492	Skin of Axilla

Z493	Skin of Anterior Trunk
Z494	Skin of Back
Z495	Skin of Buttock
Z498	Specified Skin of Trunk Nec
Z499	Skin of Trunk Nec
Z501	Skin of Arm
Z502	Skin of Hand
Z503	Skin of Finger
Z504	Skin of Leg
Z505	Skin of Foot
Z506	Skin of Toe
Z508	Skin of Specified Site Nec
Z509	Skin Nec
Z52	Chest Wall
Z534	Peritoneal Cavity
Z611	Cervical Lymph Node
Z612	Scalene Lymph Node
Z613	Axillary Lymph Node
Z614	Mediastinal Lymph Node
Z615	Paraaortic Lymph Node
Z616	Inguinal Lymph Node
Z617	Retroperitoneal lymph node
Z618	Specified Lymph Node Nec
Z619	Lymph Node Nec
Z63	Bone of Cranium
Z64	Bone of Face
Z65	Jaw
Z661	Atlas
Z662	Axis Bone
Z663	Cervical Vertebra
Z664	Thoracic Vertebra
Z665	Lumbar Vertebra

Z668	Specified Vertebra NEC
Z669	Vertebra NEC
Z68	Bone of Shoulder Girdle
Z69	Humerus
Z70	Radius
Z71	Ulna
Z74	Rib Cage
Z75	Bone of Pelvis
Z76	Femur
Z77	Tibia
Z87	Other Part of Musculoskeletal System
Z90.2	Hip NEC
O331	Base of Skull

Appendix G: Sensitivity analysis results. Odds of receiving chemotherapy

Features of patients who had chemotherapy and the odds ratios for receiving chemotherapy									
	Total population		Had chemotherapy				Adjusted OR*	95% CI	P value (LR test)
Factor	N= 3,715	%	N=2,235 (60.2%)	%					
Sex									
Female	1,797	48.4	1,102	61.3	1		1		
Male	1,918	51.6	1,133	59.1	0.91	0.80-1.04	0.97	0.84-1.12	0.666*
Age group									
<50	104	2.8	69	66.3	1.27	0.83-1.93	1.20	0.77-1.89	
50-59	477	12.8	342	71.7	1.63	1.30-2.05	1.61	1.25-2.06	
60-69	1,211	32.6	789	65.2	1.20	1.03-1.41	1.16	0.97-1.38	
70-79	1,401	37.7	852	60.8	1		1		
≥80	522	14.1	183	35.1	0.35	0.28-0.43	0.37	0.29-0.46	<0.001‡
Townsend Quintile									
Least deprived-1	466	12.5	278	59.7	1		1		
2	659	17.8	400	60.7	1.04	0.82-1.33	1.01	0.77-1.32	
3	698	18.8	424	60.7	1.05	0.82-1.33	1.11	0.85-1.45	
4	841	22.6	509	60.5	1.04	0.82-1.31	1.02	0.79-1.32	
Most deprived- 5	1,051	28.3	624	59.4	0.99	0.79-1.23	0.92	0.71-1.18	0.568
Performance status									
0	450	12.1	334	74.2	1		1		
1	1,031	27.8	796	77.2	1.18	0.91-1.52	1.44	1.11-1.97	
2	663	17.9	421	63.5	0.60	0.46-0.79	0.85	0.64-1.13	
3	423	11.4	148	35.0	0.19	0.14-0.25	0.28	0.21-0.38	
4	117	3.2	12	10.3	0.04	0.02-0.07	0.05	0.03-0.10	
Missing	1,031	27.8	524	50.8	0.36	0.28-0.46	0.44	0.34-0.58	<0.001
Charlson comorbidity index									
0	625	16.8	445	71.2	1		1		
1	575	15.5	426	74.1	1.16	0.90-1.549	1.19	0.91-1.57	
2-3	514	13.8	330	64.2	0.73	0.56-0.93	0.86	0.65-1.14	
≥4	2,001	53.9	1,034	51.7	0.43	0.36-0.53	0.52	0.42-0.64	<0.001
Stage									
Limited	785	21.1	547	69.7	1		1		
Extensive	2,818	75.9	1,633	57.9	0.60	0.51-0.71	0.88	0.73-1.08	
Missing	112	3.0	55	49.1	0.42	0.28-0.63	0.68	0.44-1.06	0.191
Network (separate logistic regression model to other factors)									
National pooled	3,715		2,235	60.2	1		1		
N1	214	5.8	108	50.5	0.67	0.52-0.87	0.88	0.66-1.18	
N2	207	5.6	120	58.0	0.91	0.70-1.19	0.75	0.57-1.00	
N3	441	11.9	276	62.6	1.11	0.92-1.33	1.0	0.82-1.22	
N4	341	9.2	178	52.2	0.72	0.59-0.89	0.70	0.56-0.88	
N5	490	13.2	318	64.9	1.22	1.03-1.46	1.31	1.08-1.58	
N6	382	10.3	237	62.0	1.08	0.89-1.32	0.93	0.75-1.15	
N7	287	7.7	182	63.4	1.15	0.91-1.43	1.24	0.97-1.59	
N8	358	9.7	196	54.7	0.80	0.66-0.98	0.71	0.57-0.89	
N9	294	7.9	191	65.0	1.23	0.98-1.55	1.30	1.00-1.69	
N10	273	7.4	137	50.2	0.67	0.53-0.84	0.70	0.54-0.90	
N11	103	2.8	67	65.0	1.23	0.83-1.84	1.33	0.87-2.03	
N12	162	4.4	119	73.5	1.83	1.30-2.58	1.95	1.36-2.80	
N13	163	4.4	106	65.0	1.23	0.90-1.69	1.45	1.03-2.04	<0.001‡
LR= likelihood ratio test, Adjusted for all other variables ‡: LR test trend *: Wald's P value. ‡:LR test in multivariate logistic model without clustering									

Appendix H: Sensitivity analysis results. Odds of 30-day mortality

Features of patients who died within 30 days of receiving chemotherapy and odds ratios for death within 30 days							
Factor	Total 30 day deaths N=174	% who died from those who received chemotherapy	OR	95% CI	Adjusted OR	95% CI	P value (LR test)
Sex							
Female	80	7.3	1		1		
Male	94	8.3	1.16	0.85-1.58	1.12	0.81-1.55	0.491*
Age group							
<50	5	7.3	0.82	0.32-2.09	0.76	0.29-2.02	
50-59	19	5.6	0.61	0.36-1.04	0.63	0.36-1.08	
60-69	69	8.8	1		1		
70-79	73	8.6	0.98	0.69-1.38	0.88	0.61-1.26	
≥80	8	4.4	0.48	0.23-1.01	0.37	0.17-0.80	0.776‡
Townsend quintile							
Least deprived- 1	14	5.0	1		1		
2	32	8.0	1.64	0.86-3.13	1.44	0.74-2.80	
3	38	9.0	1.86	0.99-3.49	1.55	0.81-2.98	
4	41	8.1	1.65	0.88-3.09	1.53	0.80-2.91	
Most deprived- 5	49	7.9	1.61	0.87-2.96	1.57	0.83-2.98	0.667
Performance status							
0	8	2.4	1		1		
1	42	5.3	2.27	1.05-4.89	2.15	0.99-4.69	
2	43	10.2	4.64	2.15-10.00	3.75	1.71-8.25	
3-4	30	18.8	9.40	4.20-21.05	6.92	3.02-15.86	
Missing	51	9.7	4.39	2.06-9.38	4.17	1.93-9.04	<0.001
Charlson comorbidity index							
0	25	5.6	1		1		
1	19	4.5	0.78	0.43-1.45	0.72	0.38-1.36	
2-3	20	6.1	1.08	0.59-1.99	0.94	0.50-1.76	
≥4	110	10.6	2.00	1.28-3.13	1.28	0.80-2.06	0.130
Stage							
Limited	22	4.0	1		1		
Extensive	149	9.1	2.40	1.51-3.79	1.68	1.03-2.74	
Missing	3	5.5	1.38	0.40-4.75	1.12	0.31-4.04	0.057
Chemotherapy							
Carboplatin+ etoposide	130	7.8	1		1		
Cisplatin + etoposide	7	3.2	0.39	0.18-0.85	0.48	0.21-1.07	
CAV	2	10.5	1.39	0.32-6.08	1.59	0.34-7.47	
Other	5	9.1	1.18	0.46-3.01	0.93	0.35-2.49	
Single platinum	22	14.6	2.01	1.24-3.27	1.71	0.99-2.95	
Missing	8	6.3	0.79	0.38-1.66	0.84	0.38-1.82	0.141
Network (separate logistic regression model to other factors)							
Pooled networks	174	7.8	1		1		
N1	10	9.3	1.21	0.64-2.28	1.10	0.58-2.10	
N2	6	5.0	0.62	0.28-1.40	0.66	0.29-1.51	
N3	23	8.3	1.08	0.72-1.60	1.10	0.73-1.67	
N4	6	3.4	0.41	0.19-0.92	0.40	0.18-0.88	
N5	32	10.1	1.33	0.95-1.85	1.17	0.84-1.64	
N6	20	8.4	1.09	0.71-1.68	1.26	0.81-1.96	
N7	23	12.6	1.71	1.14-2.58	1.79	1.14-2.80	
N8	10	5.1	0.64	0.34-1.18	0.66	0.36-1.23	
N9	23	12.0	1.62	1.08-2.44	1.50	0.97-2.31	
N10	7	5.1	0.64	0.30-1.34	0.65	0.31-1.35	
N11	2	3.0	0.36	0.09-1.48	0.39	0.09-1.67	
N12	4	3.4	0.41	0.15-1.10	0.43	0.16-1.15	
N13	8	7.6	0.97	0.48-1.96	1.03	0.49-2.14	0.015‡
*: Wald's P value test ‡: LR test for trend †: LR test in multivariate logistic model without clustering. Adjusted OR for all other factors							

Appendix I: Table of 1-year survival for all stages of SCLC

Features of patients who received chemotherapy and survived 1-year with odds ratios for 1-year survival in all stages							
Factor	Number surviving 1-year (n=695)	% surviving 1-year from those receiving chemotherapy	OR 1-year survival	95% CI	Adjusted OR 1-year survival	95% CI	P value (LR test)
Sex							
Female	404	45.3	1		1		
Male	291	33.5	0.61	0.50-0.73	0.61	0.48-0.76	<0.01
Age group							
<60	150	45.2	0.79	0.62-1.01	1.0	0.74-1.35	
60-79	498	39.4	1		1		
≥80	47	28.3	0.48	0.32-0.72	0.74	0.45-1.21	0.53¥
Townsend quintile							
Least deprived- 1	97	44.7	1		1		
2	108	37.2	0.73	0.51-1.05	0.80	0.52-1.22	
3	142	39.1	0.79	0.57-1.12	1.02	0.68-1.53	
4	185	41.3	0.87	0.63-1.21	1.01	0.68-1.50	
Most deprived- 5	163	36.8	0.72	0.52-1.00	0.88	0.59-1.31	0.61
Performance status							
0	196	54.9	1		1	1	
1	307	44.2	0.65	0.50-0.84	0.71	0.53-0.97	
2	119	28.9	0.33	0.25-0.45	0.44	0.31-0.63	
3	24	16.7	0.16	0.10-0.27	0.29	0.17-0.51	
4	1	7.7	0.07	0.01-0.53	0.05	0.00-0.63	
Missing	48	34.3	0.43	0.29-0.64	0.46	0.29-0.75	<0.01
Charlson comorbidity index							
0	240	45.4	1		1		
1	193	52.6	1.34	1.02-1.74	1.42	1.03-1.96	
2-3	128	37.0	0.71	0.54-0.93	0.84	0.60-1.17	
≥4	134	25.8	0.42	0.32-0.54	0.75	0.55-1.01	<0.01
Stage							
Limited	381	60.7	1		1		
Extensive	286	26.2	0.23	0.19-0.29	0.30	0.23-0.39	
Missing	28	66.7	1.30	0.67-2.51	1.54	0.72-3.28	<0.01
Chemotherapy							
Carboplatin+ etoposide	530	38.4	1		1		
Cisplatin + etoposide	133	67.9	3.39	2.46-4.66	1.48	0.99-2.21	
CAV	1	20.0	0.40	0.04-3.60	0.64	0.05-8.59	
Other	11	34.4	0.84	0.40-1.76	1.40	0.61-3.24	
Single platinum	14	11.1	0.20	0.11-0.35	0.42	0.23-0.79	
Missing	6	27.3	0.60	0.23-1.55	1.06	0.33-3.41	0.02
Chemotherapy cycles received							
More than planned (mean 5 cycles)	16	53.3	0.89	0.41-1.93	0.90	0.36-2.27	
Less than planned (mean 3 cycles)	275	32.0	0.37	0.27-0.50	0.47	0.32-0.68	
4 planned and received	115	56.1	1		1		
6 planned and received	203	52.5	0.86	0.61-1.21	1.22	0.82-1.83	
Received planned amount excluding 4 & 6 cycles (mean 2 cycles)	27	28.4	0.31	0.18-0.52	0.36	0.18-0.72	
Missing planned cycles	59	32.1	0.37	0.24-0.56	0.45	0.28-0.74	<0.01
Received radiotherapy							
Did not receive radiotherapy	269	27.8	1		1		
Radical (≥40gy)	233	77.4	8.91	6.58-12.09	2.94	2.04-4.25	
Palliative (<40gy)	193	39.3	1.69	1.34-2.12	1.43	1.10-1.87	<0.01
Received PCI							
No	469	33.6	1		1		
Yes	226	61.9	3.21	2.53-4.08	2.08	1.54-2.79	<0.01
¥: LR test for trend. Adjusted OR for all other factors in table							

Appendix J: Prospero protocol

PROSPERO

International prospective register of systematic reviews



Early mortality within 30 and 90 days of receiving chemotherapy for small-cell lung cancer: a systematic review

Gavin Jones, Tricia McKeever, David Baldwin, Richard Hubbard, Kelly Elimian

Citation

Gavin Jones, Tricia McKeever, David Baldwin, Richard Hubbard, Kelly Elimian. Early mortality within 30 and 90 days of receiving chemotherapy for small-cell lung cancer: a systematic review. PROSPERO 2016 CRD42016037772 Available from:

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016037772

Review question

What proportion of people who receive chemotherapy for small-cell lung cancer die within 30 and 90 days?

How does 30 and 90 day mortality vary between chemotherapy regimen?

How does 30 and 90 day mortality vary by stage?

How does 30 and 90 day mortality vary with concurrent radiotherapy?

How does 30 and 90 day mortality vary by age or performance status?

What is the survival outcome for people treated for small cell lung cancer at 1-year, 2 years and 5 years?

What is the median survival of people treated for small cell lung cancer?

Searches

We shall use EMBASE and MEDLINE (PubMed) to search for clinical trials and observational studies that include patients who have received chemotherapy approved in accordance with European Oncology guidelines.

A search engine search as well as a review of abstracts from the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and world lung cancer meetings archives will also be carried out.

We will also conduct bibliographic searches of the included papers in this study.

Additional search strategy information can be found in the attached PDF document (link provided below).

Types of study to be included

Clinical trials comparing first-line chemotherapy treatments for adult patients, i.e. > 18 years of age, with histologically proven limited or extensive stage small cell

lung cancer. We will also include observational studies that assess survival in people who receive chemotherapy for small-cell lung cancer.

Condition or domain being studied

Small-cell lung cancer is a rapidly progressive lung cancer with an appalling prognosis if left untreated. Over three quarters of people present with extensive stage cancer at diagnosis. Chemotherapy is more readily offered to patients with small-cell lung cancer because there is a high response rate and marked improvement in overall survival for many patients. It is important, however, to accurately select patients who may benefit because those with significant comorbidity and a poor performance status may be even be harmed by chemotherapy.

Many guidelines such as those developed by NICE and the European Society for Medical Oncology suggest first line treatment for limited stage small-cell lung cancer should consist of 4-6 cycles of cisplatin or carboplatin in combination with either etoposide, irinotecan, gemcitabine or topotecan. They also state that chemotherapy can be considered in those with a performance status of 2 or more and in those with significant comorbidity.

The decision about whether to offer chemotherapy in frail patients, who are often desperate to try any form of treatment, can be difficult for oncologists to make and unfortunately there has not been sufficient scientific research to help predict and inform clinicians about which patients are likely to die early following chemotherapy.

This systematic review aims to quantify the proportion of early death, within 30 and 90 days of receiving chemotherapy as well as 1-year, 2-year, 3 year and median survival in this group of people with small-cell lung cancer in order to better inform clinicians and patients of the risks of treatment.

Participants/population

PROSPERO

Inclusion criteria:

- Phase IIb, III or IV RCTs;
- Observational studies;
- First line therapy;
- Etoposide + carboplatin;
- Etoposide + cisplatin;
- Irinotecan + cisplatin;
- Gemcitabine + cisplatin;
- Topotecan + cisplatin;
- Any combination of the abovementioned drugs with a third non-chemotherapy drug which is part of routine hospital care e.g enoxaparin, oxygen, analgesia;
- Radiotherapy combined with the above chemotherapy drugs;
- Limited-stage and extensive-stage small cell lung cancer. Exclusion

criteria:

- Phase I, IIa clinical trials;
- Systematic reviews/reviews;
- Editorials;
- Second line or maintenance therapy;
- Any chemotherapy drugs not in the inclusion criteria;
- Any combination of the included chemotherapy drugs and another chemotherapy agent;
- Any combination of approved chemotherapy with erythropoiesis stimulating drugs e. g GCSF, colony stimulating factors;
- Any combination of approved chemotherapy that also includes prophylactic antibiotics;
- Trials that include Chinese herbal medicines;
- Any trial that includes Immunotherapy treatment e.g BCG vaccine;
- Trials purely investigating radiotherapy alone or prophylactic cranial irradiation;
- Adjuvant chemotherapy (after surgery).

Intervention(s), exposure(s)

Chemotherapy for small-cell lung cancer is recommended for both limited and extensive stages. Current

guidance also states that chemotherapy can be offered to those with a performance status of 2 or more with

significant comorbidity.

The current regimens approved by the European Society of Medical Oncology are:

Etoposide+ carboplatin;

Etoposide + cisplatin;

Irinotecan + cisplatin;

Gemcitabine + cisplatin;

Topotecan + cisplatin;

For people with limited disease, chemotherapy is also combined with concurrent radiotherapy. Palliative

radiotherapy maybe considered in extensive stage too.

Context

As previously stated.

Main outcome(s)

Early mortality within 30 and 90 days of receiving chemotherapy.

Timing and effect measures

We will examine 30 and 90 day mortality after the first chemotherapy dose administration.

Additional outcome(s)

How does 30 and 90 day mortality vary by: stage, chemotherapy regimen, radiotherapy administration, age and performance status? We also aim to quantify the 1-year, 2-year 5 year and median survival in this treated group of small cell lung cancer patients.

Timing and effect measures

We will examine the mortality within 30 and 90 days of receiving the first chemotherapy dose.

Data extraction (selection and coding)

The search strategy will be applied to EMBASE and MEDLINE. A Google search as well as of previous

conference abstracts and bibliographic records will also be performed.

The titles will then be screened by two reviewers and discrepancies resolved between them. Of the selected

titles, the study abstracts will next be reviewed and any discrepancies resolved between the two reviewers.

Any article for which it is not clear from the abstract that the exclusion criteria have been met will be included

in the full manuscript review.

Finally, a full manuscript review will be carried out. Any discrepancies will be passed to a third reviewer for

final decision on inclusion.

Data will be extracted from the studies using a document created in Excel by the two reviewers.

Data extracted will broadly consist of:

Study design and recruitment strategy;

Chemotherapy given including doses and route of administration;

Radiotherapy given;

Stage of cancer;

Study population age, performance status;

Proportion of people who have died at 30 days calculated either by numerical data given or via inspection of

Kaplan-Meier overall survival plots.

Data quality will also be recorded by using an amalgamation of the Cochrane method for assessing bias as

well as the Newcastle-Ottawa score.

Data analysis will be carried out using STATA14 software. Any discrepancies will be recorded and resolved

with the involvement of a third reviewer.

Risk of bias (quality) assessment

Risk of bias across studies will be assessed using the Cochrane method of assessing bias as well as Newcastle-Ottawa scoring. Any disagreements will be recorded and resolved with the involvement of an additional reviewer.

Strategy for data synthesis

We will aggregate the data and then stratify the proportions of mortality by the different factors as previously described. This will be conducted by quantitative analysis. If possible we will compare different strata by using appropriate statistical analyses and by involving a statistician if necessary.

Analysis of subgroups or subsets

We will analyse mortality according to different factors, as mentioned earlier. If data are available on the individuals who died within 30 and 90 days, we will also perform further analyses on their characteristics, however, it is unlikely that this data will be available.

Contact details for further information

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Dr Kelly Elimian. University of Nottingham

Anticipated or actual start date

16 May 2016

Anticipated completion date

05 February 2018

Funding sources/sponsors

Sponsor: University of Nottingham, Angela Shone head of research governance. RGS16029.

Funded by: University of Nottingham John Turland fund, award number 106 and the Roy Castle Lung Foundation.

Conflicts of interest

None known

Language

English

Country

England

Stage of review

Review_Completed_not_published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Antineoplastic Agents; Antineoplastic Combined Chemotherapy Protocols; Drug-Related Side Effects and Adverse Reactions; Drug Therapy; Humans; Lung; Lung Neoplasms; Mortality; Small Cell Lung Carcinoma; Treatment Outcome

Date of registration in PROSPERO

23 November 2016

Date of publication of this version

22 November 2018

Details of any existing review of the same
topic by the same authors Stage of review
at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions

23 November 2016

17 March 2017

19 April 2017

22 November 2017

Appendix K: EMBASE and MEDLINE search strategies

EMBASE Strategy

1. exp small cell carcinoma/
2. exp small cell lung cancer/
3. exp small cell carcinoma/
4. reserve cell.mp.
5. exp lung tumor/
6. lung cancer/
7. exp bronchus tumor/
8. exp Pancoast tumor/
9. ((lung* or pulmon* or bronch*) adj3 (carcin* or cancer* or tumo?r* or neoplasm* or blastoma*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
10. ("small cell lung cancer" or "small cell lung carcinoma" or (small adj cell* adj3 (carcin* or cancer* or tumo?r* or neoplasm* or blastoma*)) or SCLC).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11. ((ls-sclc or es-sclc or ((limit* or exten*) adj stage)) adj3 (sclc or small cell)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
12. ((oat or reserve) adj cell* adj3 (carcin* or cancer* or tumo?r* or neoplasm* or blastoma*)).mp.
13. ("non small cell lung cancer*" or "nonsmall cell lung cancer*" or "nonsmallcell lung cancer*" or "non-small cell lung cancer*" or "non-small-cell lung cancer* non small cell lung carcinoma*" or "nonsmall cell lung carcinoma*" or "nonsmallcell lung carcinoma*" or "non-small cell lung carcinoma*" or "non-small-cell lung carcinoma*" or NSCLC).mp.
14. exp non small cell lung cancer/
15. 13 or 14
16. (2 or 3 or 4) and (lung* or pulmon* or bronch*).ti,ab.
17. ("non small cell lung cancer" or "nonsmall cell lung cancer" or "non small cell lung carcinoma" or "nonsmall cell lung carcinoma" or NSCLC).ti,ab.
18. 15 or 17

19. 1 or 2 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
20. 19 not 18
21. exp cyclophosphamide/ or exp carmustine/ or exp fluorouracil/ or exp cancer chemotherapy/ or exp therapy/ or exp cisplatin/ or exp antineoplastic activity/ or exp antineoplastic agent/ or exp doxorubicin/
22. exp carboplatin/
23. exp etoposide/ or exp etoposide derivative/
24. (chemotherap* or antineoplastic* or anticarcinogenic* or cisplatin or carboplatin or etoposide or (anti* adj (neoplastic* or carcinogenic*))) .ti,ab.
25. 21 or 22 or 23 or 24
26. exp mortality/
27. exp death/
28. exp progression free survival/ or exp cancer survival/ or exp cancer specific survival/ or exp short term survival/ or exp disease specific survival/ or survival/ or exp long term survival/
29. exp survival rate/
30. (mortalit* or death* or survival*) .ti,ab.
31. 26 or 27 or 28 or 29 or 30
32. exp lung metastasis/
33. metasta* .ti,ab.
34. (lung adj (metasta\$ or second\$)) .mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
35. ovarian.mp.
36. 32 or 33 or 34 or 35
37. 20 and 25 and 31 and 36
38. 20 not 36
39. 25 and 31 and 38
40. clinical trial/
41. randomized controlled trial/
42. randomization/ or randomization.mp.
43. single blind procedure/
44. double blind procedure/
45. crossover procedure/

46. placebo/
47. Randomized controlled trial\$.tw.
48. Rct.tw.
49. Random allocation.tw.
50. Randomly allocated.tw.
51. Allocated randomly.tw.
52. (allocated adj2 random).tw.
53. Single blind\$.tw.
54. Double blind\$.tw.
55. Placebo\$.tw.
56. prospective study/
57. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. Case study/
59. Case report.tw.
60. Abstract report/ or letter/
61. 58 or 59 or 60
62. 57 not 61
63. clinical study/
64. Family study/
65. Longitudinal study/
66. Retrospective study/
67. Prospective study/
68. Randomized controlled trials/
69. 67 not 68
70. cohort analysis/
71. (Cohort adj (study or studies)).mp.
72. (Case control adj (study or studies)).tw.
73. (follow up adj (study or studies)).tw.
74. (observational adj (study or studies)).tw.
75. (epidemiologic\$ adj (study or studies)).tw.

76. (cross sectional adj (study or studies)).tw.

77. 63 or 64 or 65 or 66 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76

78. "systematic review"/

79. 39 and (62 or 77 or 78)

MEDLINE search strategy

- 1 exp Small Cell Lung Carcinoma/
- 2 exp Lung Neoplasms/
- 3 exp Carcinoma, Oat Cell/ or exp Carcinoma, Small Cell/
- 4 exp bronchial neoplasms/ or exp pancoast syndrome/
- 5 ((lung* or pulmon* or bronch*) adj3 (carcin* or cancer* or tumo?r* or neoplasm* or blastoma*)).ti,ab.
- 6 ("small cell lung cancer" or "small cell lung carcinoma" or SCLC or LS-SCLC or ES-SCLC).ti,ab.
- 7 ((lung* or pulmon* or bronch*) adj3 small cell* adj3 (carcin* or cancer* or tumo?r* or neoplasm*)).ti,ab.
- 8 ((lung* or pulmon* or bronch*) adj3 oat cell* adj3 (carcin* or cancer* or tumo?r* or neoplasm*)).ti,ab.
- 9 ((lung* or pulmon* or bronch*) adj3 ((limit* or exten*) adj stage adj3 small cell*)).ti,ab.
- 10 exp Carcinoma, Non-Small-Cell Lung/
- 11 ("non small cell lung cancer" or "nonsmall cell lung cancer" or "non small cell lung carcinoma" or "nonsmall cell lung carcinoma" or NSCLC).ti,ab.
- 12 (2 or 3 or 4) and (lung* or pulmon* or bronch*).ti,ab. Limiting the more general MeSH terms for neoplasms/ small cell cancers to "lung"
- 13 1 or 5 or 6 or 7 or 8 or 9 or 12 SCLC and related text terms
- 14 13 not (10 or 11) SCLC excluding NSCLC
- 15 antineoplastic agents/ or exp anticarcinogenic agents/ or exp antineoplastic protocols/ or exp antineoplastic combined chemotherapy protocols/
- 16 exp cancer chemotherapy/ or exp chemotherapy/ or exp cisplatin/ or exp carboplatin/ or exp etoposide/
- 17 (chemotherap* or antineoplastic* or anticarcinogenic* or cisplatin or carboplatin or etoposide or (anti* adj (neoplastic* or carcinogenic*))).ti,ab.
- 18 15 or 16 or 17 Chemotherapy terms
- 19 exp Mortality/
- 20 exp Death/
- 21 exp Survival/

22 exp Survival Rate/
 23 (mortalit* or death* or survival*).ti,ab.
 24 19 or 20 or 21 or 22 or 23 Mortality terms
 25 Lung Neoplasms/sc [Secondary]
 26 exp Neoplasm Metastasis/
 27 metasta*.ti,ab.
 28 25 or 26 or 27 Metastasis terms
 29 14 not 28 SCLC (excluding NSCLC) also excluding metastasis
 30 29 and 24 and 18 SCLC and mortality and chemotherapy

Appendix L: Summary table of included studies

Summary of included studies														
Study description					Participants				Inclusion criteria			Treatments given		
Author	Year commenced	Country	Design	Quality	Age limit	Number evaluated	Median age	% Male	Life expectancy	Performance status	Stages included	Chemotherapy combination with reported survival outcome	Radiotherapy	PCI
S Abdelwahab ¹⁴⁸	2003	Egypt	Cohort	18	<75 years Not given	27	62	90.0	>3 months	0-2	Limited	Irinotecan+cisplatin	Yes	Yes
S Abdelwahab ¹⁴⁹	2012	Egypt	Cohort	14.5		30	61	93.0	Not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
S Akyurek ¹⁵⁰	1998	Turkey	Cohort	16	Any	70	55	92.9	Any/not given	0-3	Limited	Cisplatin+etoposide	Yes	Yes
M Altinbas ¹⁵¹	2001	Turkey	Cohort	14.5	Any	67	56	89.6	Any/not given	0-3	Both	Cisplatin+etoposide	Not stated	No
A Araujo ¹⁵²	2002	Portugal	Cohort	19	18-75	24	57.5	100	>3 months	0-2	Extensive	Cisplatin+etoposide	Not stated	Not stated
S Arinc ¹⁵³	1995	Turkey	Cohort	14	Any	208	56.5	91.4	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Not stated
Y Ariyoshi ¹⁵⁴	1988	Japan	Cohort	20.5	<75	59	65	83.1	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
A Artal-Cortes ¹⁵⁵	1994	Spain	RCT	19	<75	202	60	98.5	>3 months	>60	Both	Cisplatin+etoposide	Yes	Yes
H Asamoto ¹⁵⁶	1992	Japan	Cohort	15	Any	57	66	89.5	>3 months	0-2	Both	Cisplatin+etoposide	No	No
S Baka ⁵¹	1999	UK	RCT	20.5	≥18	141	65	53.0	Any/not given		Both	Platinum+etoposide	Yes	Yes
C Baldotto ¹⁵⁷	2001	Brazil	Cohort	18	Any	40	65	67.5	Any/not given	3 & 4	Both	Platinum+etoposide	Yes	No
JM Beith ¹⁵⁸	1981	Australia	RCT	13	Any	64		78.0	Any/not given	Any	Both	Cisplatin+etoposide	Yes	Yes
C Bettington ¹⁵⁹	2000	Australia	Cohort	16	Any	41			Any/not given	Any	Limited	Platinum+etoposide	Yes	Yes
J Bishop ¹⁶⁰	1987	Australia	Cohort	21.5	Any	94	62	75.0	Any/not given	<4	Both	Carboplatin+etoposide	No	Yes
C Boni ¹⁶¹	1982	Italy	Cohort	21.5	≤75	47	59	86.0	Any/not given	Any	Both	Cisplatin+etoposide	Yes	Yes
J Bonner ¹⁶²	1990	USA	RCT	11.5	Any	262		57.5	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
P Bunn ¹⁶³	1989	North America	RCT	18.5	Any	108	60	60.2	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Not stated
G Y Chen ¹⁶⁴	1997	China	Cohort	20.5	18-70	57	60	87.7	Any/not given	≥60	Limited	Cisplatin+etoposide	Yes	No
B Chewaskulyong ¹⁶⁵	1998	Thailand	Cohort	16.5	Any	19	59	78.2	Any/not given	≥50	Both	Cisplatin+etoposide	Yes	Yes
Su-hee Cho ¹⁶⁶	2010	S Korea	Cohort	21	Any	36	66	70.0	Any/not given	0-3	Extensive	Cisplatin+etoposide	Not stated	Not stated

M Colbeck ¹⁶⁷	1997	Australia	Cohort	7.5	Not given	168		55.0	Any/not given		Both	Carboplatin+etoposide	Not stated	Not stated
S Cuffe ¹⁶⁸	1999	USA and Canada	Cohort	14	>50	10	66	30.0	Any/not given	Any	Both	Platinum+etoposide/irinotecan	Yes	Yes
D De Ruyscher ¹⁶⁹	2002	Netherlands	Cohort	19	≥18	27	62	67.0	Any/not given	0-1	Limited	Carboplatin+etoposide	Yes	Yes
J Dimitroulis ¹⁷⁰	2003	Greece	RCT	16	>18	55	63	83.6	>3 months	0-2	Both	Cisplatin+etoposide	Not stated	Not stated
J R Eckardt ¹⁷¹	2001	International	RCT	18	>18	784	59.7	79.0	>3 months	0-2	Both	Topotecan+cisplatin Cisplatin+etoposide	Not stated	Not stated
L Einhorn ¹⁷²	1989	USA	RCT	17.5	Any	82	61	68.0	Any/not given	50-100	Extensive	Cisplatin+etoposide	Not stated	Not stated
P M Ellis ¹⁷³	1996	Australia	Cohort	15	Any	103	64.7	56.0	Any/not given		Both	Carboplatin+etoposide	Yes	Yes
W K Evans ¹⁷⁴	1981	Canada	Cohort	19.5	Any	31	61	77.4	Any/not given	0-3	Both	Cisplatin+etoposide	Yes	Yes
W K Evans ¹⁷⁵	1985	Canada	Cohort	20	<80	32	66	73.5	Any/not given	0-2	Extensive	Carboplatin+etoposide	Not stated	Yes
W K Evans ¹⁷⁶	1988	Canada	Cohort	20.5	>65	47	69	53.0	Other	0-2	Both	Carboplatin+etoposide	Yes	Yes
C Faivre-Finn ⁷⁴	2008	International	RCT	20	≥18	547	62	54.5	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
C Faivre-Finn ¹⁷⁷	2011	UK	Cohort	16	Any	76	61	66.0	Any/not given	0-1	Limited	Cisplatin+etoposide	Yes	Not stated
F Figoli ¹⁷⁸	1984	Italy	Cohort	15.5	<75	51	62	84.6	Any/not given	>40	Both	Cisplatin+etoposide	Yes	Yes
T Fink ¹⁷⁹	2002	Germany and Austria	RCT	17	18-75	680	61.3	68.4	Any/not given	0-2	Extensive	Topotecan+cisplatin Cisplatin+etoposide	Not stated	Not stated
M Fukuda ¹⁸⁰	2000	Japan	Cohort	17	<75 years	34	67	85.0	12 weeks	0-1	Limited	Irinotecan+cisplatin	Yes	Yes
M Fukuoka ¹⁸¹	1985	Japan	RCT	20.5	<75	97	64	80.0	Any/not given	0-3	Both	Cisplatin+etoposide	No	No
M Giuliani ¹⁸²	1997	Canada	Cohort	15.5	Any	227		57.0	Any/not given		Limited	Platinum+etoposide	Yes	Yes
F Greco ¹⁸³	1992	USA	RCT	16.5	Any	60	62.1	63.0	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Not stated
I B Ha ¹⁸⁴	2006	Korea	Cohort	18.5	Any	31	65	93.5	Any/not given	0-1	Limited	Platinum+etoposide	Yes	Yes
J Hainsworth ¹⁸⁵	1992	International	RCT	19.5	Not given	60	62.1	63.0	>12 weeks	0-2	Both	Cisplatin+etoposide	Yes	Not stated
J Y Han ¹⁸⁶	2003	Korea	RCT	19	>18	120	63	89.0	Any/not given	0-2	Extensive	Irinotecan+cisplatin	No	No
D Han ¹⁸⁷	2009	China	Cohort	19.5	<75	35	54	74.0	>6months	0-2	Limited	Cisplatin+etoposide	Yes	Yes
J Y Han ¹⁸⁸	2001	Korea	Cohort	20.5	>18	35	63	94.0	Any/not given	0-2	Limited	Platinum+etoposide/irinotecan	Yes	Yes

J Y Han ¹⁸⁹	2001	Korea	Cohort	21	>18	37	62	78.0	Any/not given	0-3	Extensive	Irinotecan+cisplatin	Not stated	Not stated
J Y Han ¹⁹⁰	2006	Korea	Cohort	20	>18	61	65	92.0	Any/not given	0-2	Extensive	Irinotecan+cisplatin	Not stated	Not stated
T J Han ¹⁹¹	2004	Korea	Cohort	18	Any	80	62	83.9	Any/not given	0-2	Limited	Carboplatin+etoposide	Yes	Yes
N Hanna ¹⁹²	2000	International	RCT	19.5	Any	331	62	57.4	Any/not given	0-2	Extensive	Irinotecan+cisplatin Cisplatin+etoposide	Not stated	Not stated
YS Hong ¹⁹³	2002	Korea	Cohort	23	≥18	54	64	90.7	Any/not given	0-3	Extensive	Irinotecan+cisplatin	Not stated	Not stated
X Hu ¹⁹⁴	2002	china	RCT	18	18-75	85	56	82.4	Any/not given	≥80	Limited	Cisplatin+etoposide	Yes	Yes
A Hugli ¹⁹⁵	1993	European	Cohort	22	<70	52	54	79.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
S Hwa Bae ¹⁹⁶	2003	S Korea	RCT	17	<80	30	65	85.7	>3 months	0-2	Extensive	Irinotecan+cisplatin	No	No
A Inal ¹⁹⁸	2001	Turkey	Cohort	18	Any	161	57	90.7	Any/not given	0-3	Both	Cisplatin+etoposide	Not stated	Not stated
C Jara ¹⁹⁹	1993	Spain	Cohort	12.5	Any	95		95.0	Any/not given	Any	Both	Platinum+etoposide	Yes	No
H C Jeong ²⁰⁰	2002	S Korea	Cohort	21	≥18	20	64	80.0	≥3 months	0-2	Limited	Irinotecan+cisplatin	Yes	Yes
B Jeremic ²⁰¹	1988	Yugoslavia	RCT	20.5	<70	103	59	60.1	Any/not given	>50	Limited	Platinum+etoposide	Yes	Yes
B Jeremic ²⁰²	1997	Yugoslavia/ Serbia	Cohort	19.5	≥70	72	73	62.5	Any/not given	≥60	Limited	Carboplatin+etoposide	Yes	No
S Jezdic ²⁰³	1995	Serbia and Montenegro	RCT	11	Not given	101			Any/not given		Both	Cisplatin+etoposide Carboplatin+etoposide	Not stated	Not stated
D Johnson ²⁰⁴	1986	USA	RCT	18.5	Any	83	62.5	79.5	Any/not given	0-2	Both	Cisplatin+etoposide	Not stated	Yes
D Johnson ²⁰⁵	1987	USA	Cohort	19.5	Any	34	61	55.9	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
S Kaasa ²⁰⁶	2015		RCT	11.5	Not given	157	63	52.0	Not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
M H Kang ²⁰⁷	2006	Korea/USA	Cohort	14.5	Any	187		86.6	Any/not given	0-3	Both	Platinum+etoposide/irinotecan	Yes	Yes
I Karam ²⁰⁸	2004	Canada	Cohort	15.5	Any	536	72.5	46.4	Any/not given	Any	Both	Cisplatin+etoposide Carboplatin+etoposide	Yes	Yes
S Karger ²⁰⁹	2003	Korea	Cohort	19.5	≥18	28	63.5	78.6	Any/not given	0-2	Extensive	Irinotecan+cisplatin	Not stated	Not stated
M Kelley ²¹⁰	2003	USA	Cohort	21	≥18	75	61	56.0	Any/not given	0-2	Limited	Platinum+etoposide/irinotecan	Yes	Yes
Hoon Gu Kim ²¹¹	2003	Korea	Cohort	21	≥65	46	70	80.4	Any/not given	0-3	Extensive	Irinotecan+cisplatin	Not stated	Not stated
R Komaki ²¹²	2003	USA and Canada	Cohort	19	≥18	71	63	48.0	Any/not given	0-1	Limited	Cisplatin+etoposide	Yes	Yes

K Kubota ²¹³	1999	Japan	Cohort	20.5	<75	30	64	90.0	Any/not given	0-2	Limited	Platinum+etoposide/irinotecan	Yes	Yes
K Kubota ²¹⁴	2002	Japan	RCT	19	20-70	258	61	81.0	Any/not given	0-1	Limited	Platinum+etoposide/irinotecan	Yes	Yes
S Kudoh ²¹⁵	1992	Japan	Cohort	22	≤75	75	64	77.3	>3 months	0-2	Both	Irinotecan+cisplatin	Yes	Yes
C Langer ²¹⁶	2014	International	RCT	21	≥18	82	62	61.0	Any/not given	0-2	Extensive	Carboplatin+etoposide	Not stated	Yes
P Lara ²¹⁷	2002	USA	RCT	18	Any	651	63	56.5	>3 months	0-1	Extensive	Cisplatin+etoposide Irinotecan+cisplatin	Not stated	Not stated
S Larive ²¹⁸	1994	France	Cohort	21.5	≥70	34	73.7	88.0	Any/not given	0-2	Both	Carboplatin+etoposide	Yes	No
C Laura ²¹⁹	1992	USA	Cohort	14	>65	4337	73	51.2	Any/not given		Both	Platinum+etoposide	Yes	Yes
A B Law ²²⁰	2001	UK	Cohort	16.5	Any	66	65	41.1	Any/not given	0-2	Limited	Platinum+etoposide	Yes	Yes
Y J Lee ²²¹	2003	Korea	Cohort	13	Any	76	56	87.0	Any/not given	0-2	Both	Platinum+etoposide/irinotecan	Yes	Yes
J E Lee ²²²	2002	Korea	Cohort	15	≥18	19	62	100	Any/not given	0-2	Limited	Irinotecan+cisplatin	Yes	Yes
J Lee ²²³	2009	Korea	Cohort	17	Any	47	68	89.4	Any/not given	0-2	Limited	Platinum+etoposide	Yes	Yes
J Lee ²²⁴	2005	Korea	Cohort	19.5	Any	41	63	90.2	Any/not given	Any	Limited	Cisplatin+etoposide	Yes	Not stated
S H Lee ²²⁵	1998	S Korea	Cohort	21	Any	44	60	82.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
SM Lee ⁶⁵	2003	UK	RCT	21.5	>18	359	65	56.0	>8 weeks	0-3	Both	Carboplatin+etoposide	Yes	Yes
C Li ²²⁶	2004	China	Cohort	22	≥18	29	55	82.8	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
S Liu ²²⁷	2004	China	Cohort	14.5	≥65	247	70	81.4	Any/not given	<80 ≥80	Both	Platinum+etoposide	Yes	Yes
W Liu ²²⁸	2005	China	Cohort	17.5	18-80	445	59	76.0	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Yes
P Loehrer ²²⁹	1989	USA	RCT	20.5	Any	84	61	67.9	Any/not given	≥50	Extensive	Cisplatin+etoposide	Not stated	Not stated
S Luikart ²³⁰	1993	USA Canada	Cohort	16.5	Any	51			>2 months	0-2	Extensive	Carboplatin+etoposide	Not stated	Yes
K Matsui ²³¹	1992	Japan	Cohort	17.5	≥70	38	78	79.0	Any/not given	0-3	Both	Carboplatin+etoposide	Yes	Not stated
D Mavroudis ²³²	1997	Greece	RCT	18.5	18-75	71	64	90.0	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Yes
E Mclay ²³³	1993	USA	RCT	19	≥18	154	62.5	55.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
A Miller ²³⁴	1990	USA	RCT	17	≥16	306		68.9	>2 months	0-2	Extensive	Cisplatin+etoposide	No	Yes

H Minami ²³⁵	1991	Japan	Cohort	19.5	<80	74		82.4	Any/not given	0-2	Both	Carboplatin+etoposide	Yes	Not stated
Y Minegishi ²³⁶	2002	Japan	Cohort	20.5	Any	17	69	82.0	>3 months	0-2	Both	Carboplatin+etoposide	Not stated	Not stated
E Mitchell ²³⁷	1986	USA Canada	Cohort	16	Not given	35			≥2 months	0-2	Extensive	Cisplatin+etoposide	Not stated	Yes
H Miyamoto ²³⁸	1986	Japan	RCT	18.5	<79	42	63	76.0	Any/not given	0-3	Both	Cisplatin+etoposide	Yes	Not stated
K Mori ²³⁹	1987	Japan	Cohort	20.5	≤79	39	61.2	89.7	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Yes
P Murphy ²⁴⁰	1989	USA	Cohort	23.5	Any	22	56	68.2	Any/not given	0-2	Extensive	Cisplatin+etoposide	Not stated	Yes
A Naidu ²⁴¹	2006	USA	Cohort	10.5	Not given	36			Any/not given	Not given	Limited	Irinotecan+cisplatin	Yes	Yes
H Niell ²⁴²	1998	USA	RCT	20	≥18	282	62	46.0	>6 weeks	0-2	Extensive	Cisplatin+etoposide	Not stated	Not stated
K Noda ²⁴³	1995	Japan	RCT	22	≤70	154	52	85.7	>3 months	0-2	Extensive	Cisplatin+etoposide Irinotecan+cisplatin	Yes	Not stated
H Okamoto ²⁴⁴	1995	Japan	Cohort	20.5	≥70	36	73	88.9	≥2 months	0-2	Both	Carboplatin+etoposide	Yes	Not stated
K Okamoto ²⁴⁵	2003	Japan	Cohort	17	≥70	12	72.5	67.0	Any/not given	0-1	Limited	Cisplatin+etoposide	Yes	Yes
M Oset ²⁴⁶	1993	Spain	Cohort	20	<75	23	59	96.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
A Pereira ²⁴⁷	2002	Brazil	Cohort	8.5	Not given	40			Any/not given	0-1	Extensive	Cisplatin+etoposide	Not stated	Not stated
P Pfeiffer ²⁴⁸	1988	Denmark	Cohort	23.5	<70	106	60	67.9	Any/not given	0-4	Both	Carboplatin+etoposide	Yes	No
J L Pujol ²⁴⁹	1996	France	RCT	19.5	<75	109	59.3	77.1	Any/not given	0-2	Extensive	Cisplatin+etoposide	Yes	Yes
E Quoix ²⁵⁰	1997	France	Cohort	21.5	>70	38	75	78.9	>3 months	0-2	Both	Carboplatin+etoposide	Not stated	Not stated
E Quoix ²⁵¹	2004	International	RCT	14.5	≥18	41	61	70.7	>3 months	0-2	Extensive	Topotecan+cisplatin	Not stated	Not stated
B Reymen ²⁵²	2004	Netherlands	Cohort	16	Any	119	66	58.0	Any/not given	0-2	Limited	Carboplatin+etoposide	Yes	Yes
B Roth ²⁵³	1985	USA	RCT	19	≥18	148	62.2	83.1	Any/not given	0-3	Extensive	Cisplatin+etoposide	Not stated	Not stated
K Rowland ²⁵⁴	1990	North America	RCT	17.5	Any	121		52.9	Any/not given	0-2	Extensive	Cisplatin+etoposide	Yes	Yes
C Rudin ²⁵⁵	2008	USA	RCT	21	>18	15	66	40.0	Any/not given	0-2	Extensive	Carboplatin+etoposide	Not stated	Not stated
A Ruiz-Valdpenas ²⁵⁶	2003	Spain	Cohort	10.5	Not given	96			Any/not given	Not given	Both	Cisplatin+etoposide Carboplatin+etoposide	Not stated	Not stated

E Samantas ²⁵⁷	1992	Greece	Cohort	19.5	Any	60	66	97.0	Any/not given	≥2	Both	Carboplatin+etoposide	Yes	Yes
S Schild ²⁵⁸	1996	USA	Cohort	19.5	Any	76	63	51.3	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
S Schild ²⁵⁹	1990	USA/Canada	RCT	13	Any	263	61	57.4	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
J Schiller ²⁶⁰	1995	USA	RCT	19	≥18	402	63	64.0	Any/not given	0-2	Extensive	Cisplatin+etoposide	Not stated	Not stated
J Schiller ²⁶¹	1994	USA	Cohort	14.5	Any	34	61	77.0	Any/not given	0-2	Extensive	Cisplatin+etoposide	Not stated	Yes
A Schmittl ²⁶²	2002	Germany	RCT	15	Any	110	63	65.0	>3 months	≥50	Extensive	Carboplatin+etoposide	Not stated	Yes
J P Sculier ²⁶³	1993	European	RCT	18	≤75	204	59	80.1	Any/not given	≥60	Limited	Cisplatin+etoposide	Yes	No
Y Segawa ²⁶⁴	1995	Japan	Cohort	18.5	≤75	37	66	94.6	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
U Seifart ²⁶⁵	1999	Germany	RCT	19.5	18-72	84	61	79.8	>2 months	>70	Extensive	Topotecan+cisplatin	Not stated	Not stated
I Sekine ²⁶⁶	2003	Japan	RCT	18.5	20-70	54	63	79.6	>3 months	0-2	Extensive	Irinotecan+cisplatin	Not stated	Not stated
I Sekine ²⁶⁷	2006	Japan	RCT	17	≥70	30	75	80.0	≥2 months	0-2	Extensive	Carboplatin+etoposide	Not stated	Yes
Y Shi ²⁶⁸	2010	China	RCT	18.5	18-70	62	57	75.8	>3 months	0-2	Extensive	Cisplatin+etoposide Irinotecan+cisplatin	Not stated	Not stated
T Shimizu ²⁶⁹	1998	Japan	Cohort	16.5	≥75	7	78	71.4	Any/not given	0-1	Limited	Platinum+etoposide	Yes	Yes
T Shukuya ²⁷⁰	2002	Japan	Cohort	17.5	≥75	20	78	75.0	Any/not given	0-2	Limited	Platinum+etoposide Carboplatin+etoposide	Yes	Yes
D V Skarlos ²⁷¹	1993	Greece	RCT	20	≥18	81	61	91.6	Any/not given	0-2	Limited	Carboplatin+etoposide	Yes	Yes
D V Skarlos ²⁷²	1987	Greece	RCT	20.5	<75	143	60	93.0	Any/not given	0-2	Both	Cisplatin+etoposide Carboplatin+etoposide	Yes	Yes
I E Smith ²⁷³	1984	UK	Cohort	18.5	Any	52	62	80.8	Any/not given	0-3	Both	Carboplatin+etoposide	No	No
M Socinski ²⁷⁴	2006	International	RCT	15	>18	455	62.6	73.0	Any/not given	0-2	Extensive	Carboplatin+etoposide	Not stated	Not stated
J Sohn ²⁷⁵	2002	Korea	Cohort	19	>18	33	60	84.8	Any/not given	0-2	Limited	Irinotecan+cisplatin	Yes	Yes
M Sorensen ²⁷⁶	2001	Denmark	Cohort	24	18-75	43	59	62.8	Any/not given	0-2	Extensive	Topotecan+cisplatin	Not stated	Not stated
Y Sun ²⁷⁷		China	RCT	10	>18	150	57.45	75.3	Any/not given	0-1	Extensive	Cisplatin+etoposide	Not stated	No
J M Sun ²⁷⁸	2003	S Korea	RCT	19	Any	219	60	88.6	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
Y Sun ²⁷⁹	2008	China	RCT	19	>18	150	59	75.3	>3 months	0-1	Extensive	Cisplatin+etoposide	Not stated	Yes

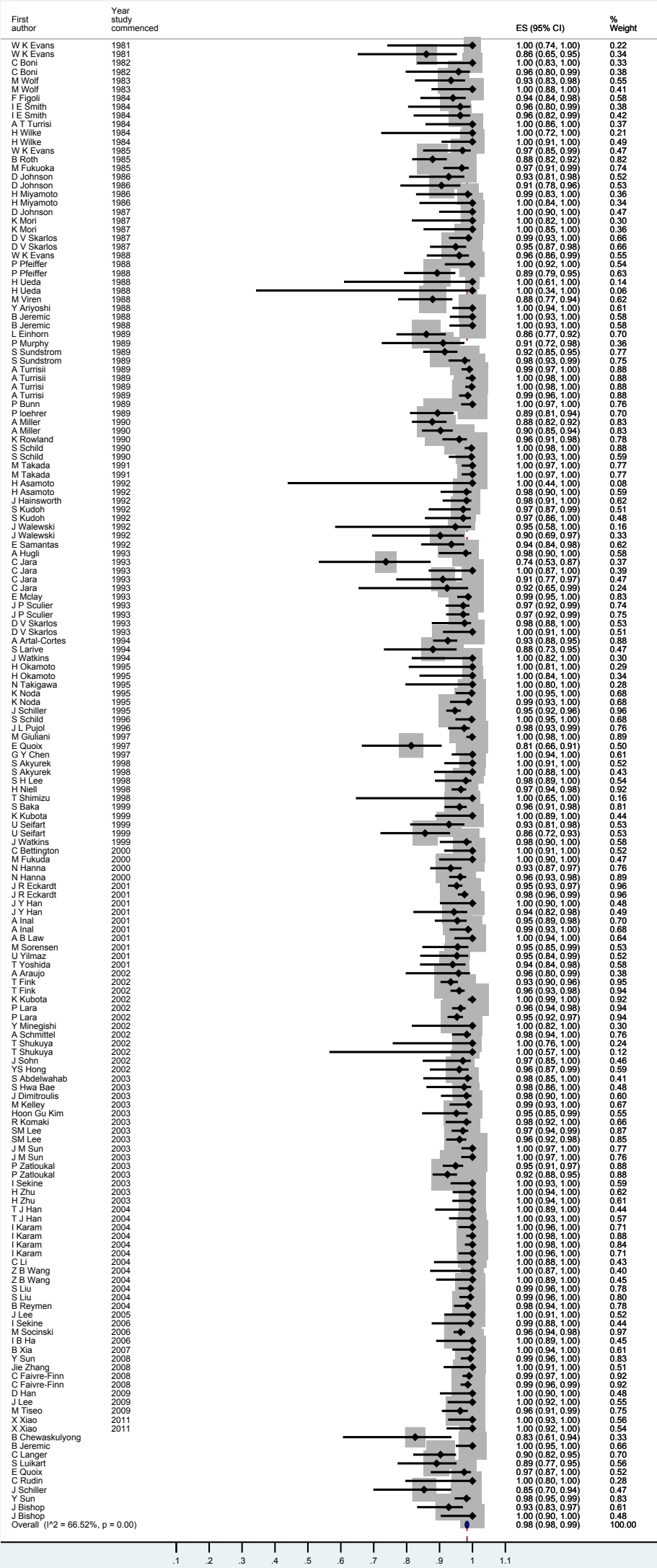
S Sundstrom ²⁸⁰	1989	Norway	RCT	18.5	18-75	218	64	66.0	Any/not given	0-2	Both	Cisplatin+etoposide	Yes	Yes
M Takada ²⁸¹	1991	Japan	RCT	17	<75	228	65	81.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
N Takigawa ²⁸²	1995	Japan	Cohort	20.5	≤75	15	61	93.0	Any/not given	0-2	Extensive	Irinotecan+cisplatin	Not stated	Not stated
T Terashima ²⁸³	2000	Japan	Cohort	18.5	Any	95	67	79.0	Any/not given	0-2	Extensive	Irinotecan+cisplatin Cisplatin+etoposide Carboplatin+etoposide	Not stated	Not stated
K Thammakumpee ²⁸⁴	1999	Thailand	Cohort	16.5	Any	61			Any/not given		Both	Cisplatin+etoposide	Yes	Not stated
M Tiseo ²⁸⁵	2009	Italy	RCT	20	≥18	103	63	68.0	>12 weeks	0-2	Extensive	Cisplatin+etoposide	No	Yes
A T Turrisi ²⁸⁶	1984	USA	Cohort	16	Any	23	56	52.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
A Turrisi ⁷³	1989	USA	RCT	16.5	Any	417	61	58.5	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
H Ueda ²⁸⁷	1988	Japan	Cohort	16.5	>80	8	82	62.5	Any/not given	Any	Both	Carboplatin+etoposide	Not stated	Not stated
B Valladeres ²⁸⁸	2004	Spain	Cohort	12	Not given	44	62	82.0	Any/not given		Limited	Cisplatin+etoposide	Yes	Yes
J Van Loon ²⁸⁹	2004	Netherlands	Cohort	17	≥18	60	66	66.7	Any/not given	0-2	Limited	Carboplatin+etoposide	Yes	Yes
M Veslemes ¹³⁵	1998	Greece	RCT	17.5	≤76	69	59	94.2	Any/not given	0-3	Both	Cisplatin+etoposide	Yes	No
M Viren ²⁹⁰	1988	Finland	Cohort	22	≤75	61	62	84.0	Any/not given	0-2	Extensive	Carboplatin+etoposide	Not stated	Not stated
J Walewski ²⁹¹	1992	Poland	Cohort	19.5	<75	26		69.0	Any/not given	>50	Both	Cisplatin+etoposide	Yes	No
Z B Wang ²⁹²	2004	China	Cohort	18	Any	57		80.7	Any/not given	1-4	Both	Cisplatin+etoposide	Yes	Yes
J Watkins ²⁹³	1994	USA	Cohort	16.5	Any	17	59	58.8	Any/not given		Limited	Platinum+etoposide	Yes	Yes
J Watkins ²⁹⁴	1999	USA	Cohort	15	Any	52	52	62.0	Any/not given		Limited	Platinum+etoposide	Yes	Yes
H Wilke ²⁹⁵	1984	Germany	Cohort	10.5	≤70	47	58	89.4	Any/not given	≥40	Both	Cisplatin+etoposide	Yes	Yes
M Wolf ²⁹⁶	1983	Germany	RCT	19.5	<70	73	57	89.0	Any/not given	>50	Both	Cisplatin+etoposide	Yes	Yes
B Xia ²⁹⁷	2007	China	Cohort	15	>18	59	58	86.0	Any/not given	0-2	Limited	Cisplatin+etoposide	Yes	Yes
X Xiao ²⁹⁸	2011	China	RCT	20	Any	93	56	62.5	Any/not given	0-2	Extensive	Cisplatin+etoposide Platinum+etoposide/irinotecan	Not stated	Not stated
U Yilmaz ²⁹⁹	2001	Turkey	Cohort	20	≥16	41	62	88.0	Any/not given	0-2	Limited	Carboplatin+etoposide	Yes	Yes

T Yoshida ³⁰⁰	2001	Japan	Cohort	21	Any	52	71	96.0	Any/not given	Any	Both	Platinum+etoposide	Yes	No
P Zatloukal ³⁰¹	2003	International	RCT	18	18- 75	405	61	76.3	Any/not given	0-1	Extensive	Cisplatin+etoposide Irinotecan+cisplatin	Yes	No
Jie Zhang ³⁰²	2008	China	RCT	17	Any	40	59	92.5	Any/not given	0-2	Extensive	Cisplatin+etoposide	Yes	Yes
H Zhu ³⁰³	2003	China	Cohort	14.5	Any	119	62	80.7	Any/not given		Extensive	Platinum+etoposide	Yes	No

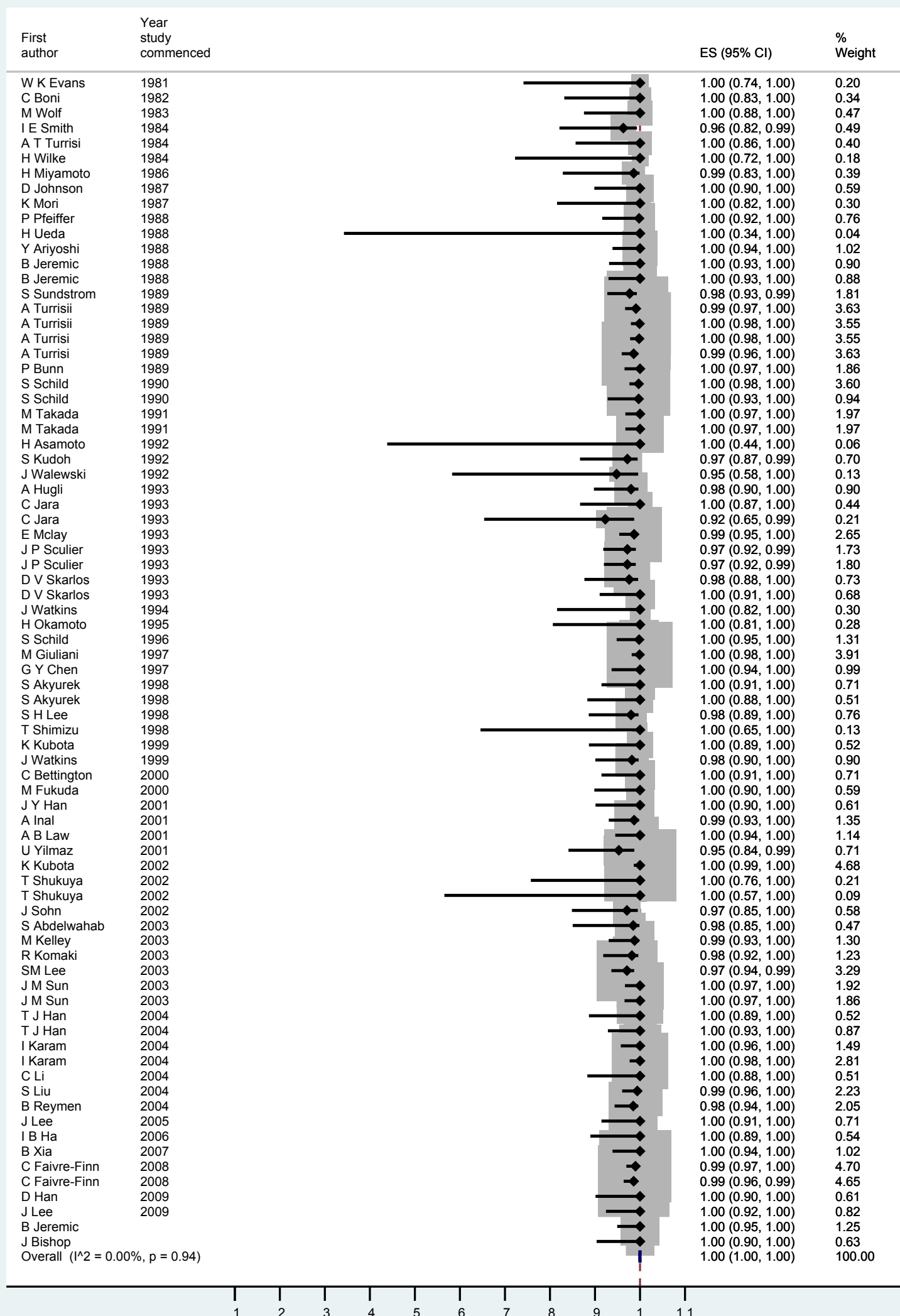
Appendix M: Forest plots

Forest plots

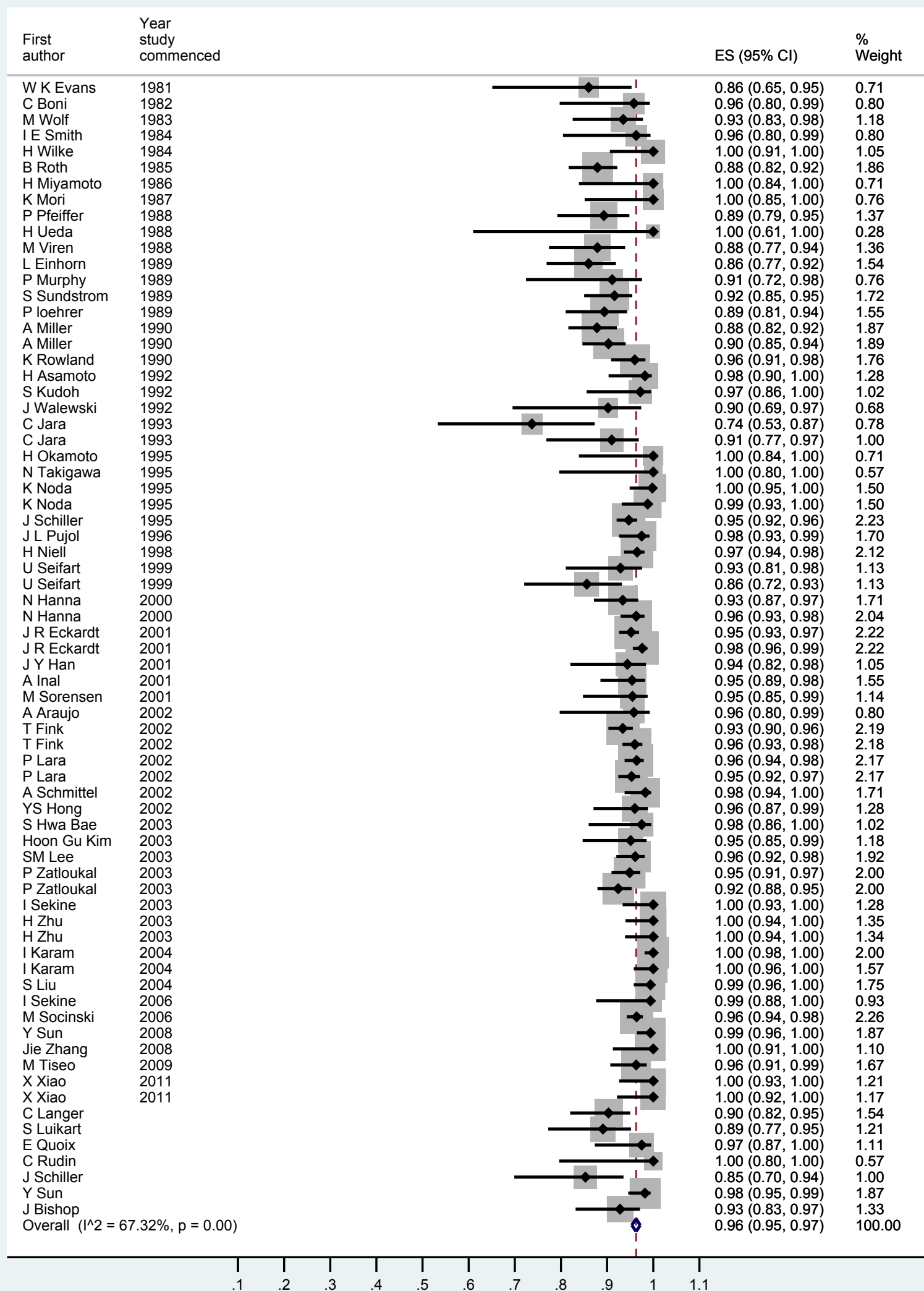
30-day survival



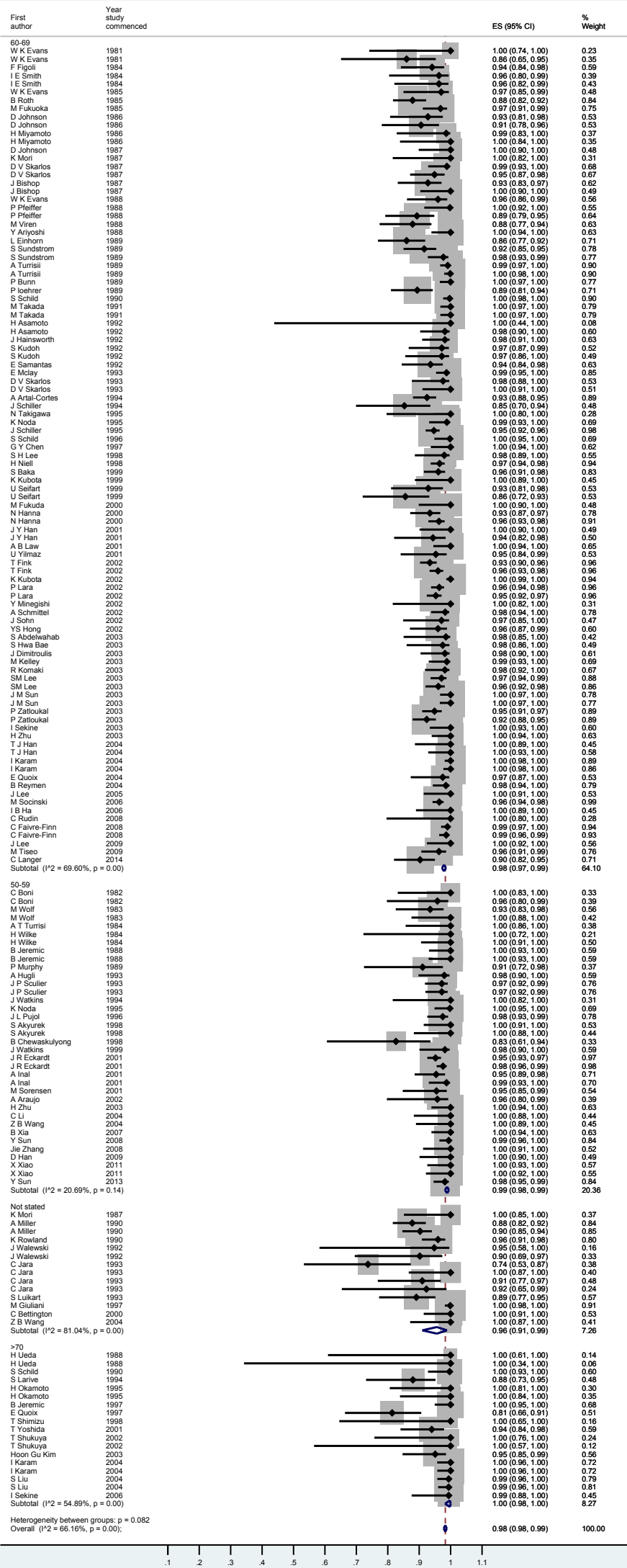
30 day survival after chemotherapy

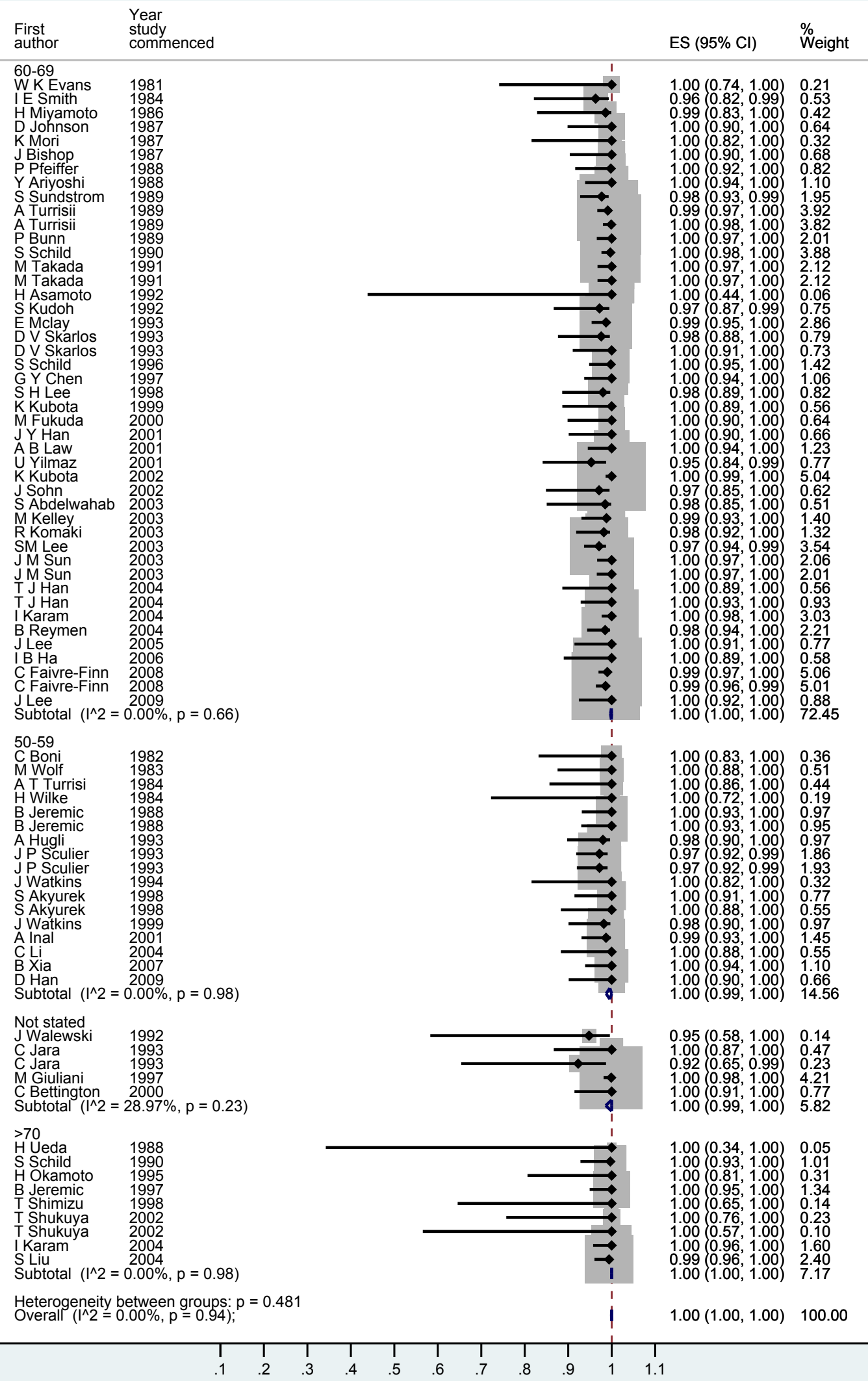


30 day survival after chemotherapy in limited stage

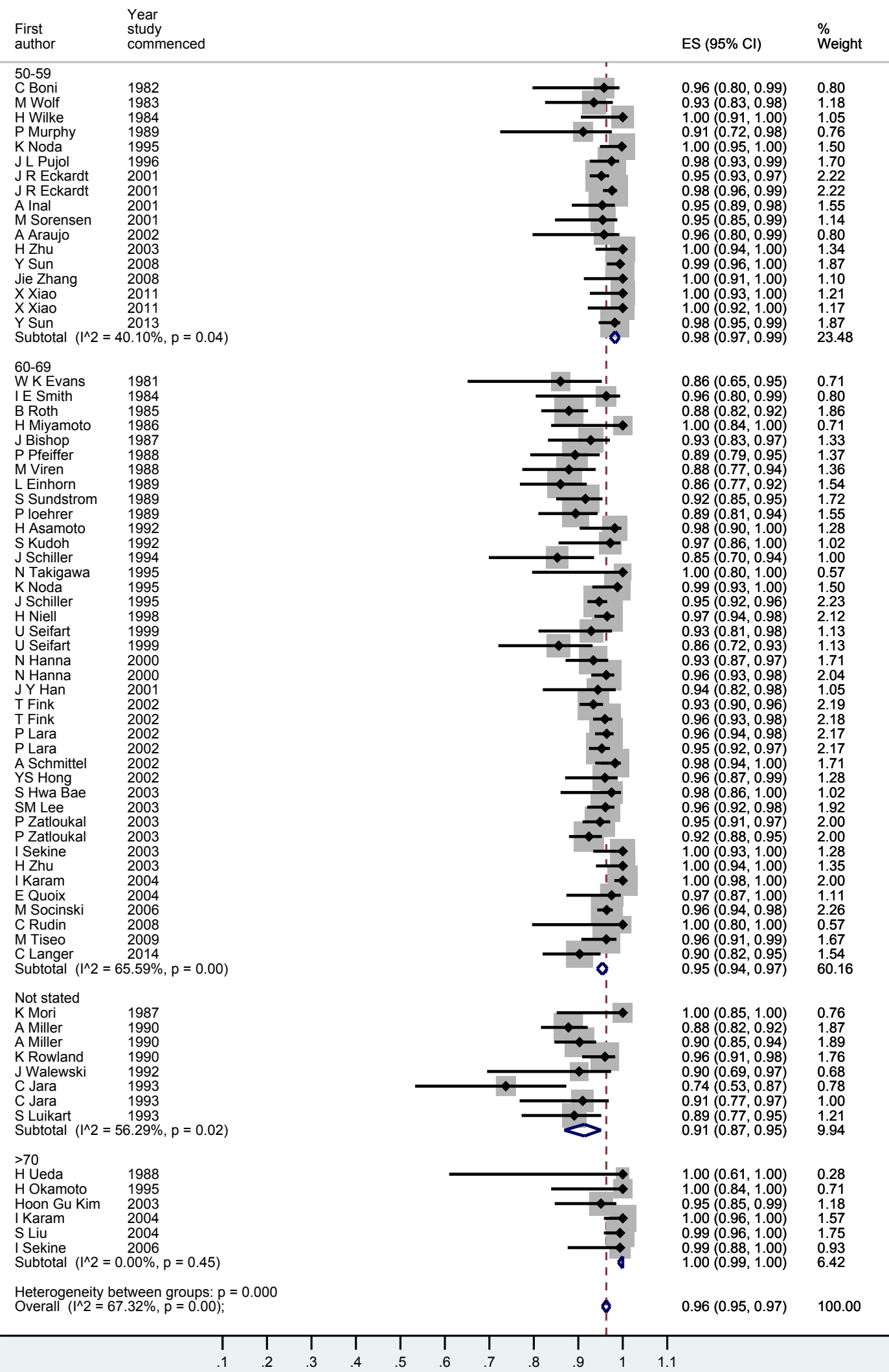


30 day survival after chemotherapy in extensive stage

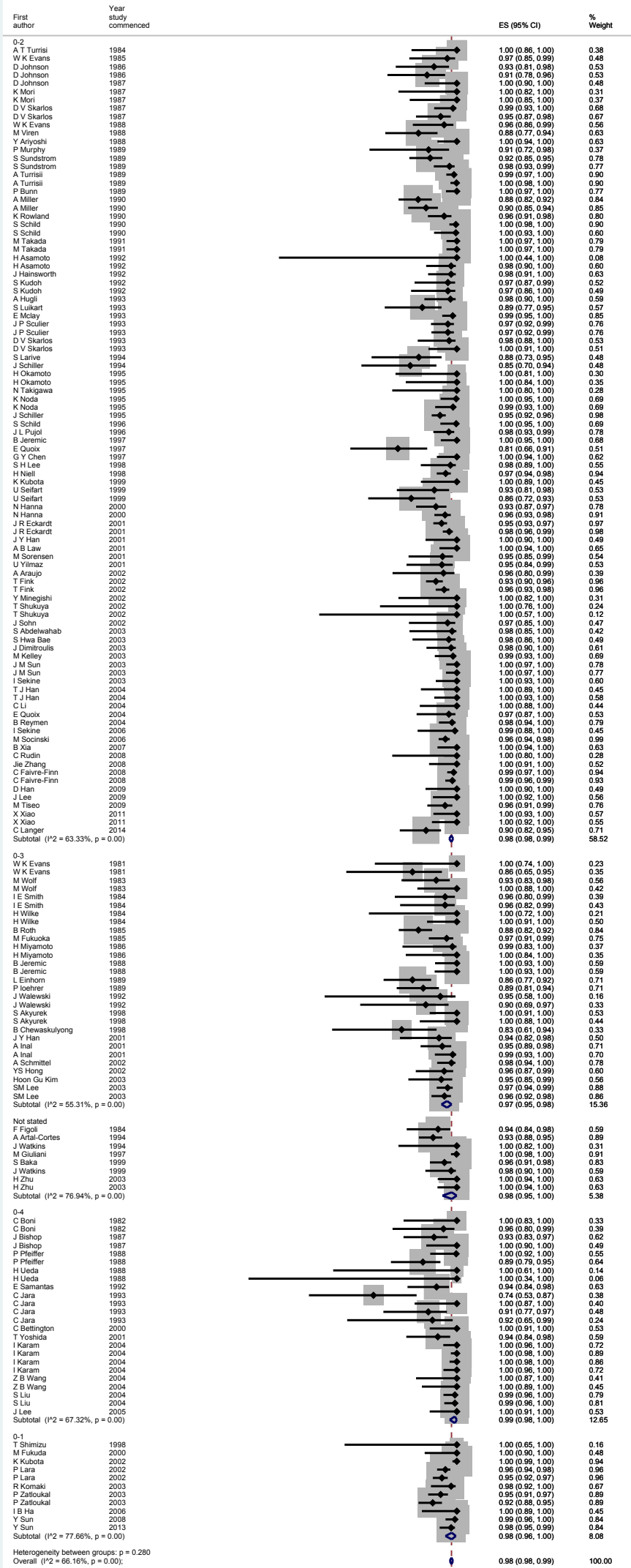


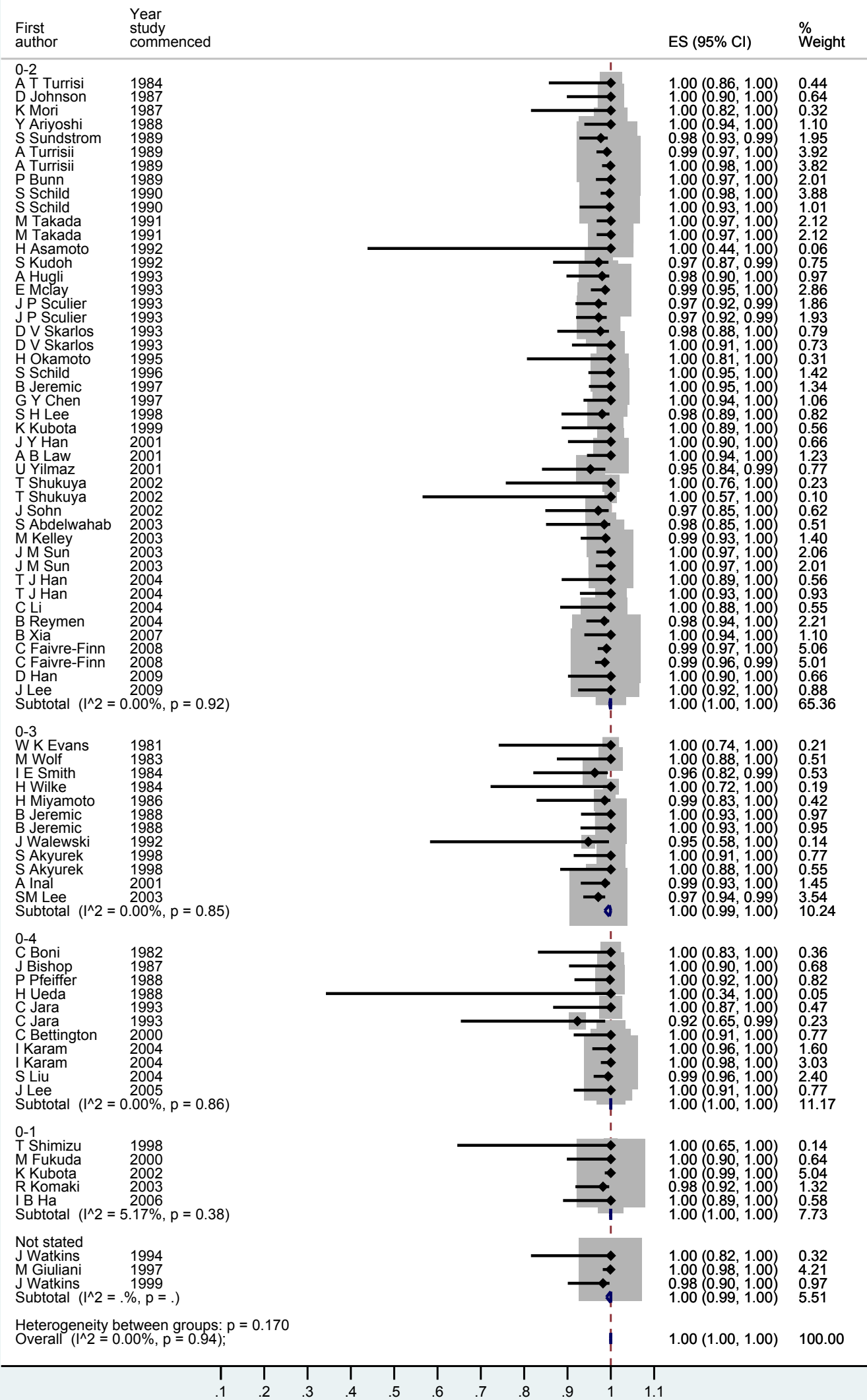


Proportion of 30 day survival in limited stage by median participant age

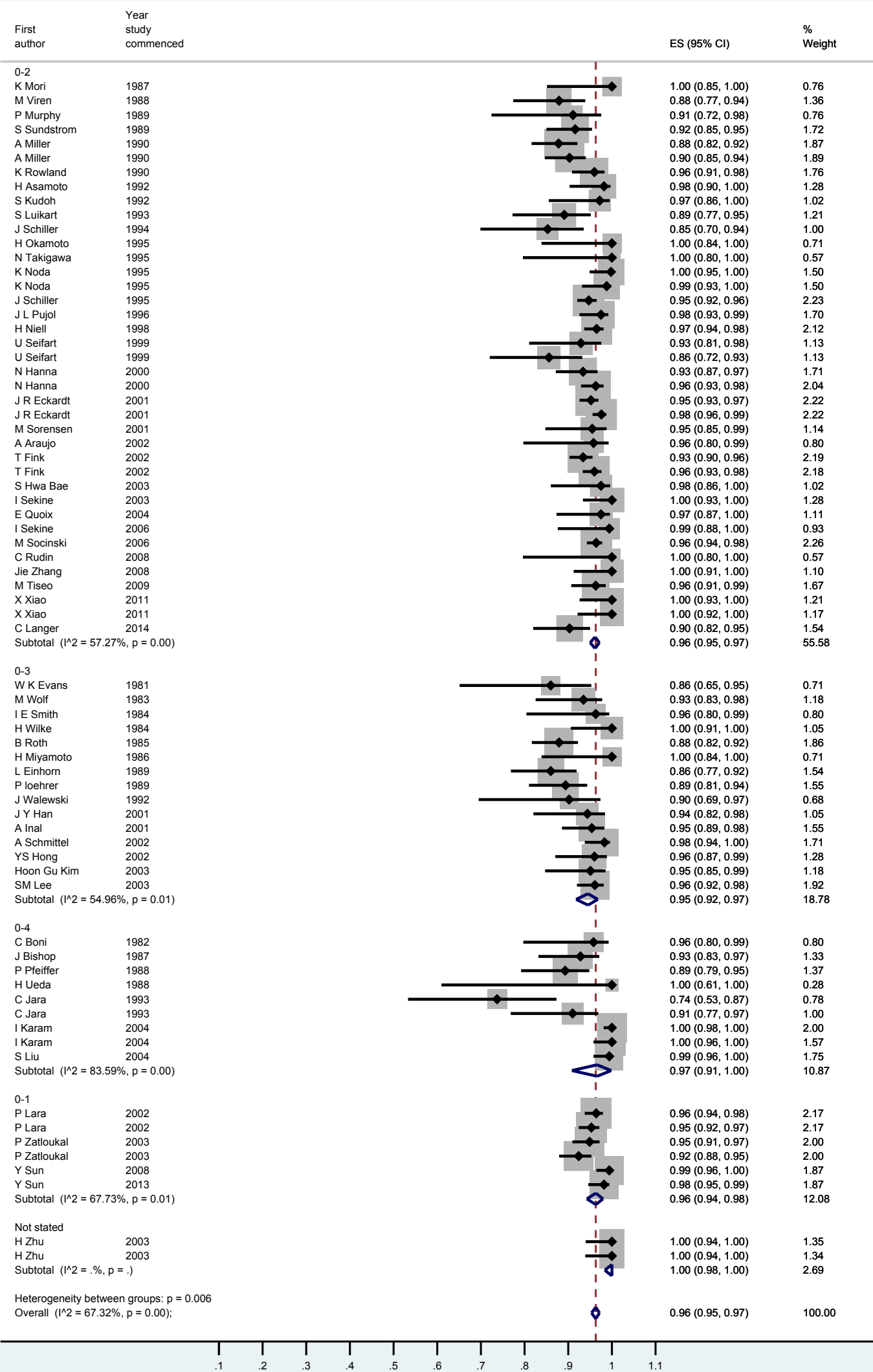


Proportion of 30 day survival in extensive stage by median participant age

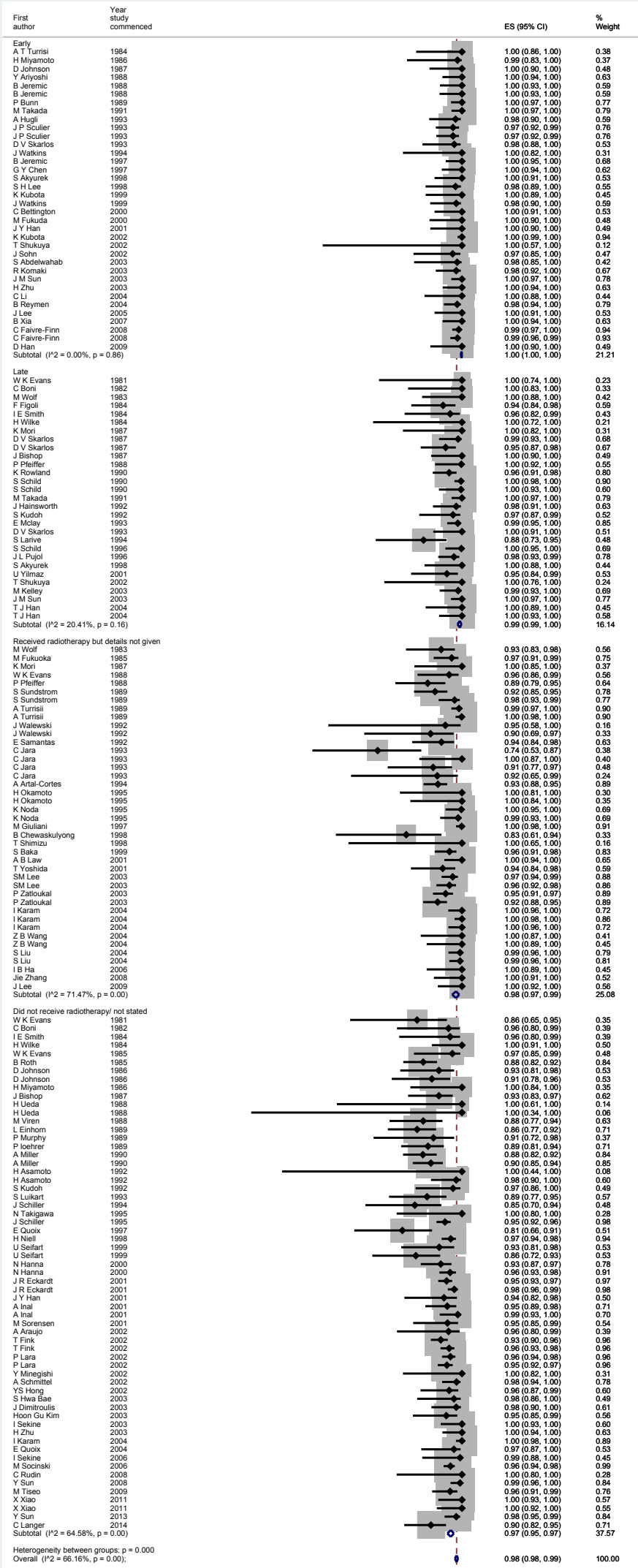


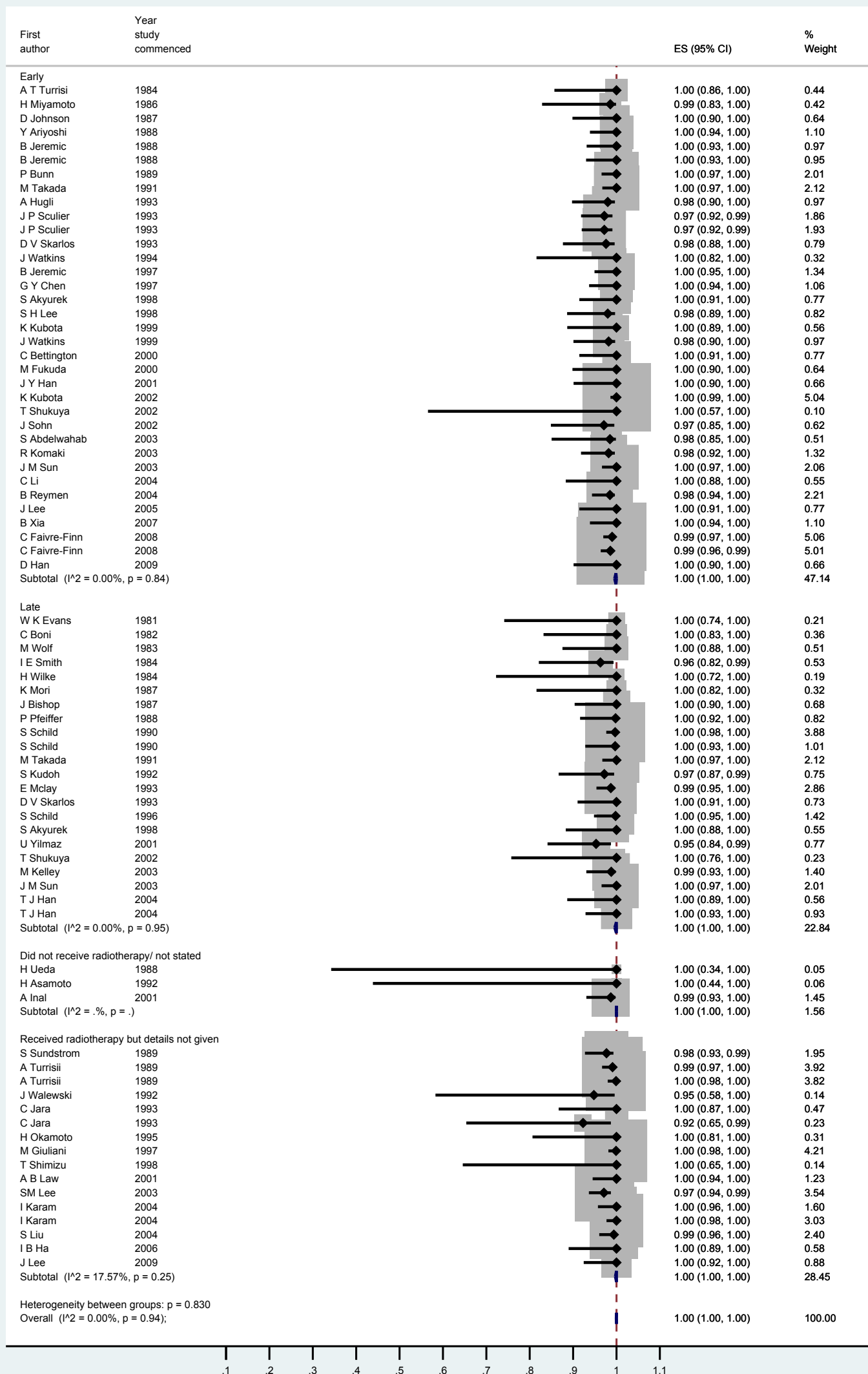


Proportion of 30 day survival in limited stage by PS

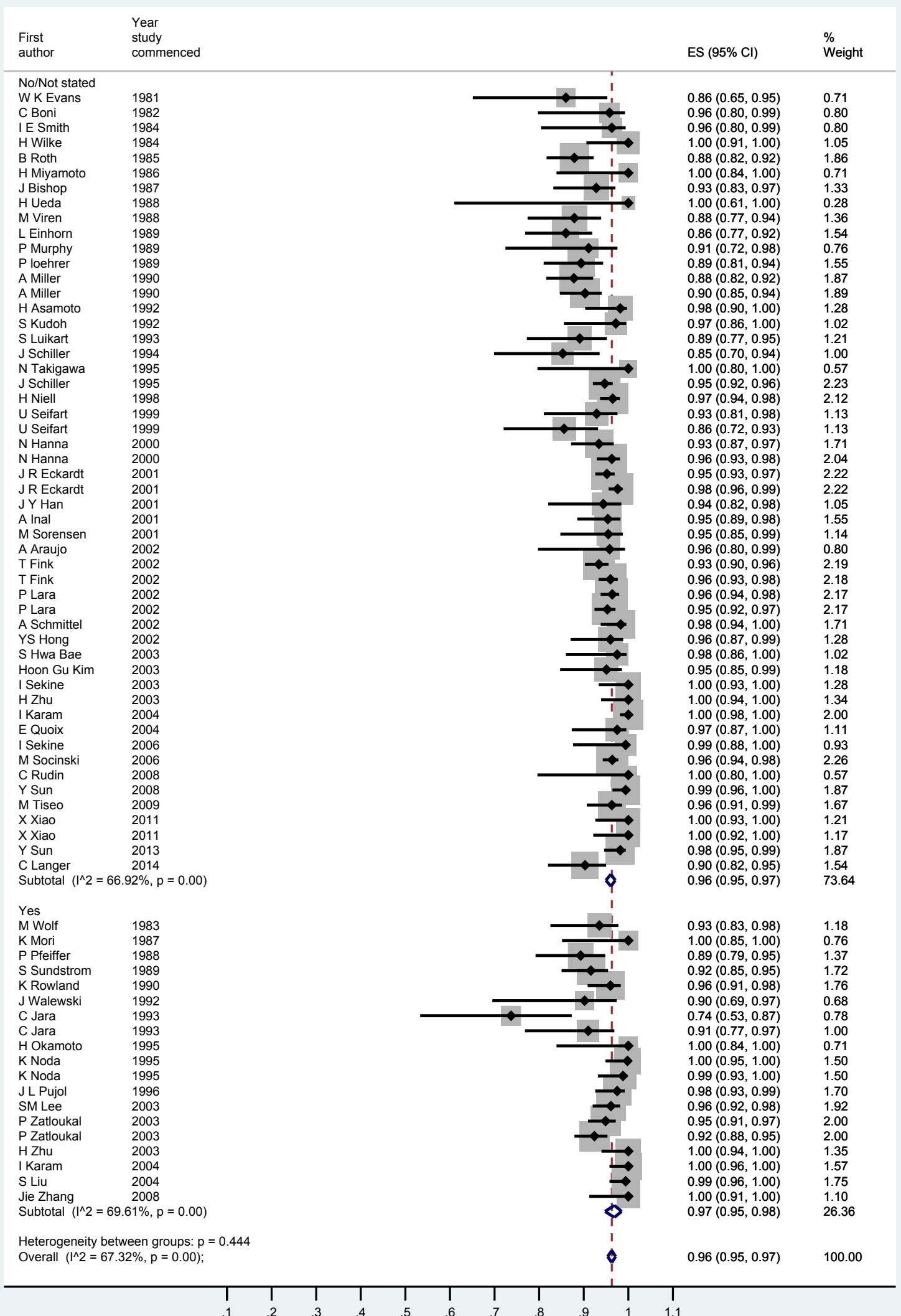


Proportion of 30 day survival in extensive stage by PS

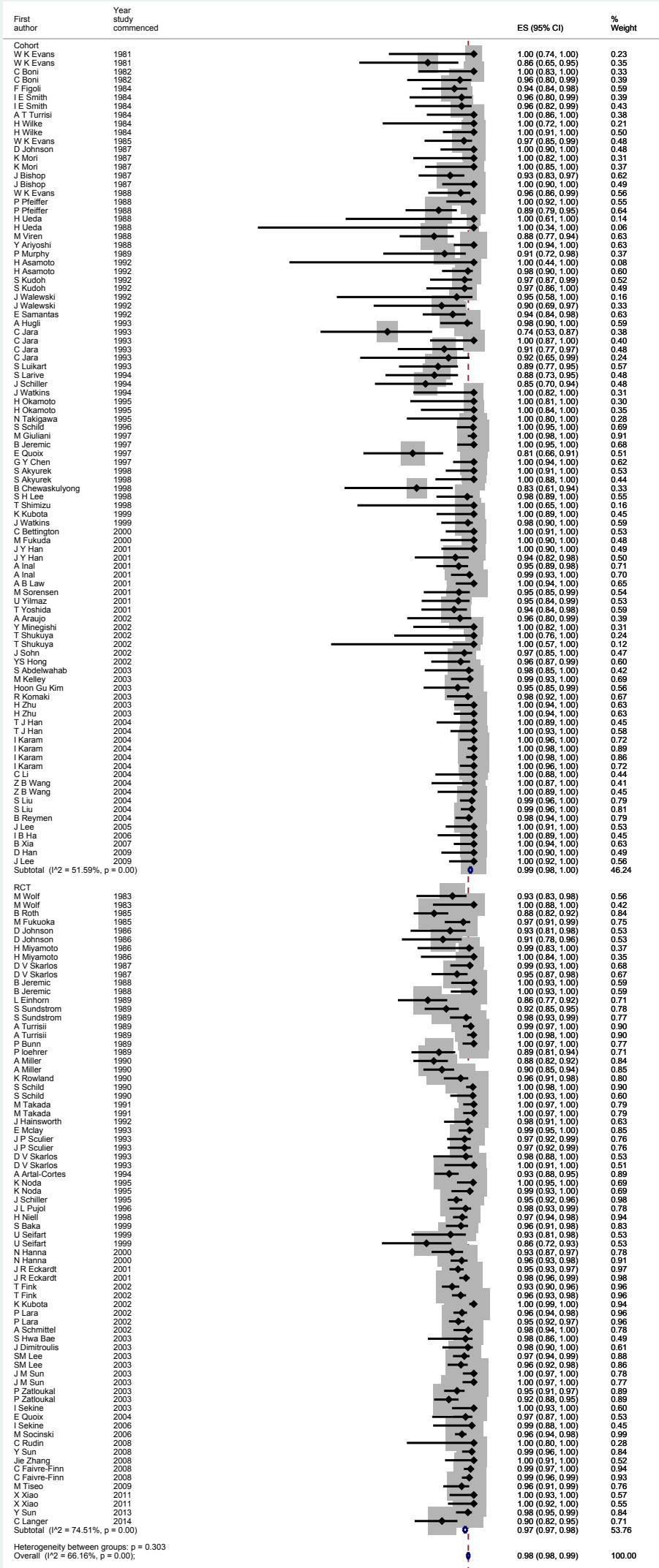




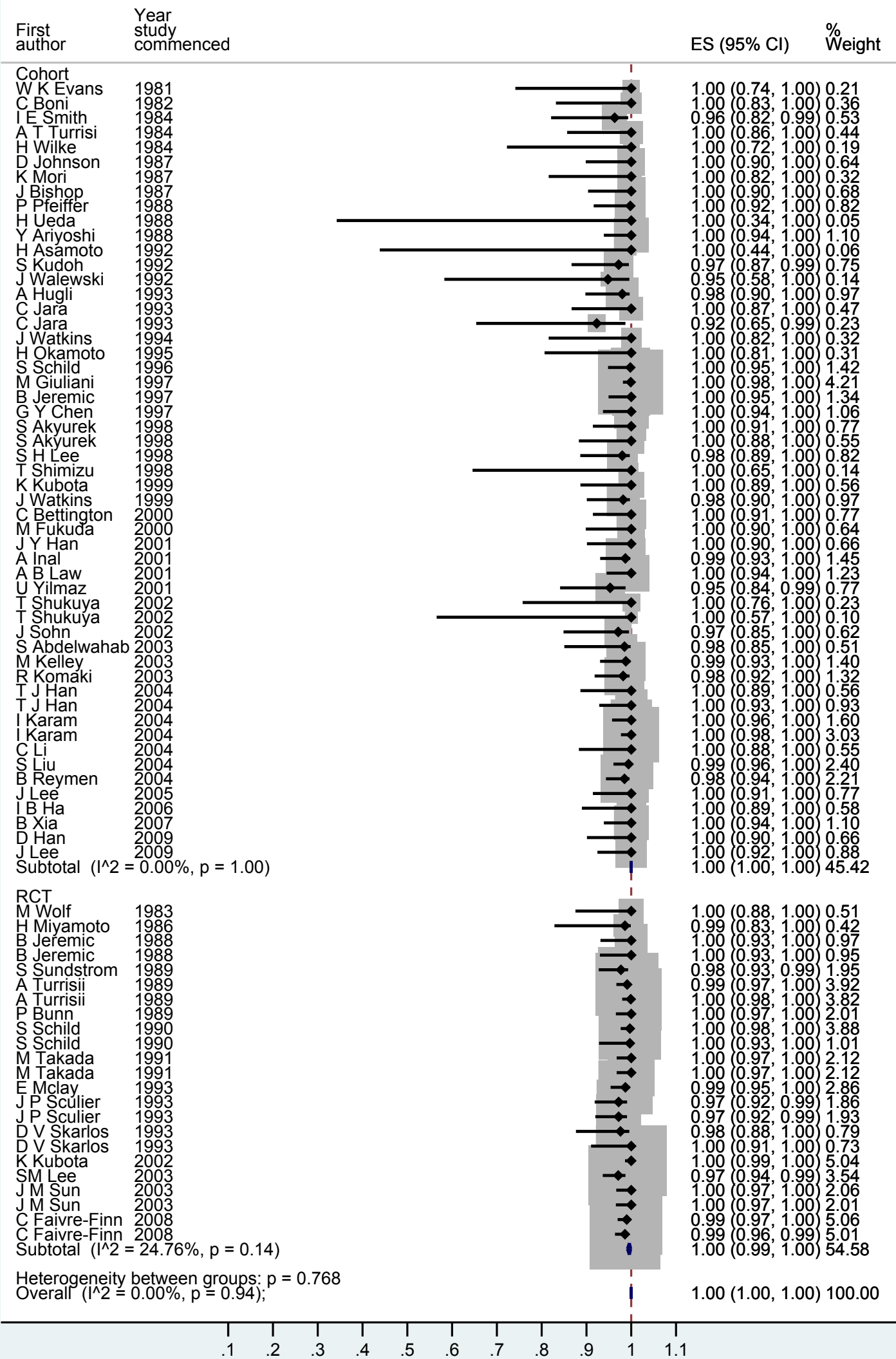
Proportion of 30 day survival in limited stage by radiotherapy

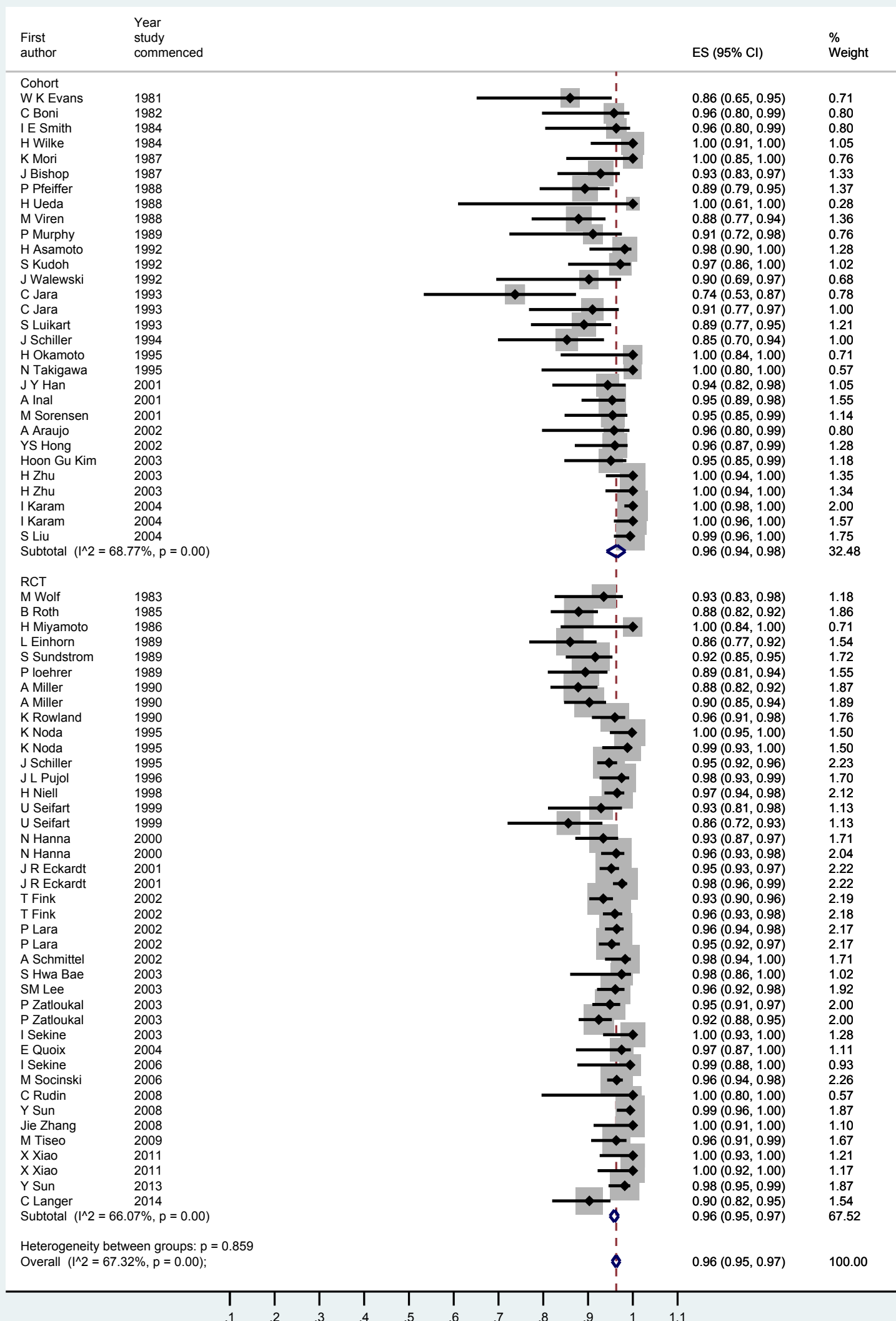


Proportion of 30 day survival in extensive stage by radiotherapy

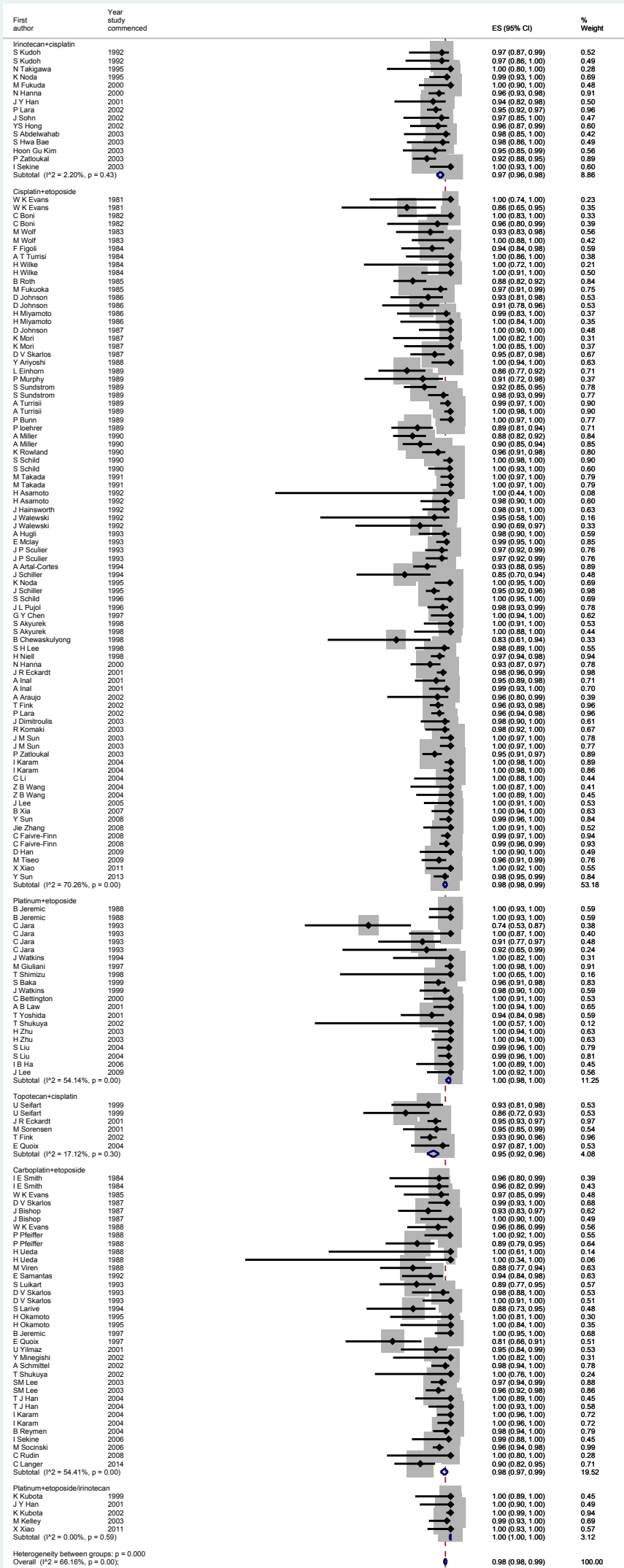


30 day survival after chemotherapy by study design

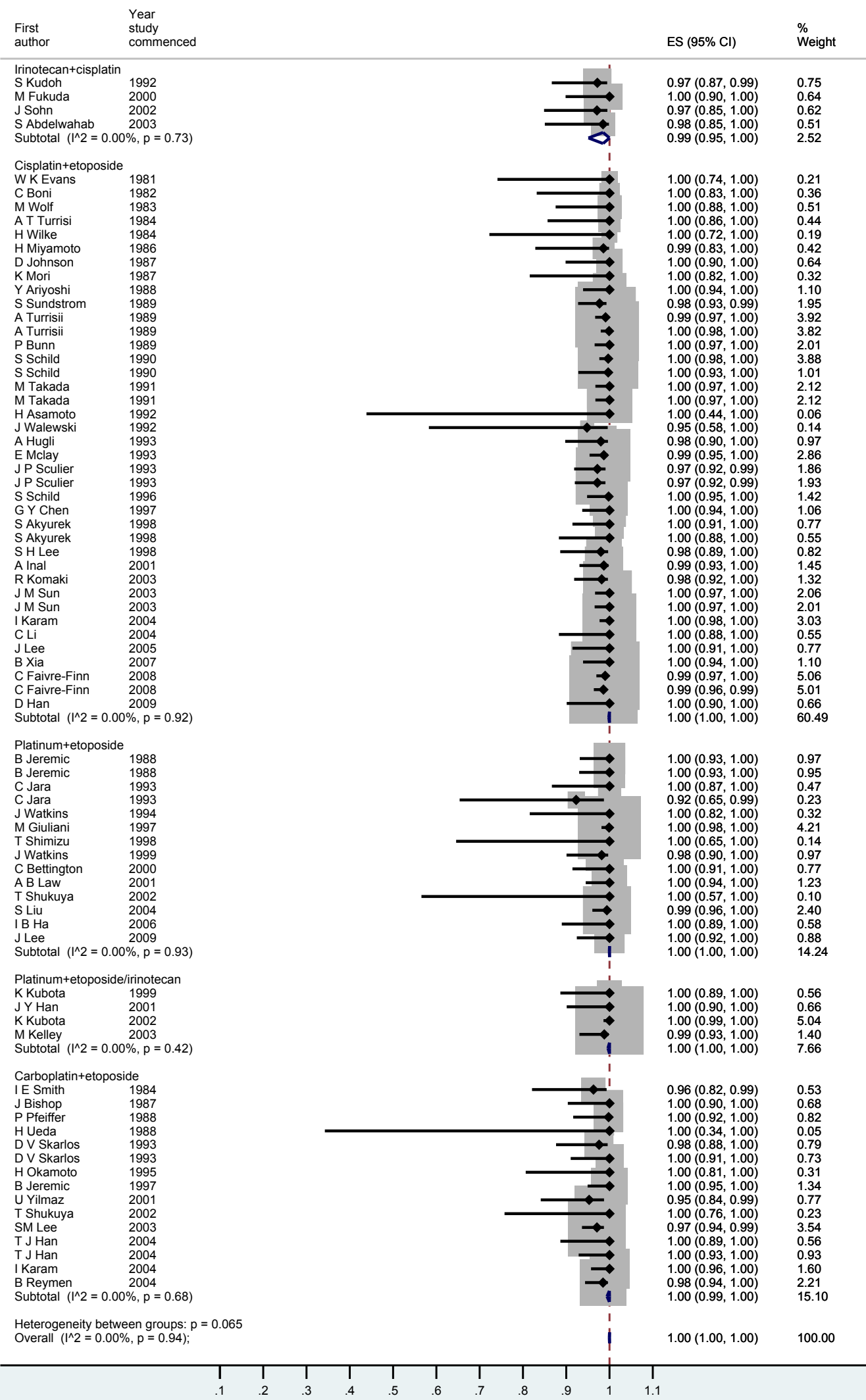


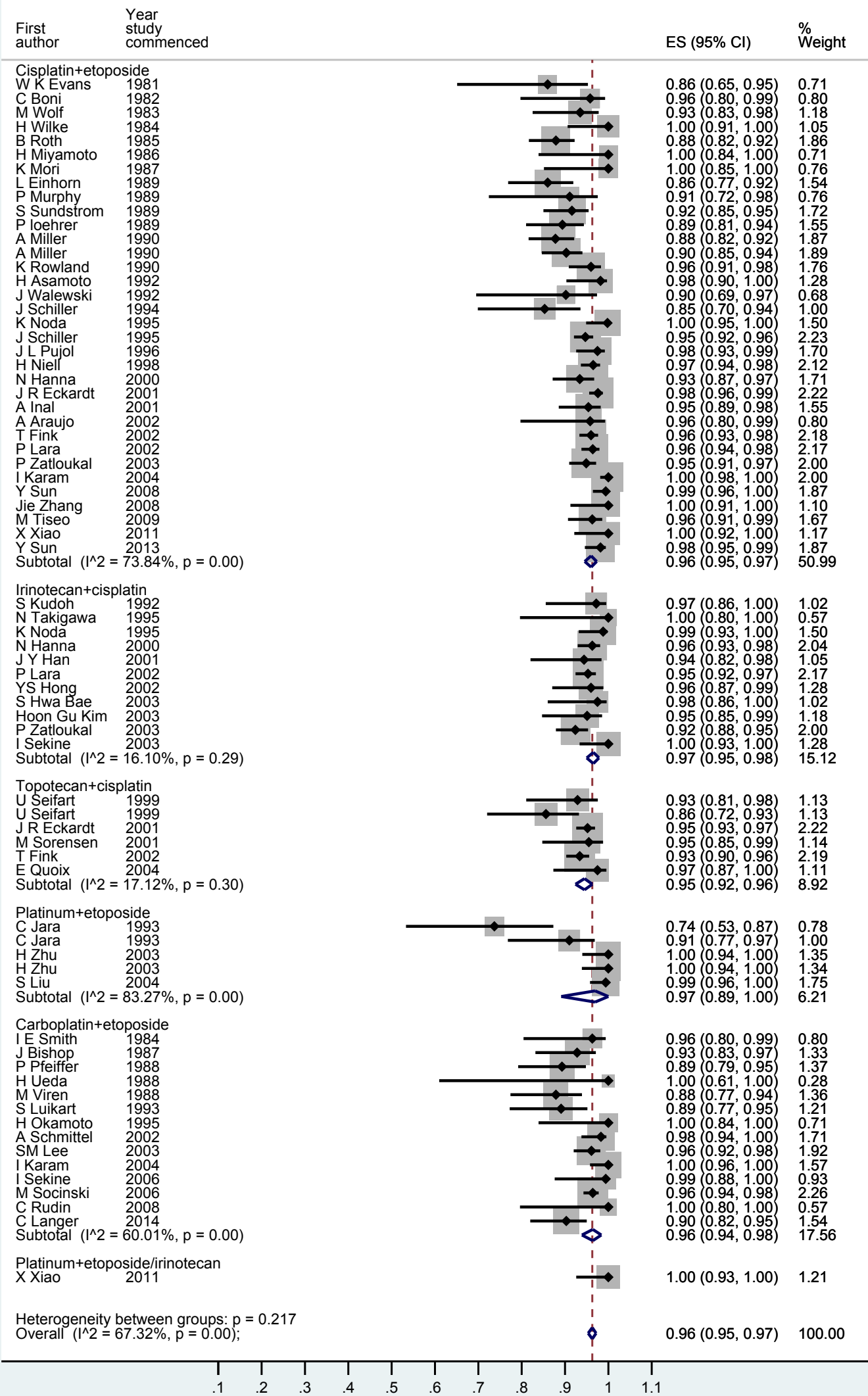


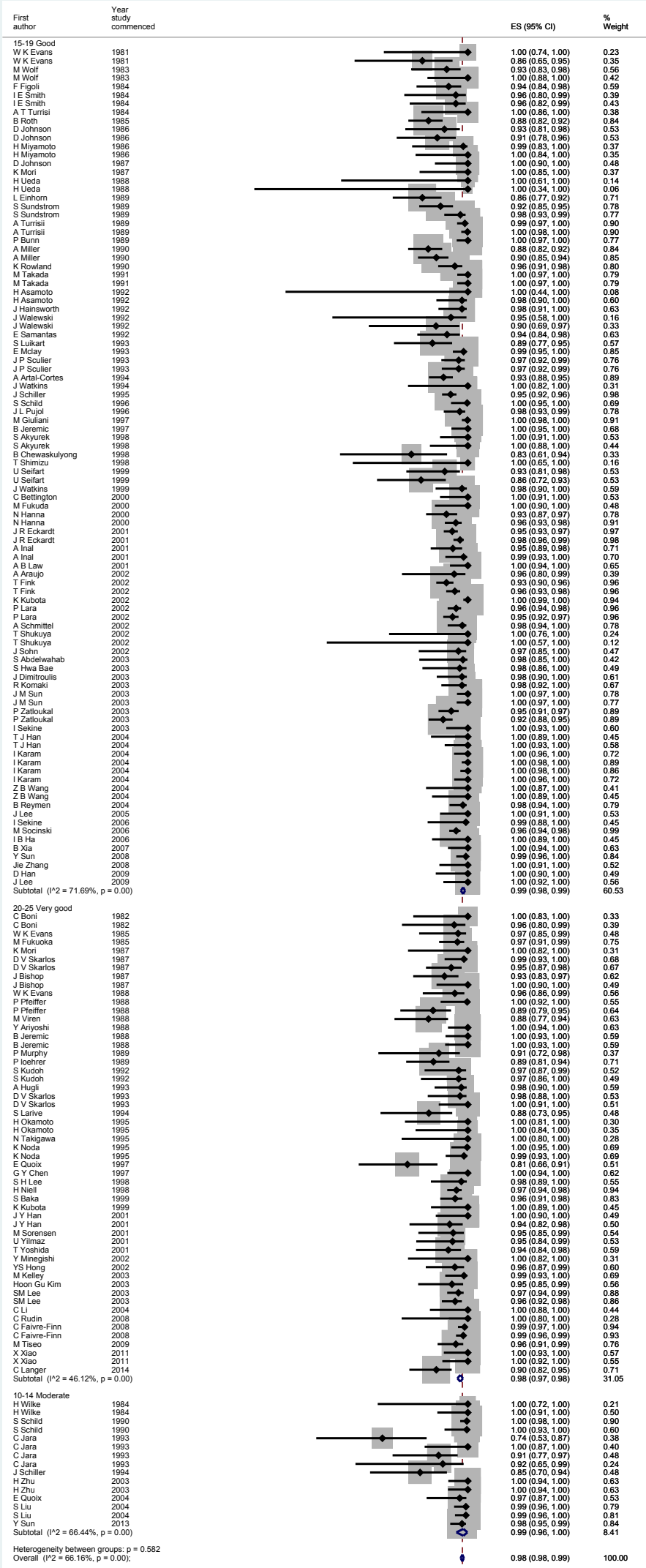
Proportion of 30 day survival in extensive stage by study design



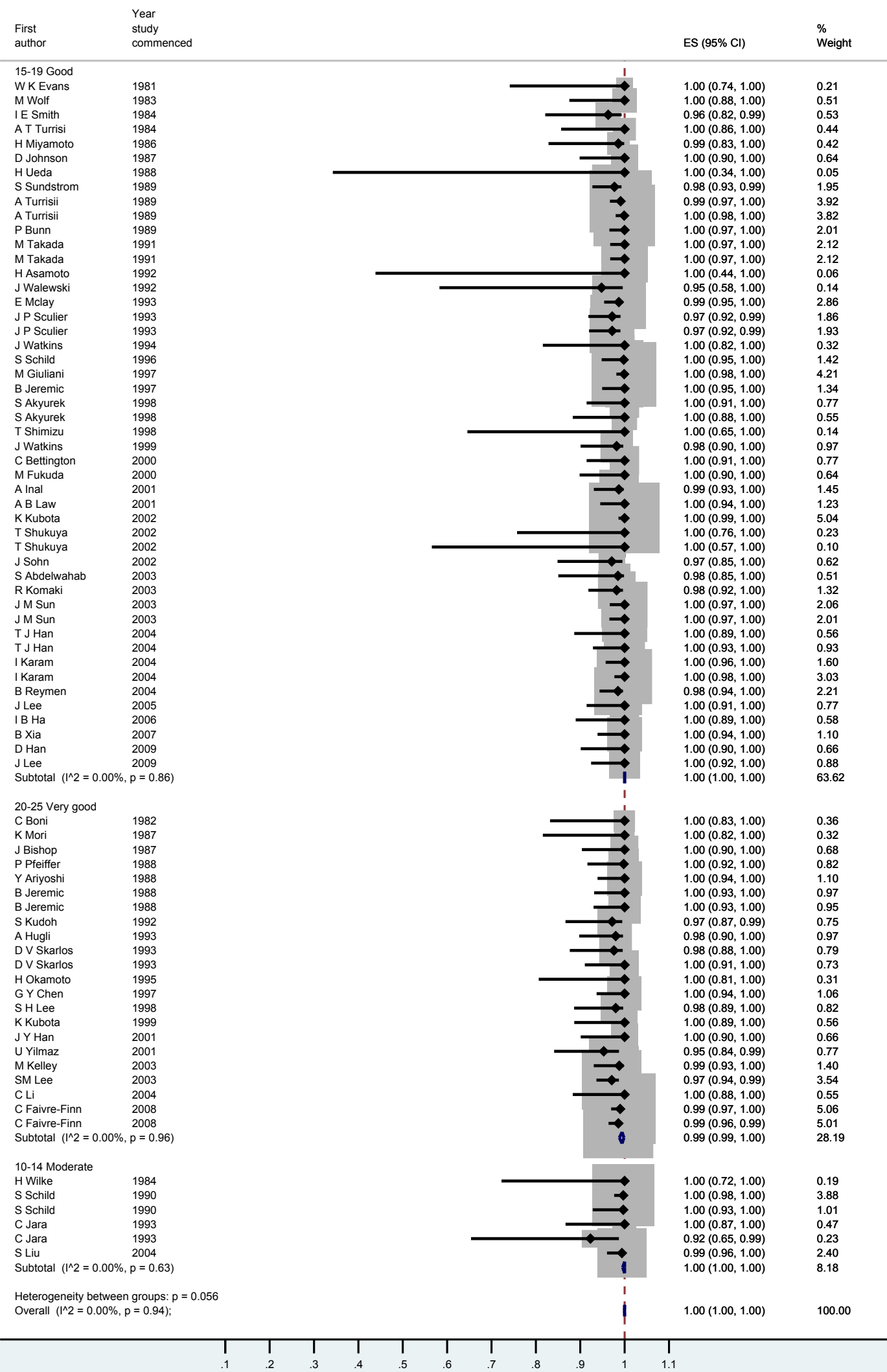
30 day survival after chemotherapy by drug

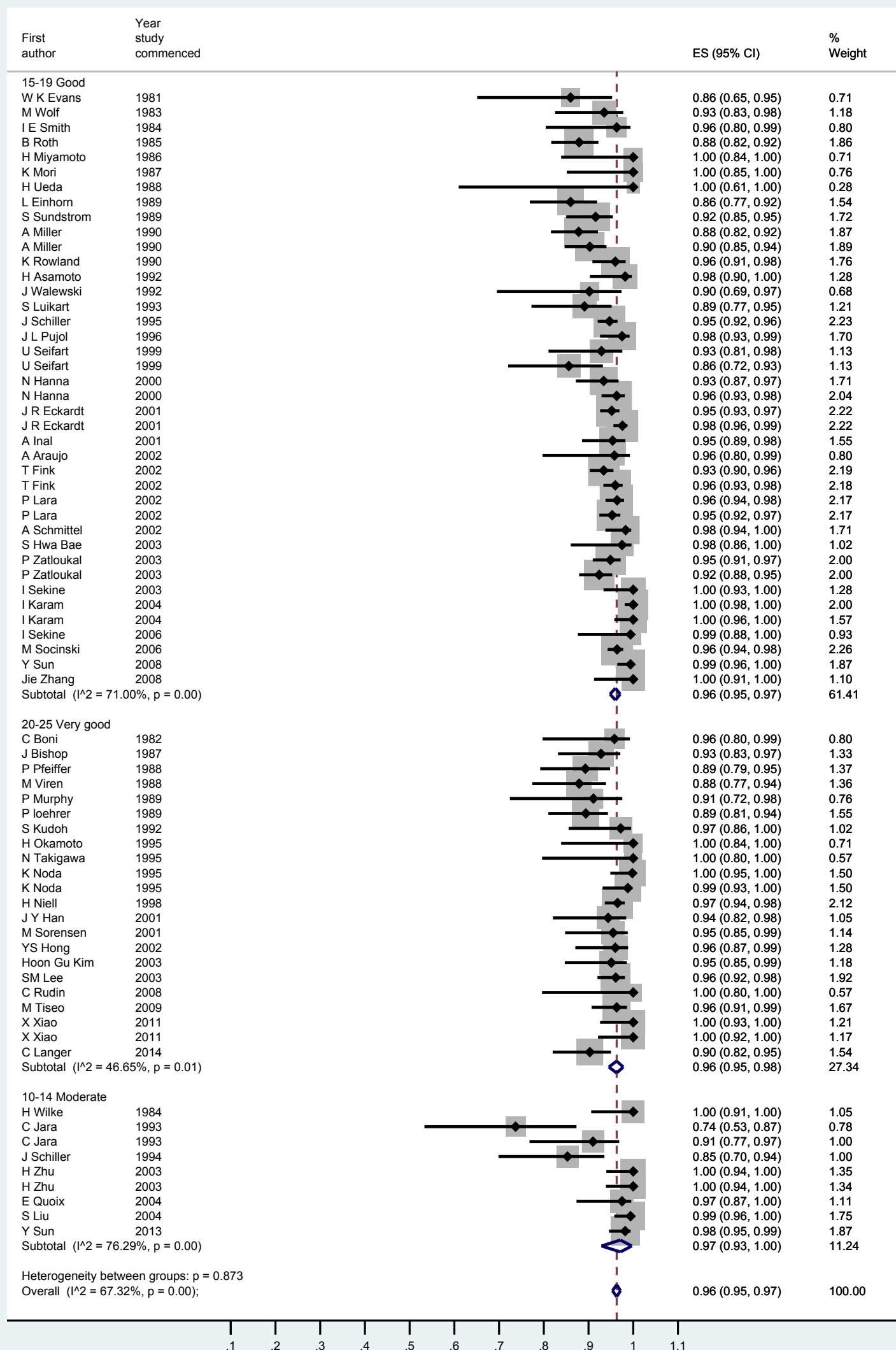




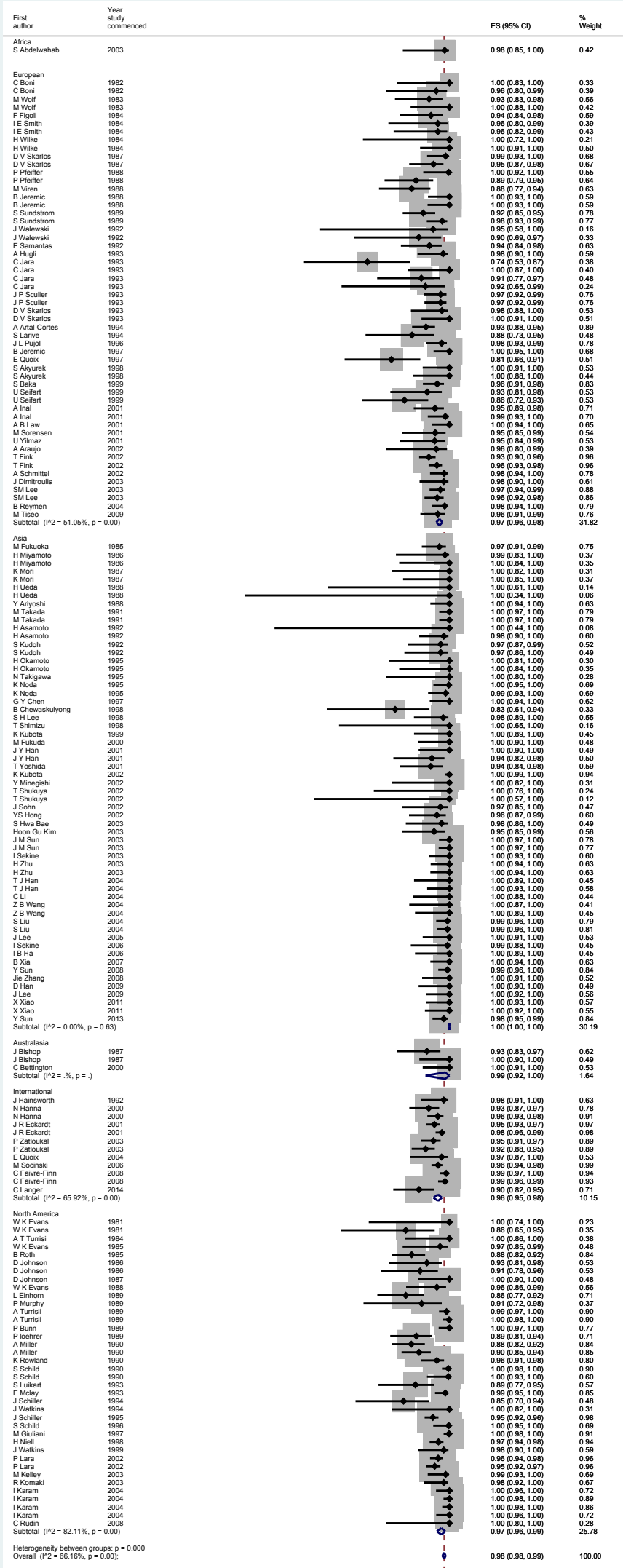


30 day survival after chemotherapy by quality score

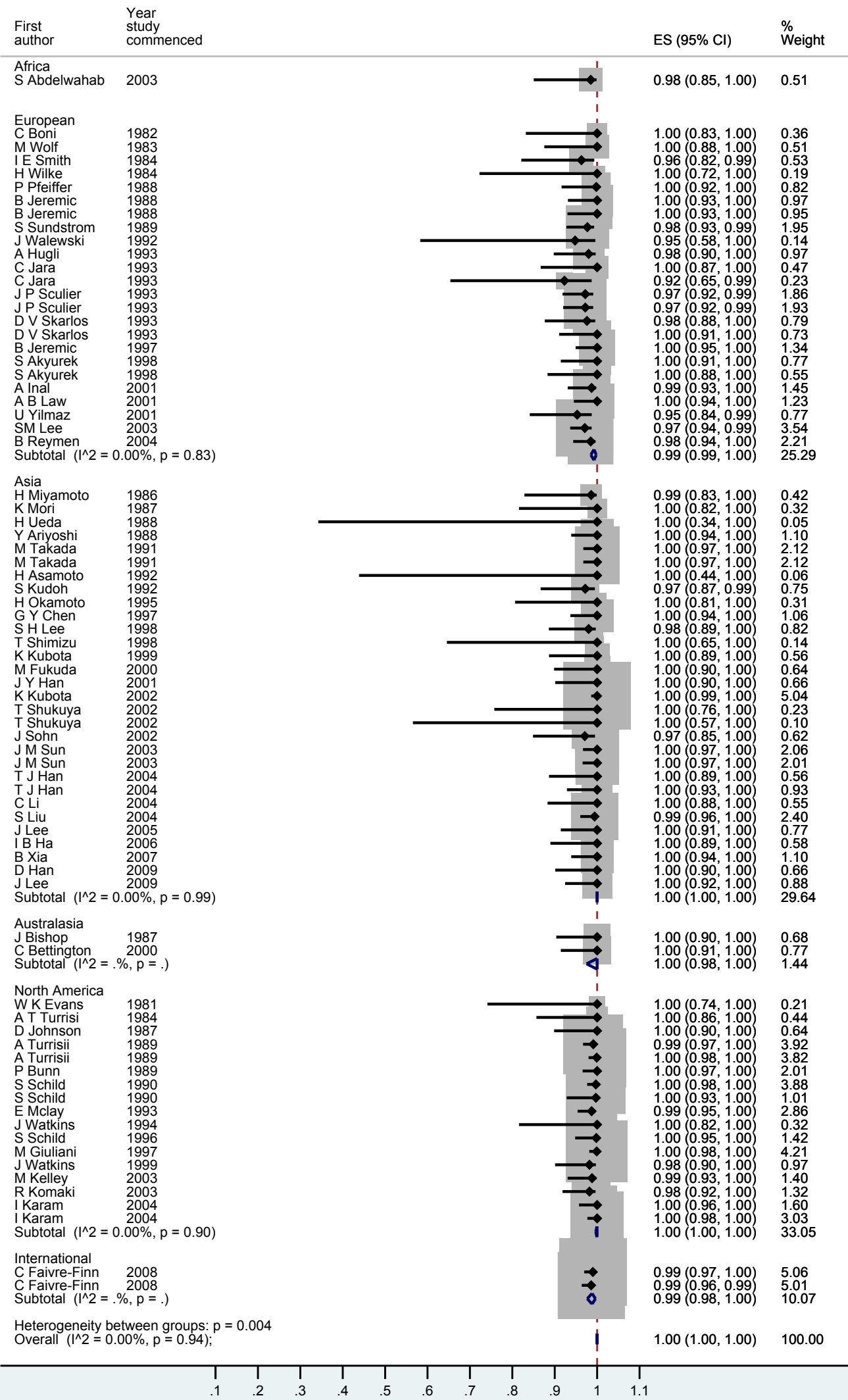


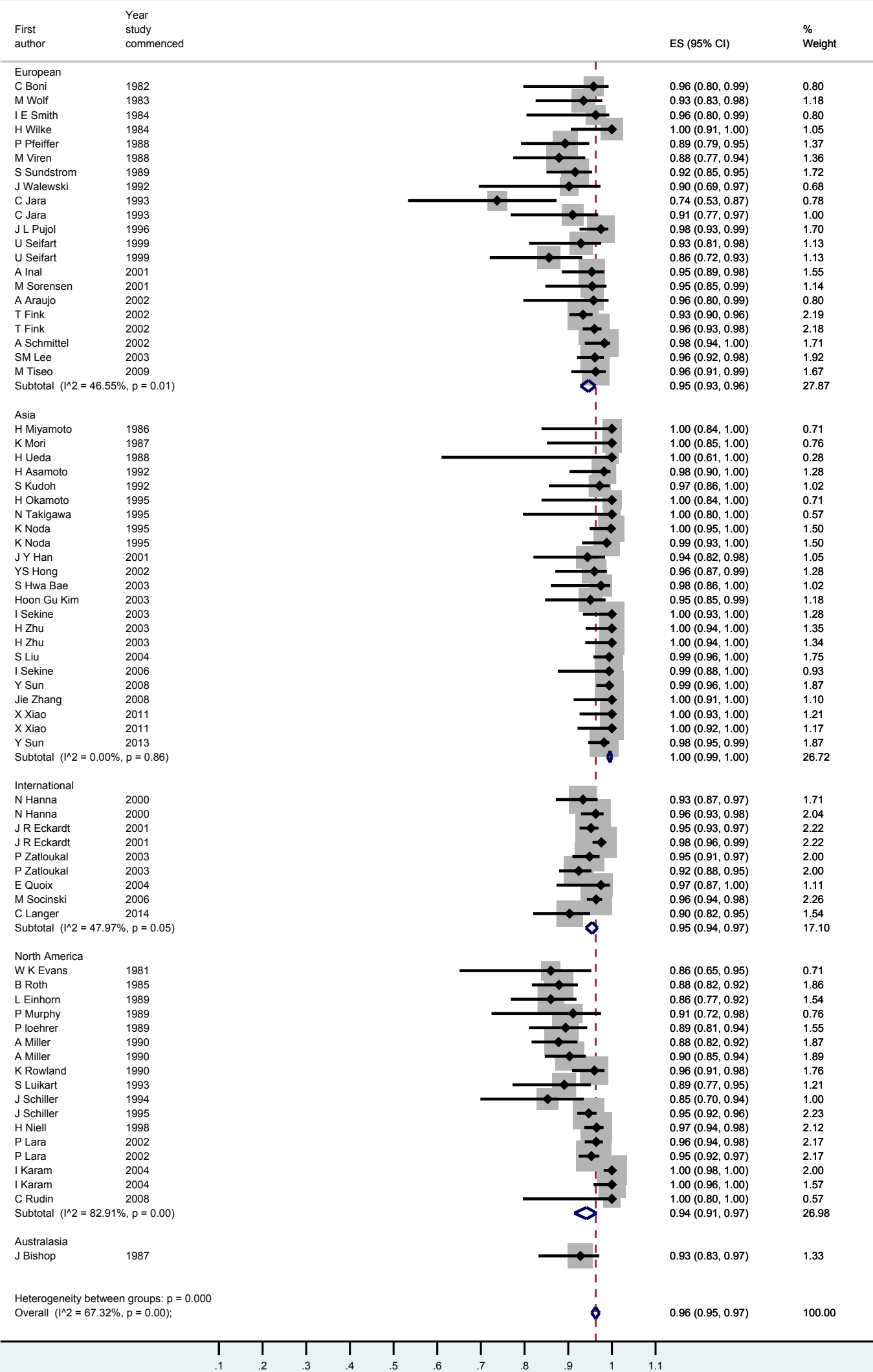


Proportion of 30 day survival in extensive stage by quality score

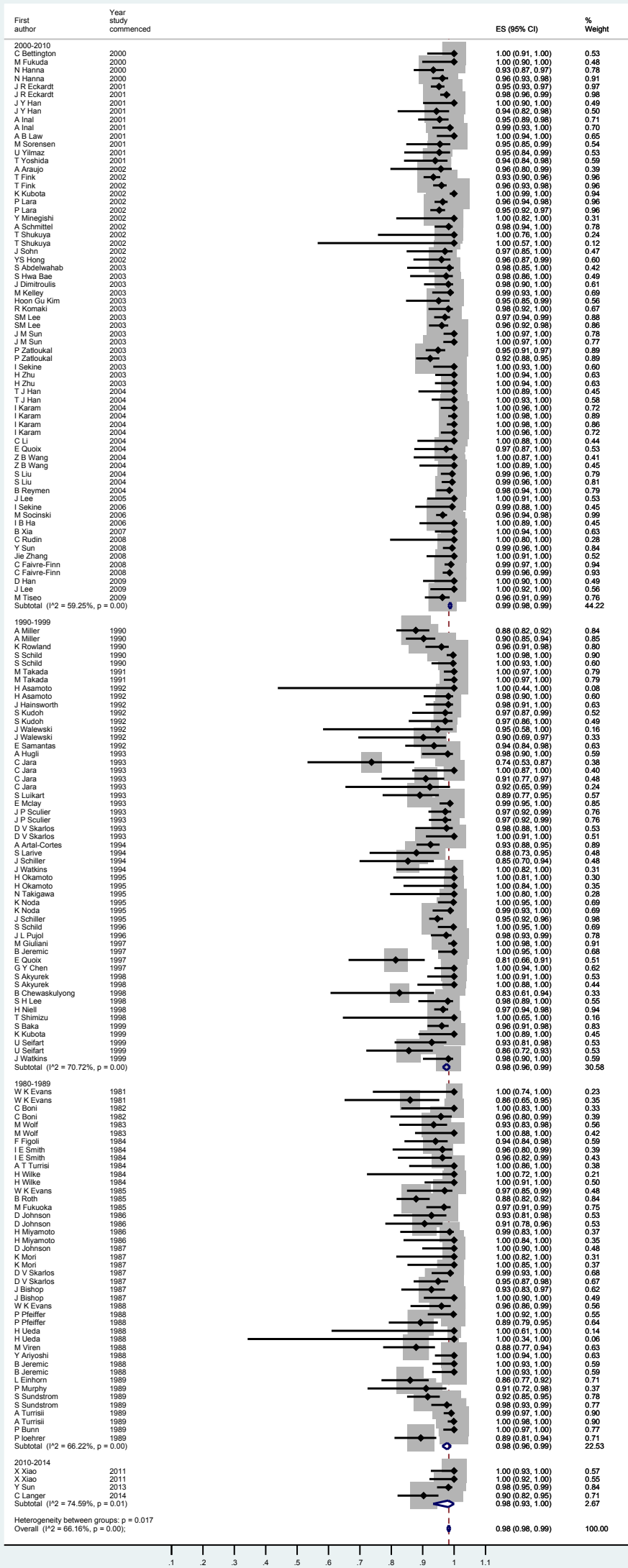


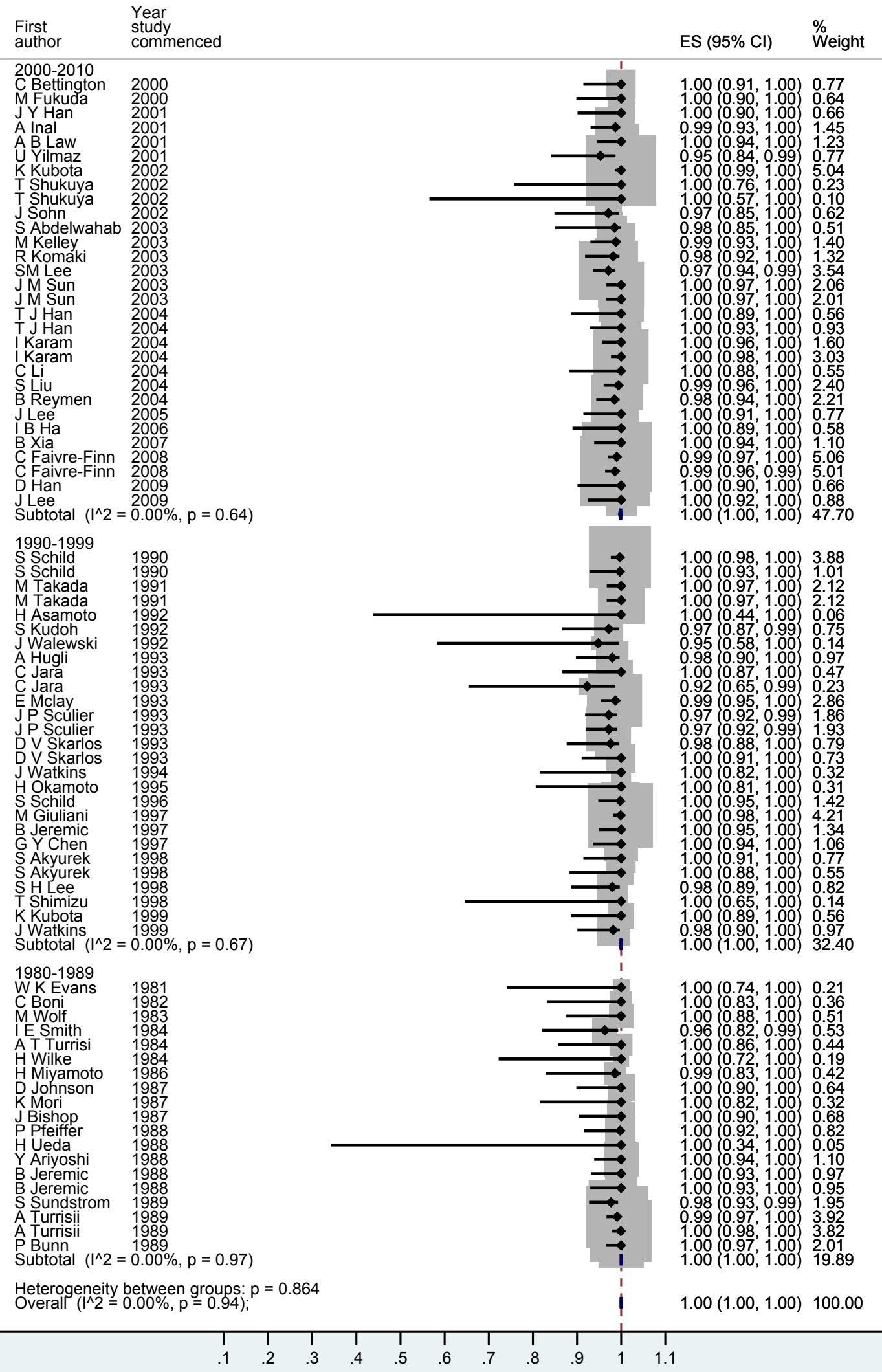
30 day survival after chemotherapy by region

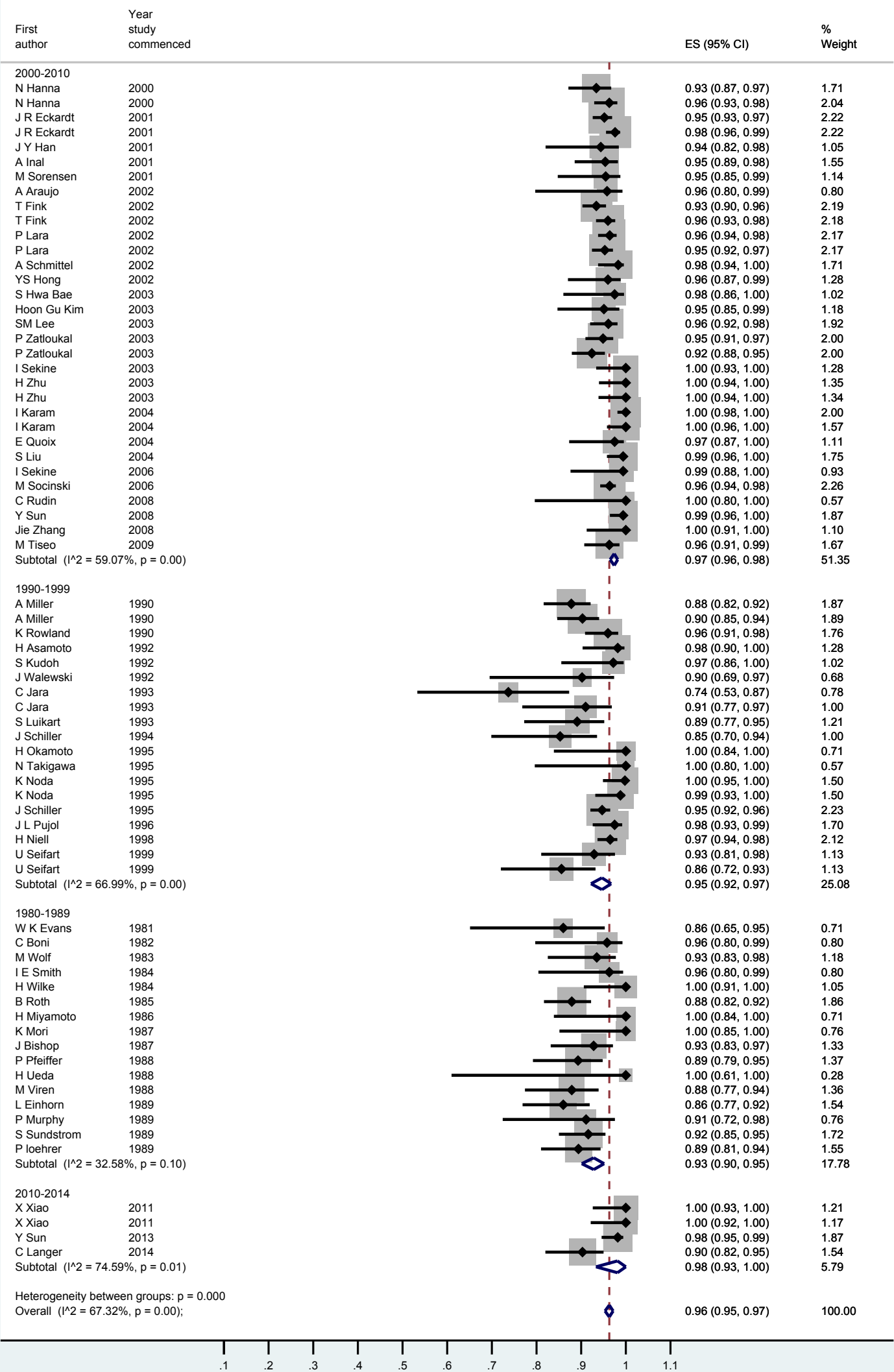




Proportion of 30 day survival in extensive stage by region

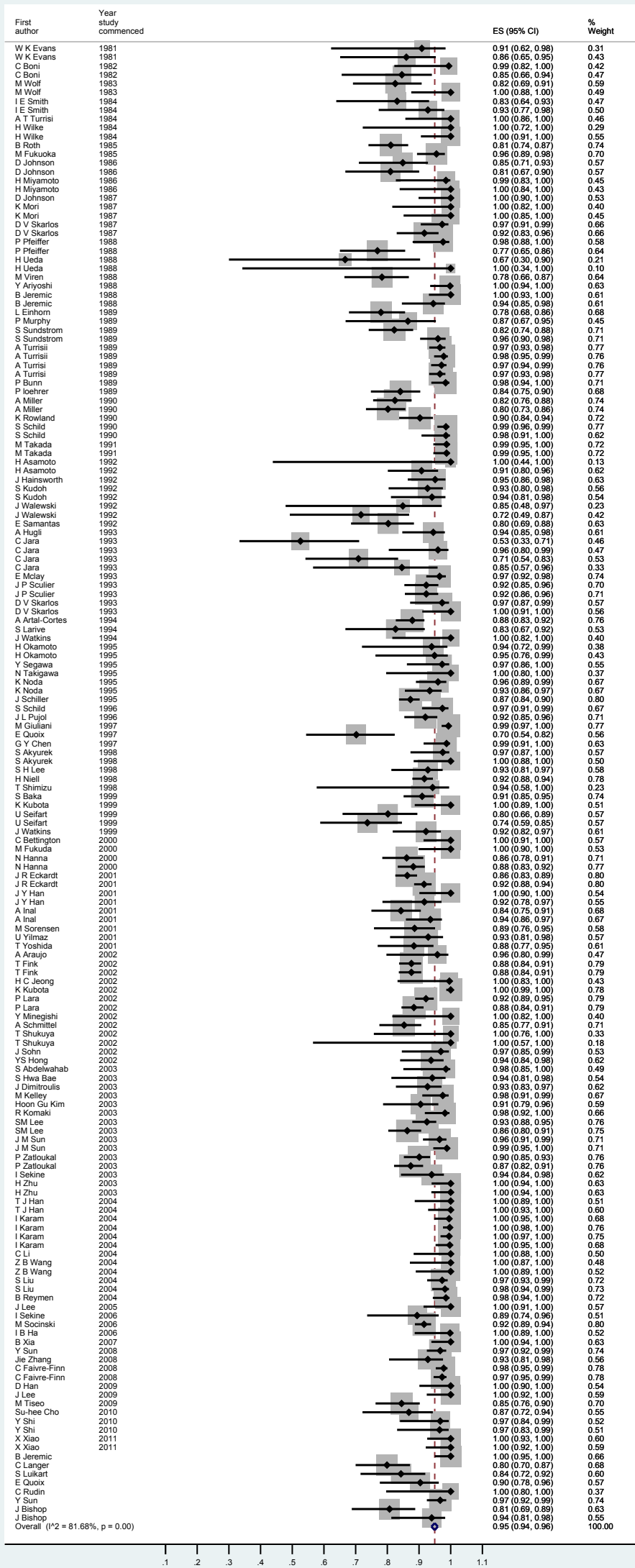




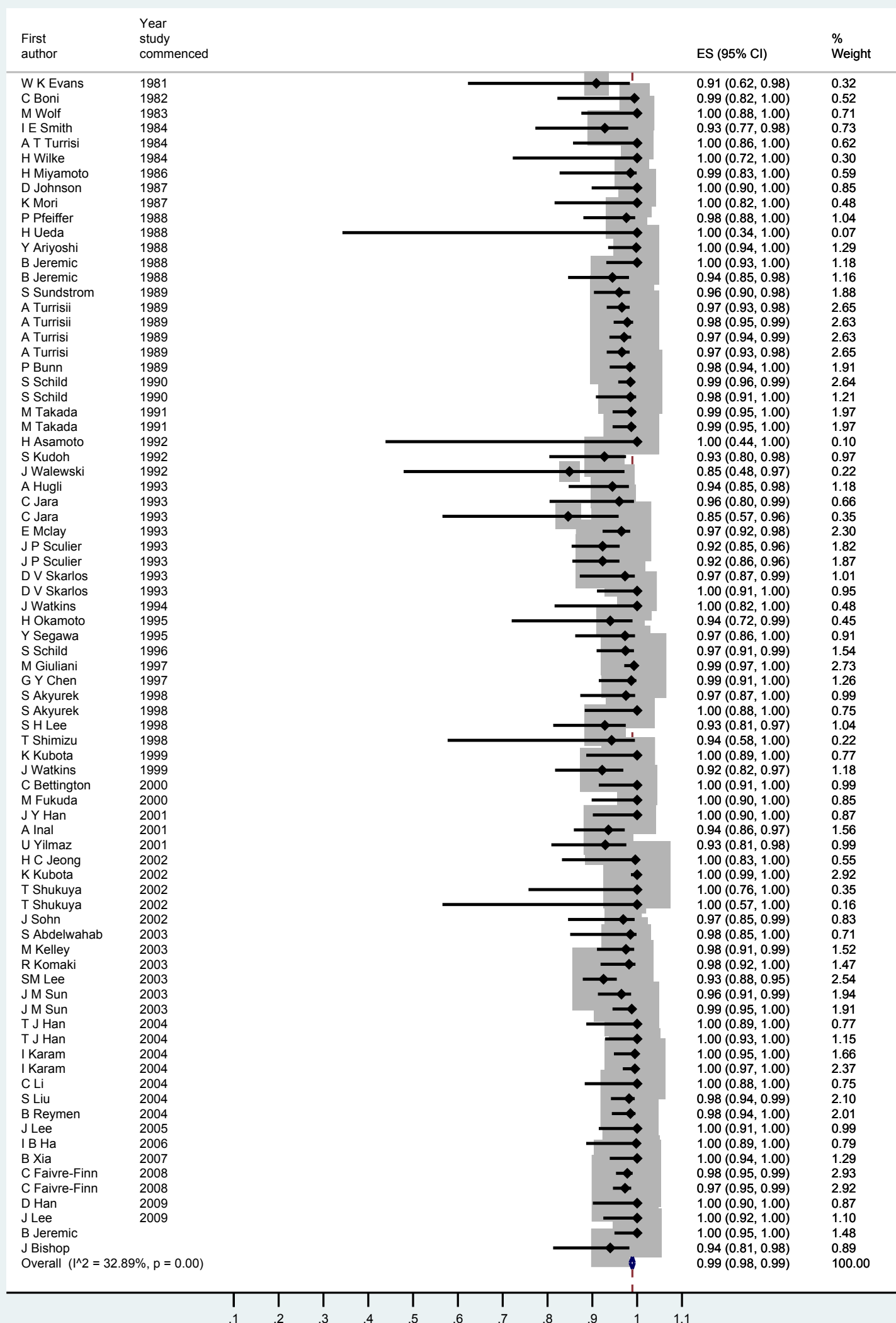


Proportion of 30 day survival in extensive stage by study year

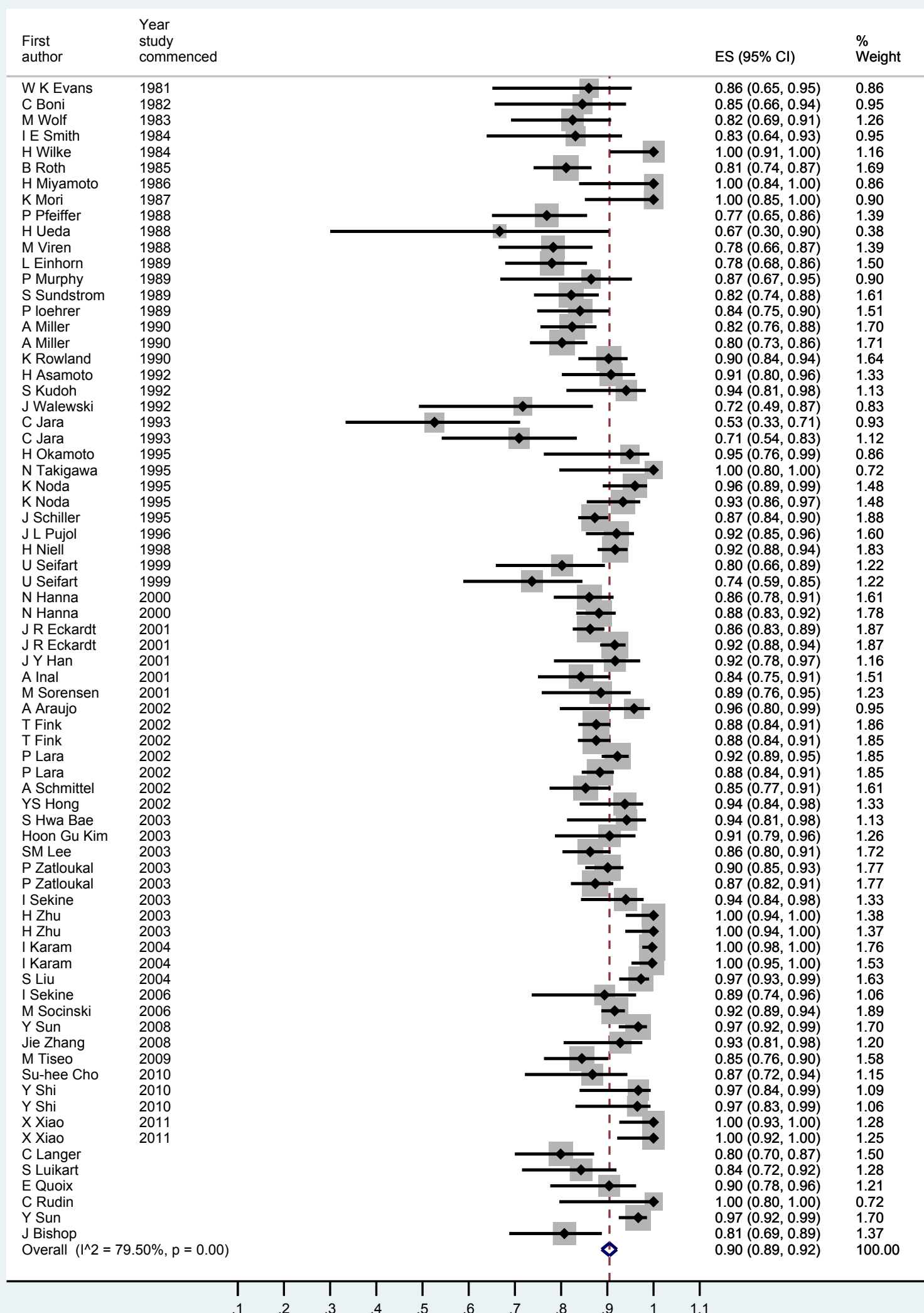
90 day survival



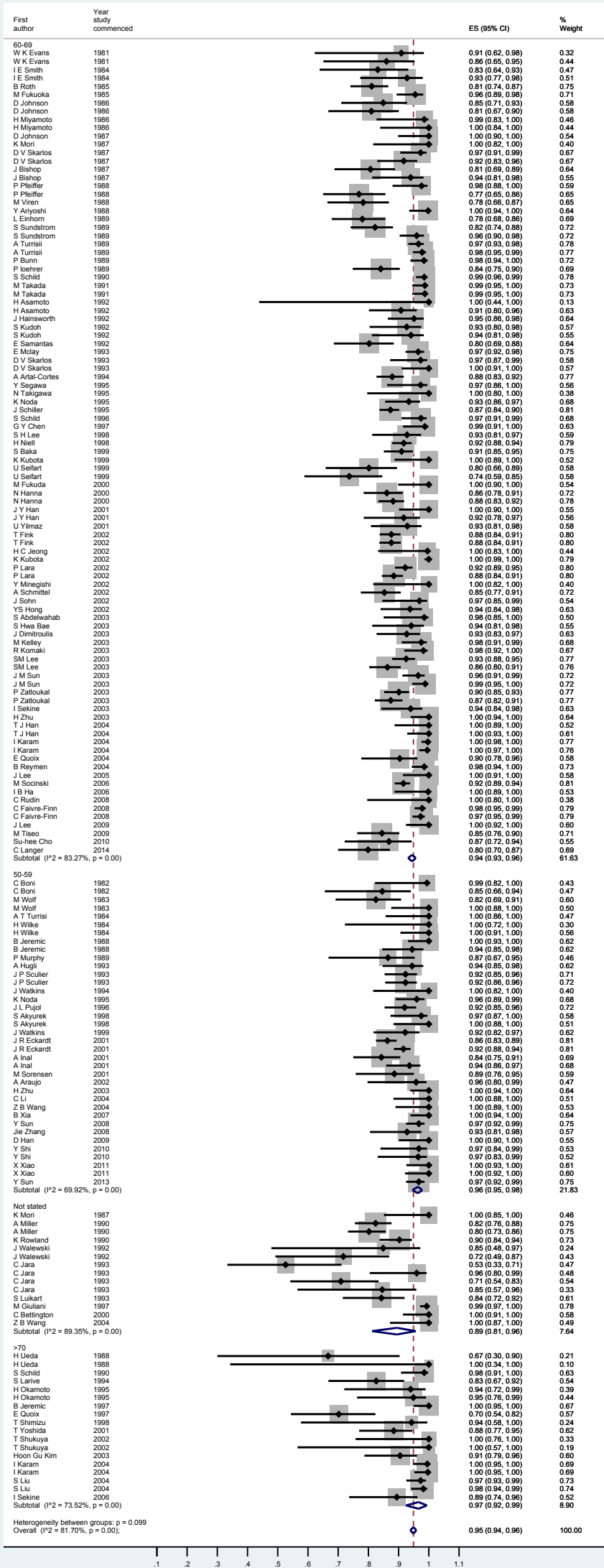
90 day survival after chemotherapy



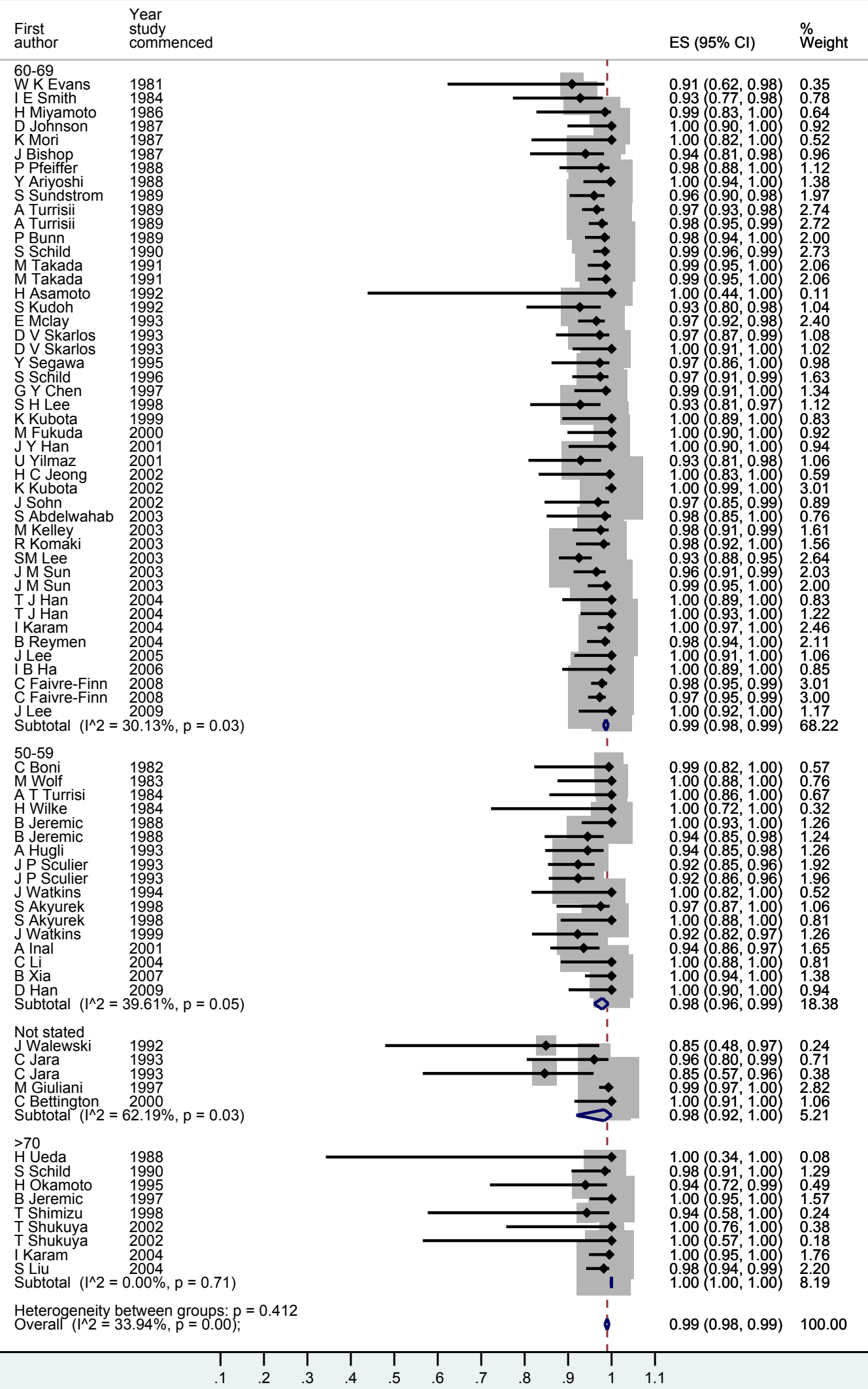
90 day survival after chemotherapy in limited stage



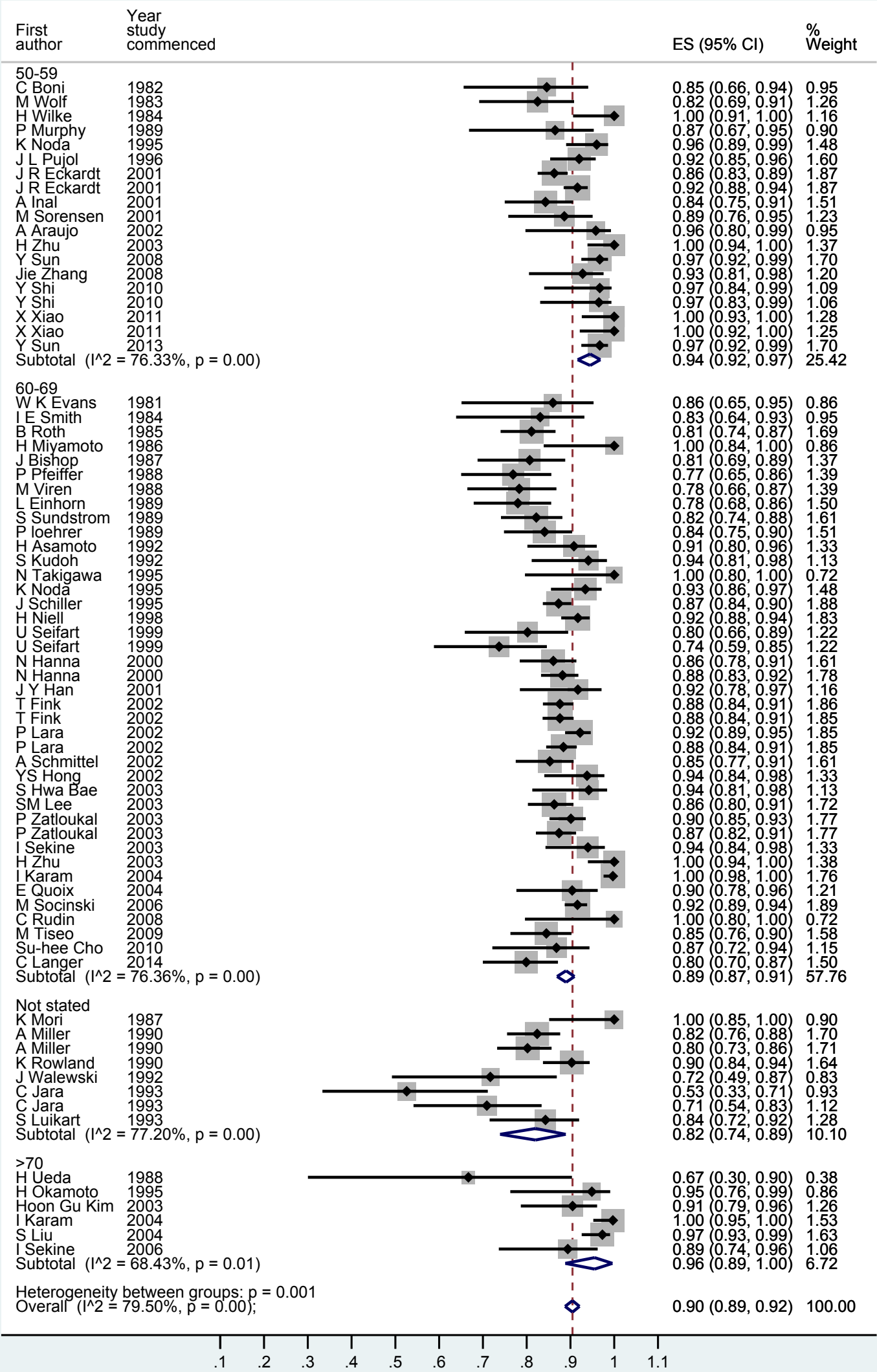
90 day survival after chemotherapy in extensive stage



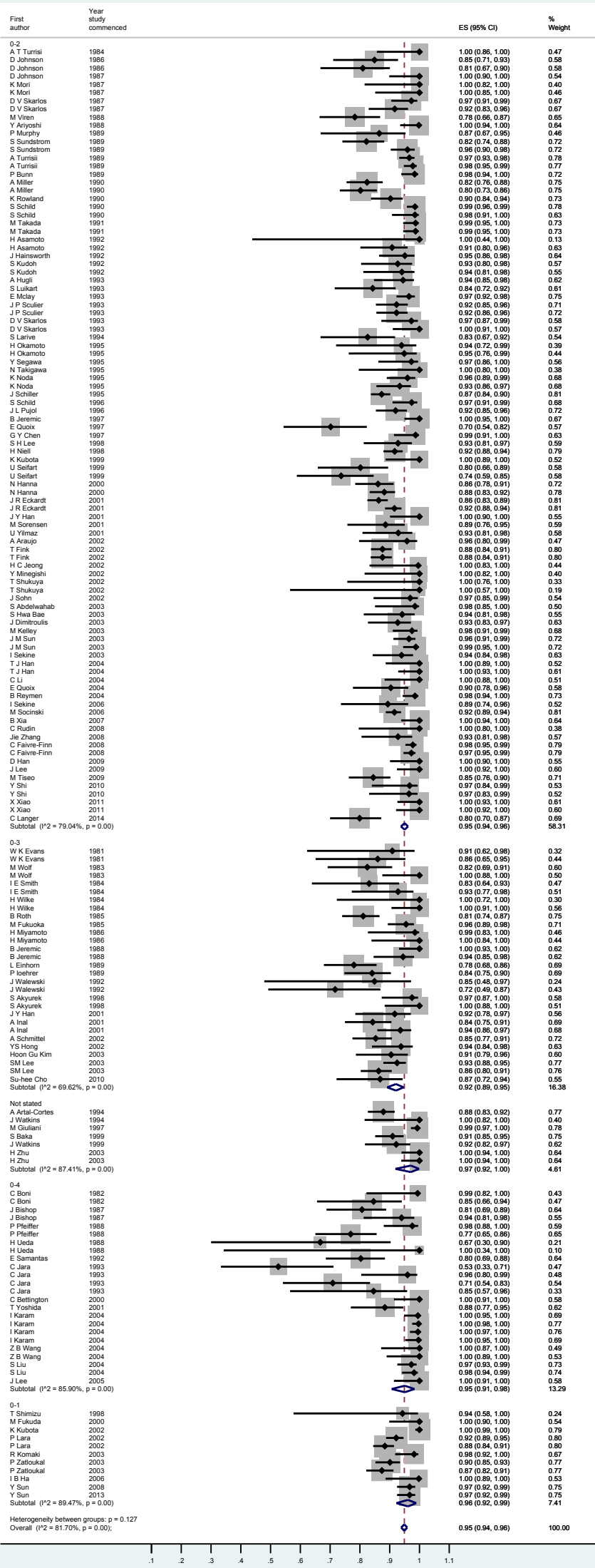
Proportion of 90 day survival by median participant age

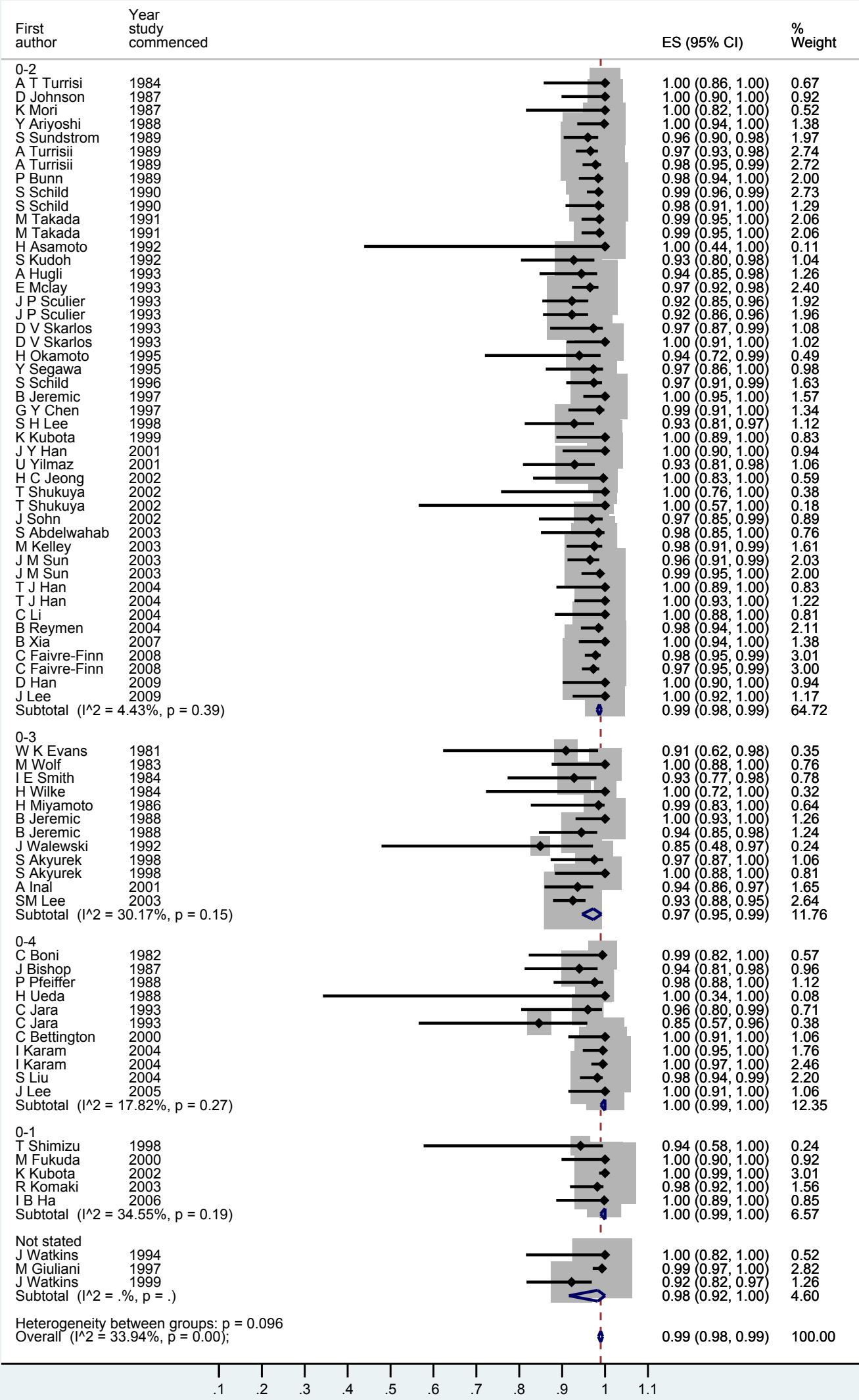


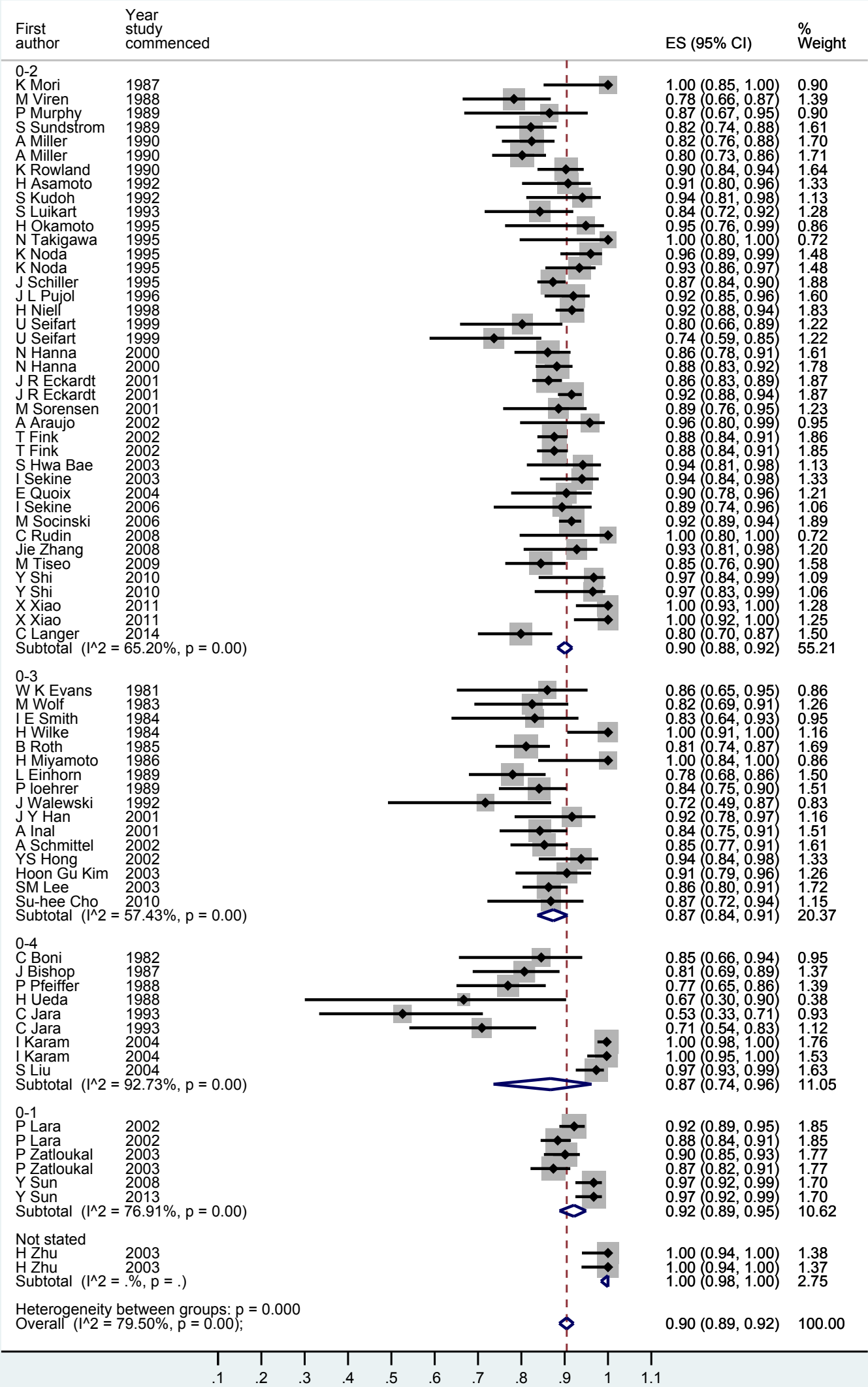
Proportion of 90 day survival in limited stage by median participant age

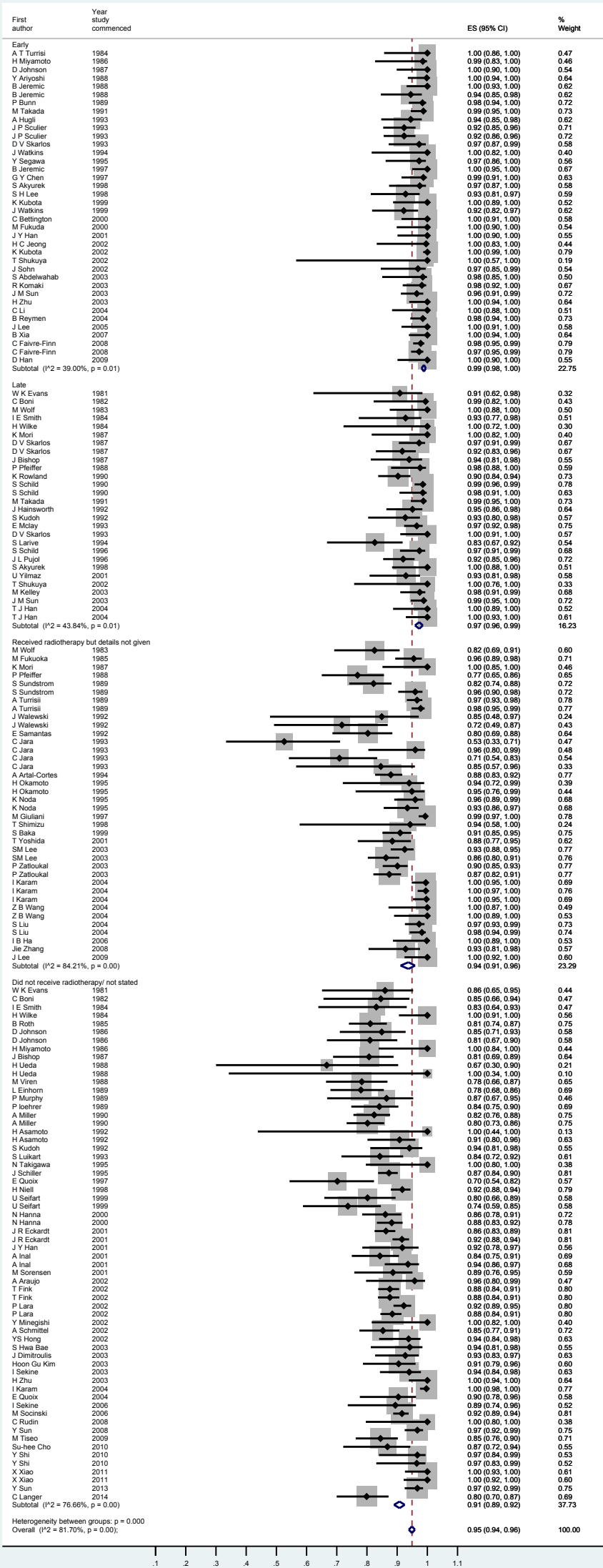


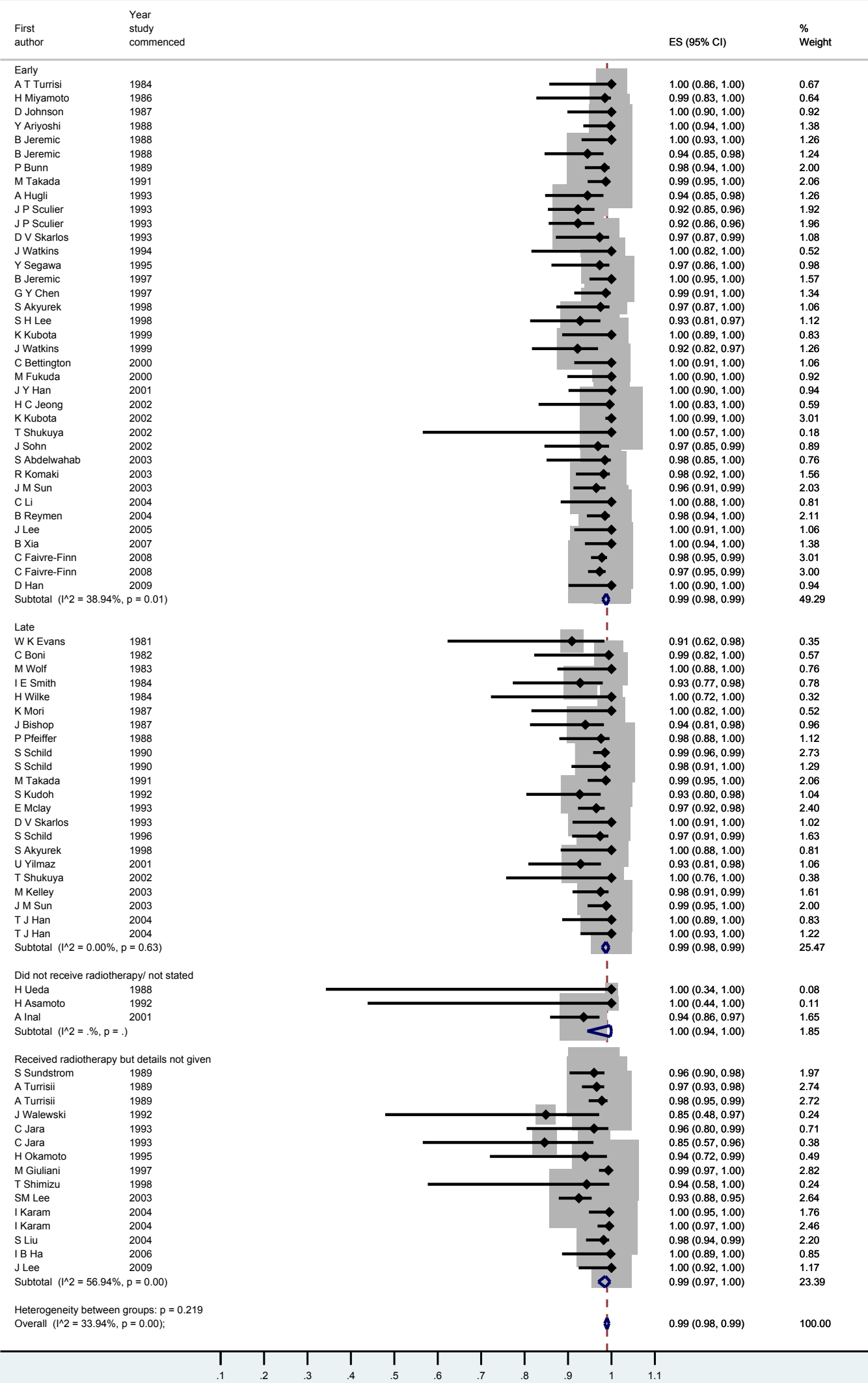
Proportion of 90 day survival in extensive stage by median participant age

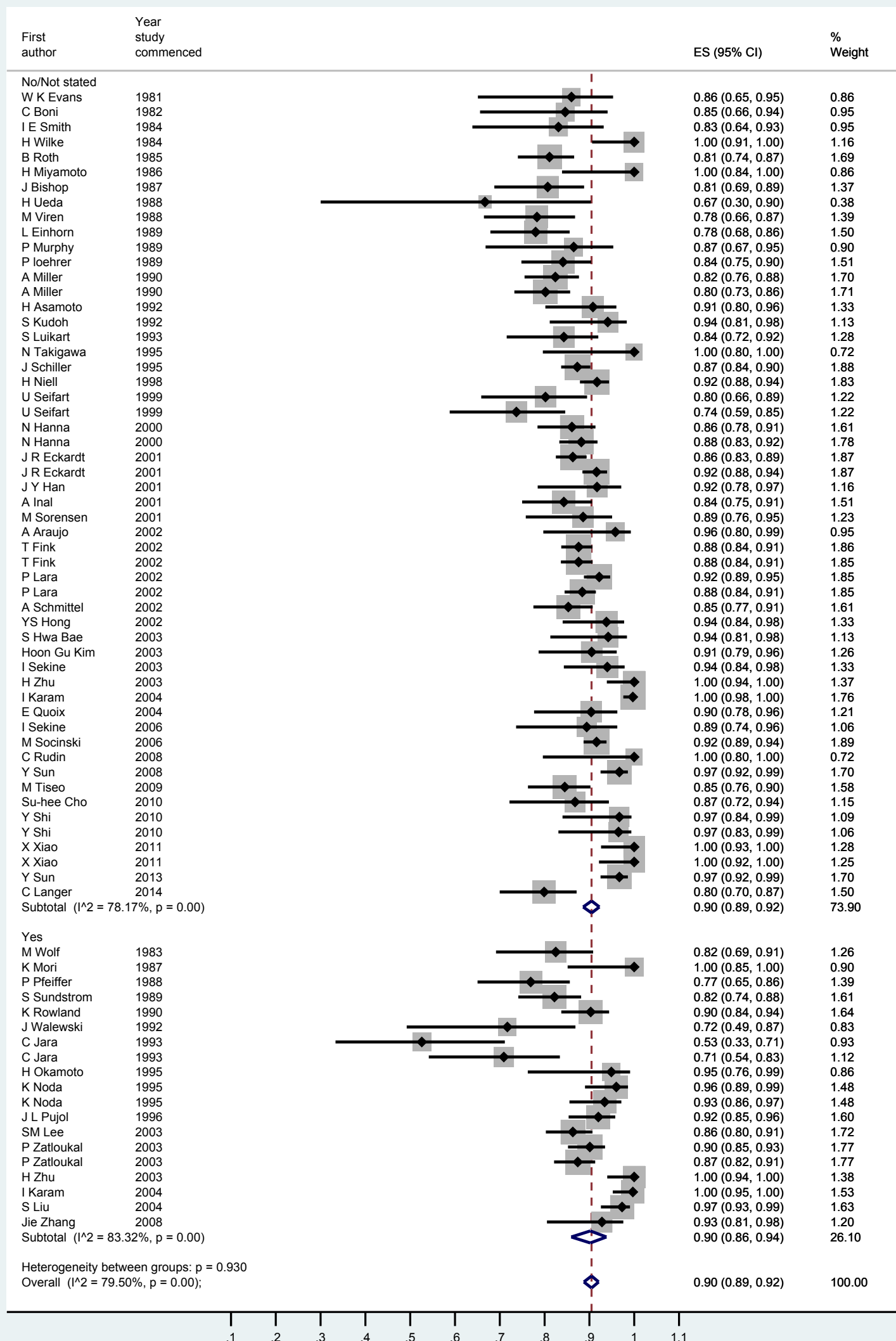


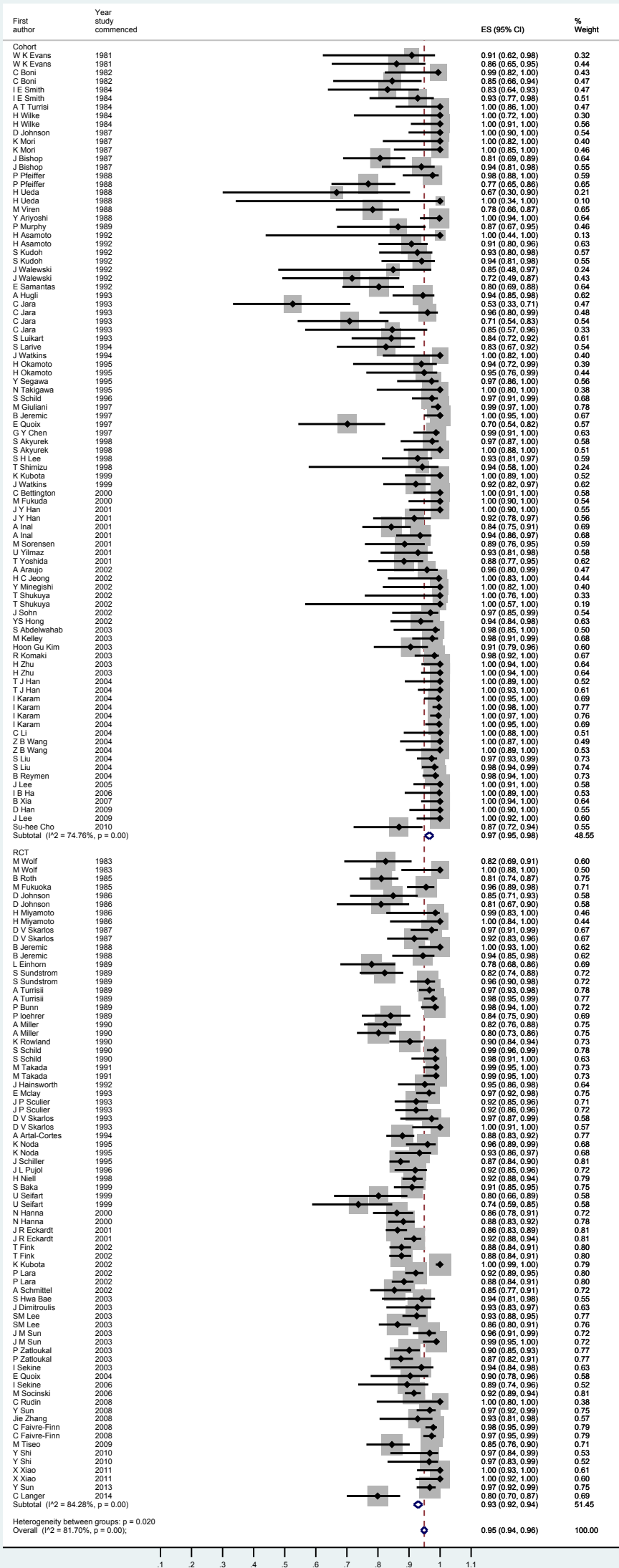




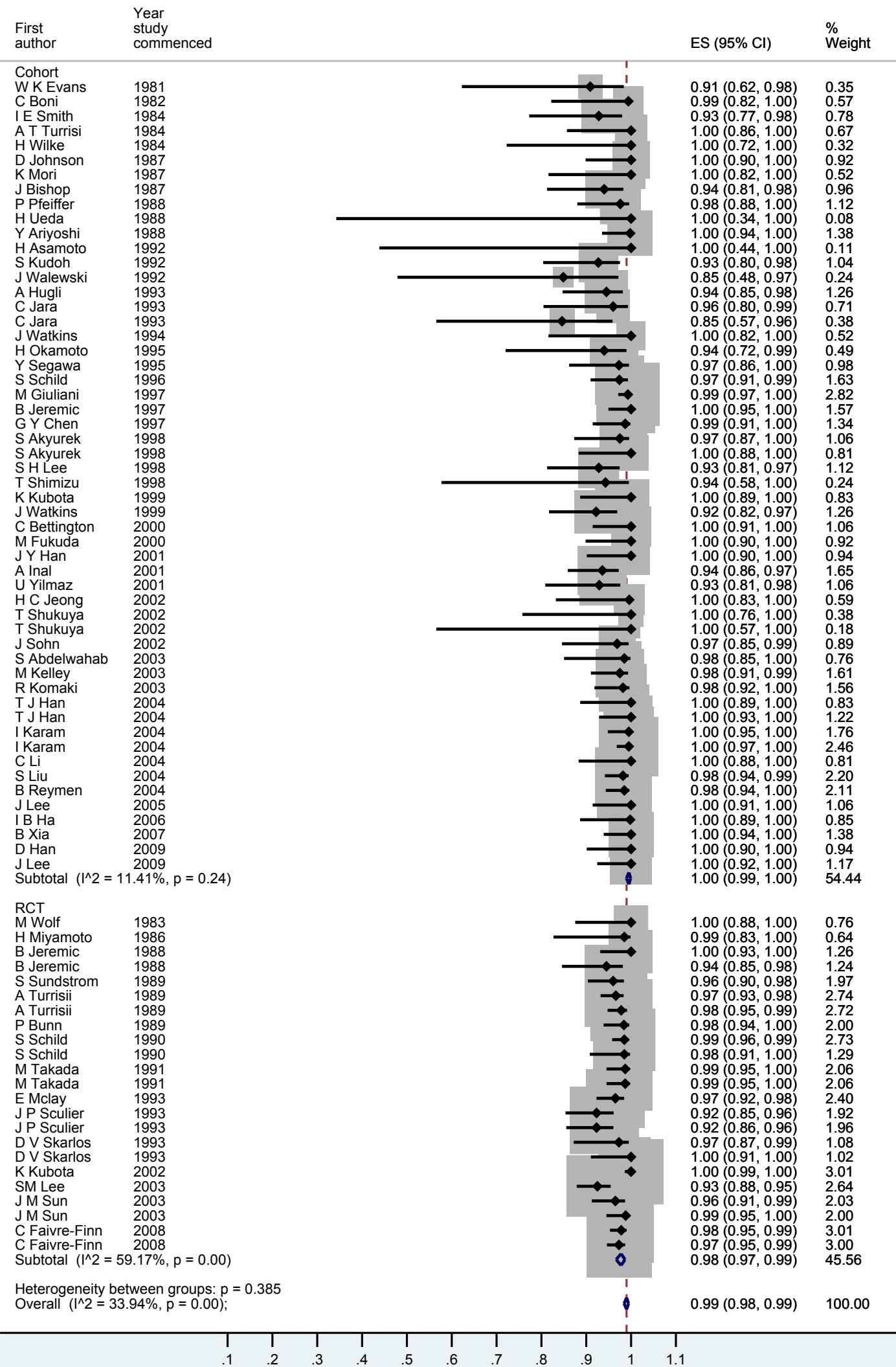




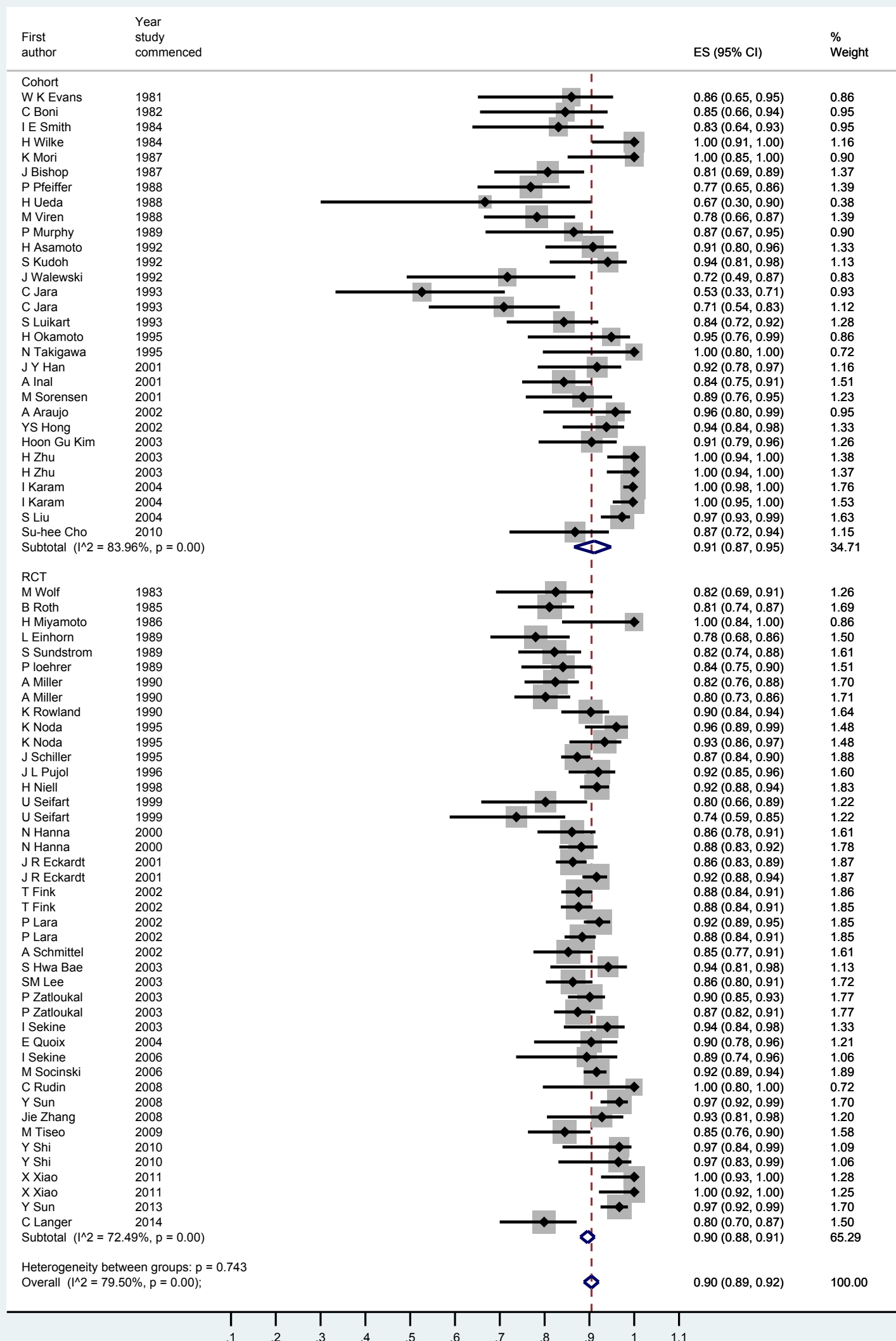




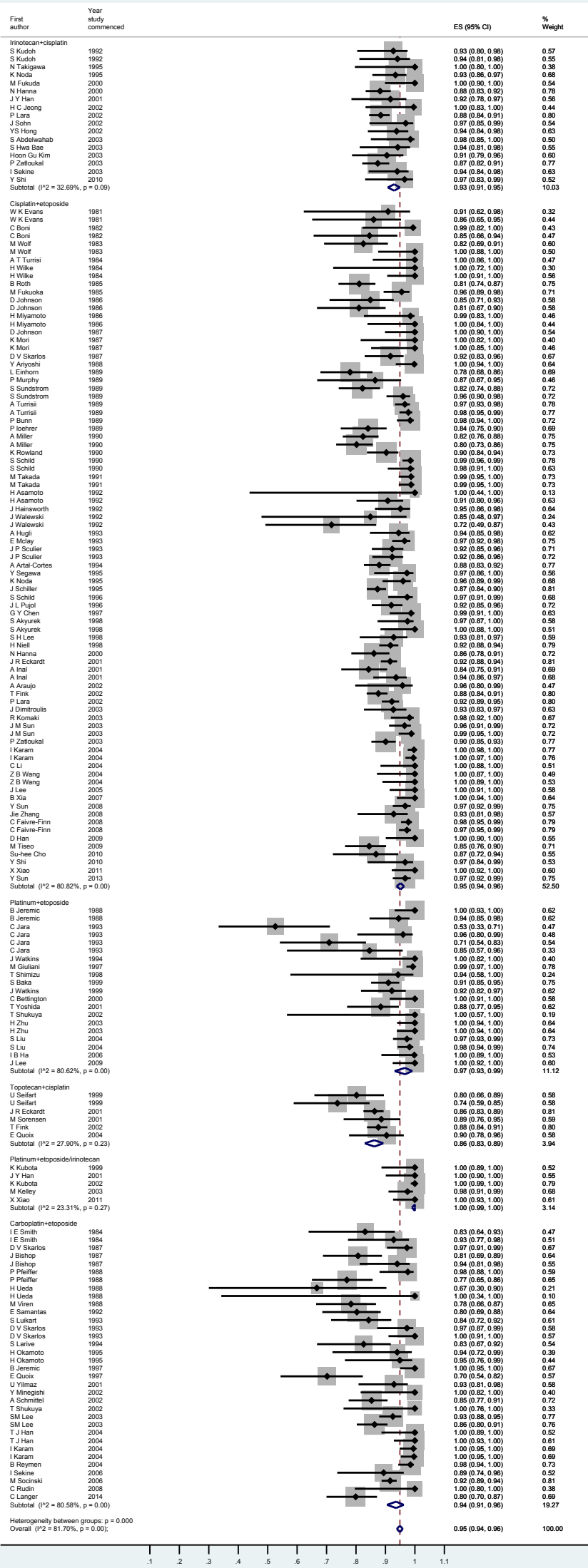
90 day survival after chemotherapy by study design



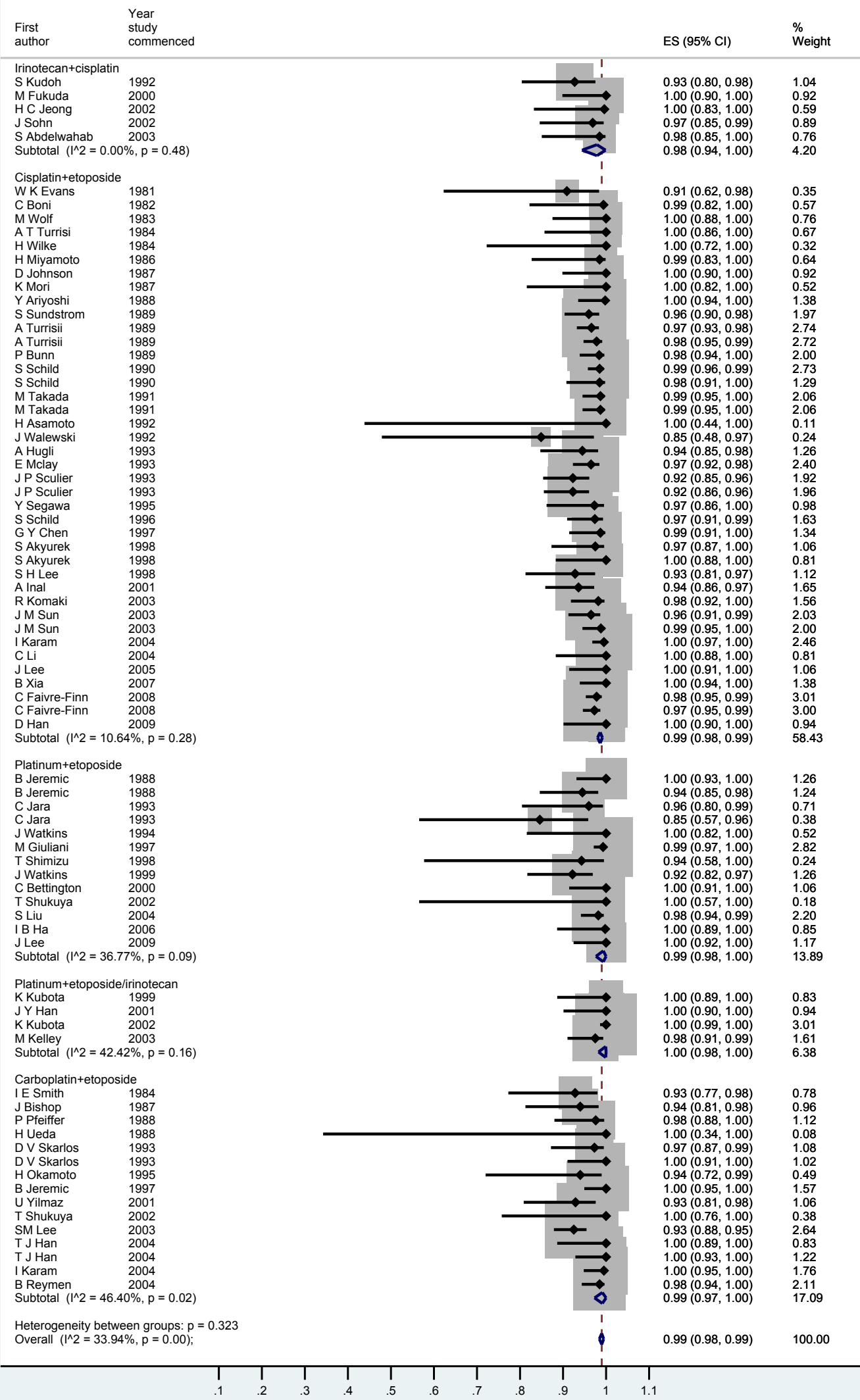
Proportion of 90 day survival in limited stage by study design

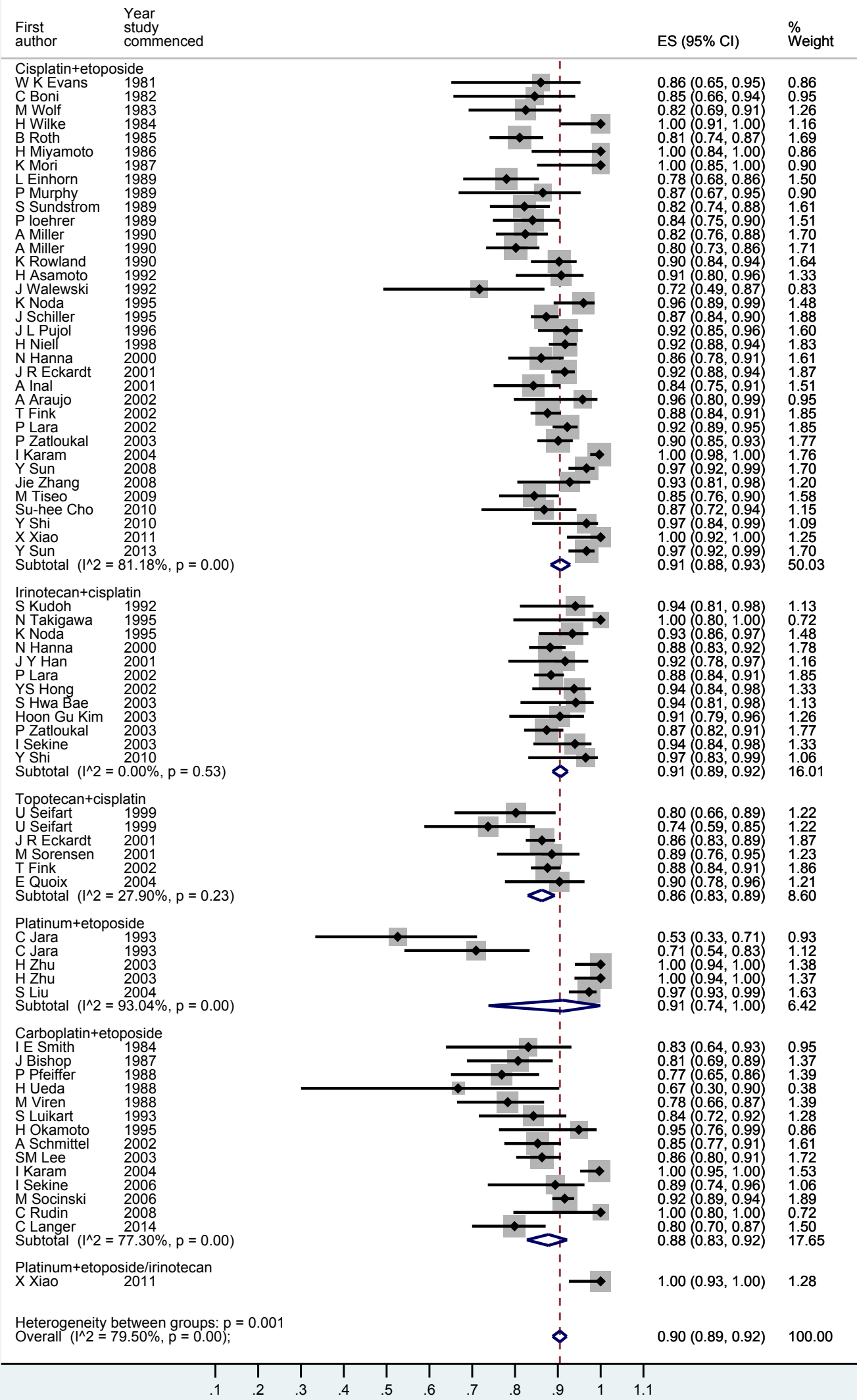


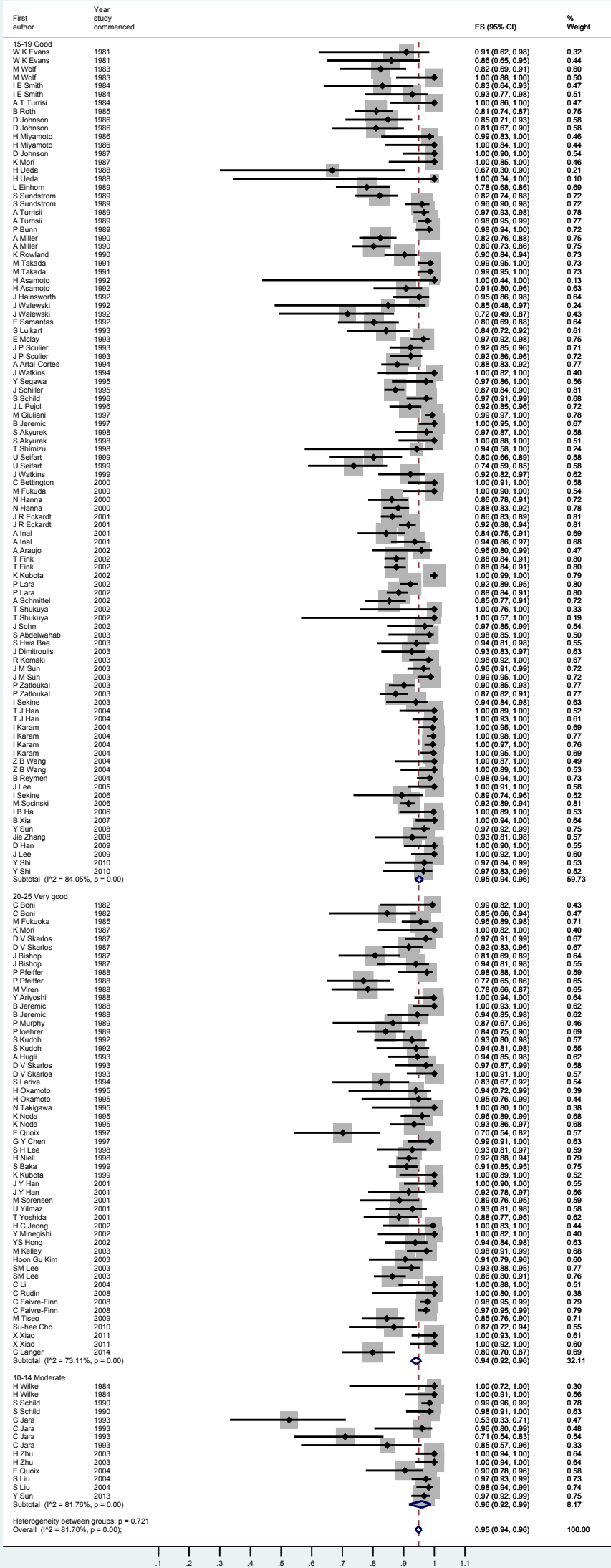
Proportion of 90 day survival in extensive stage by study design



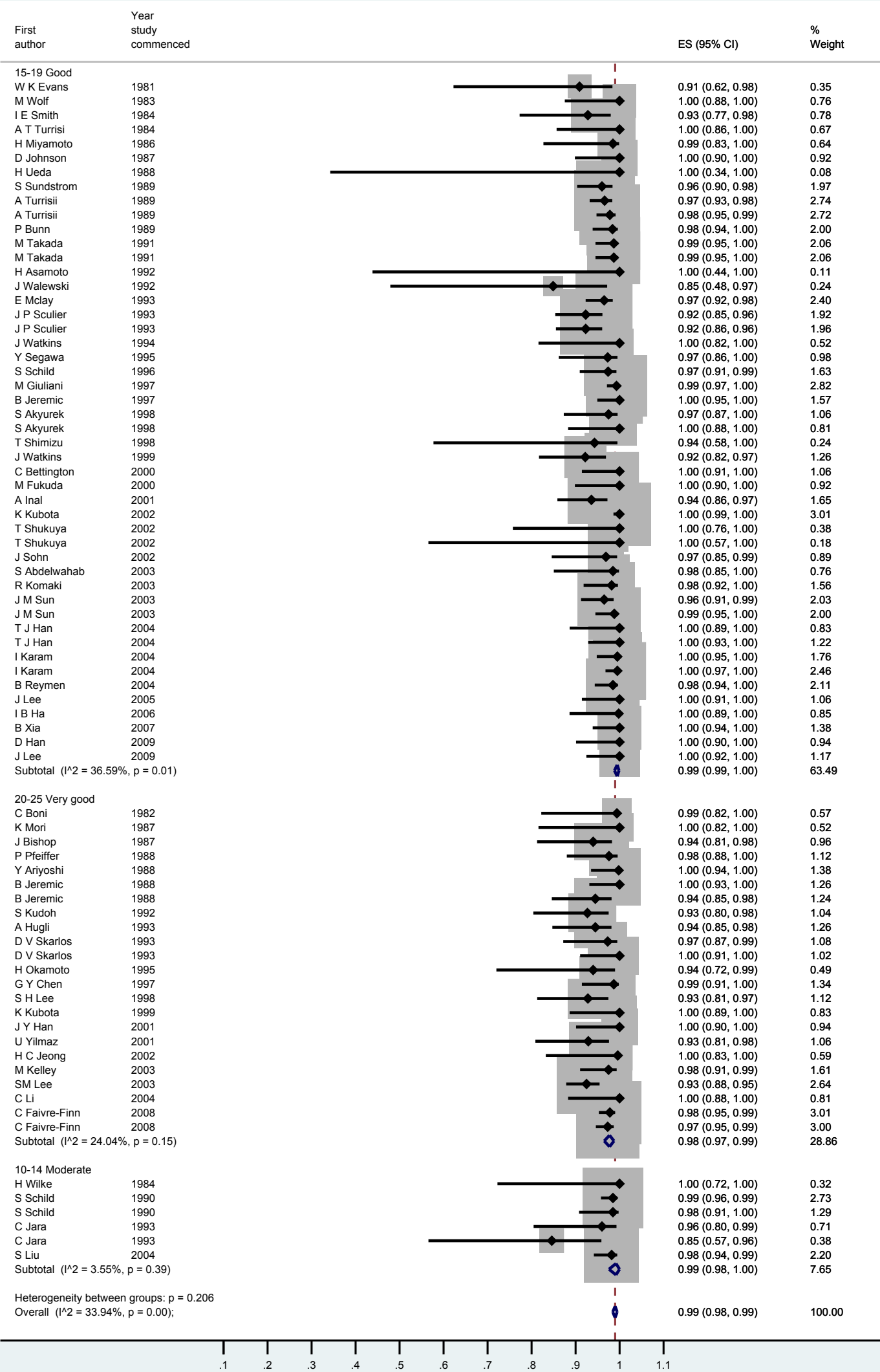
90 day survival after chemotherapy by drug

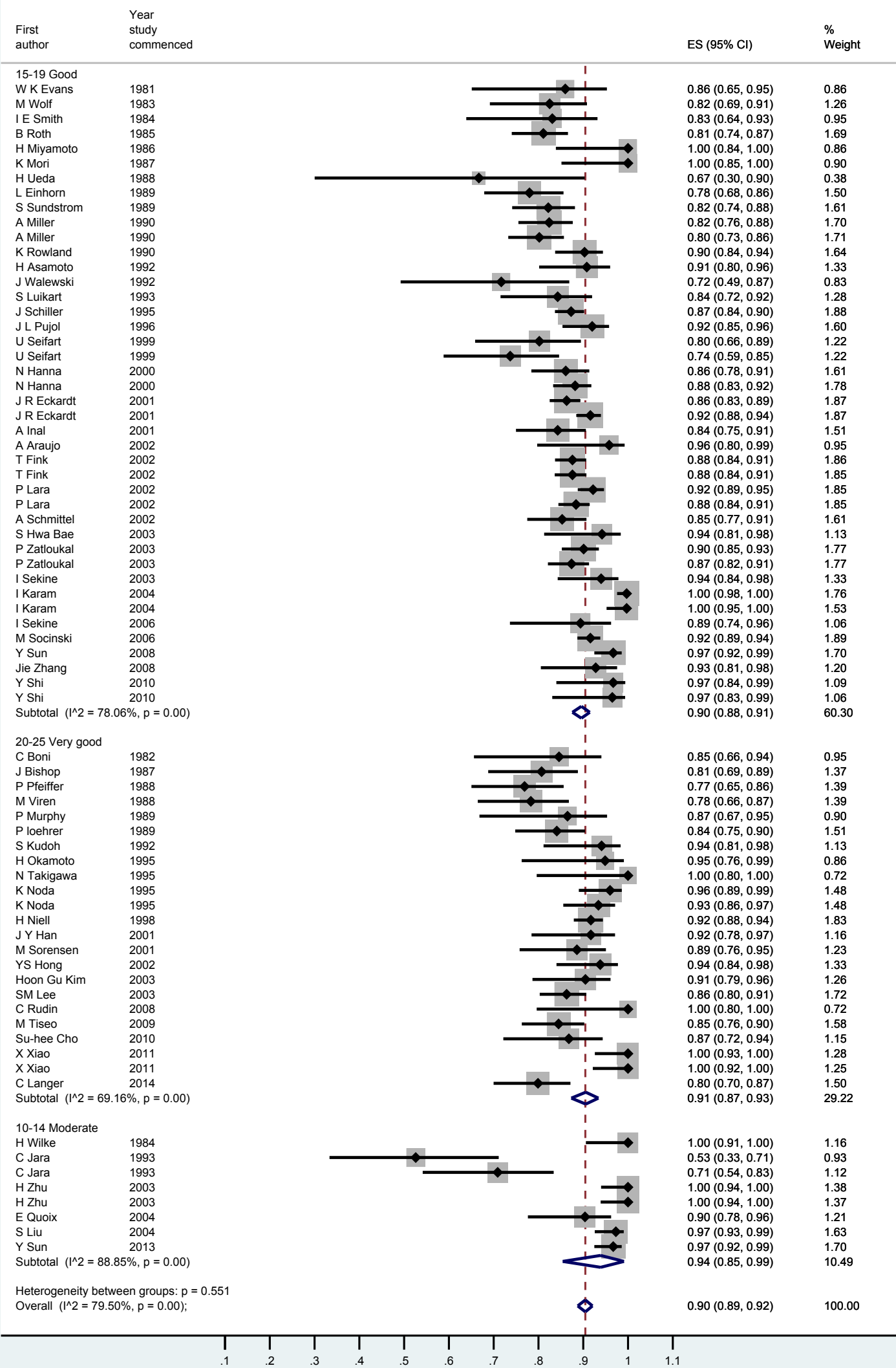


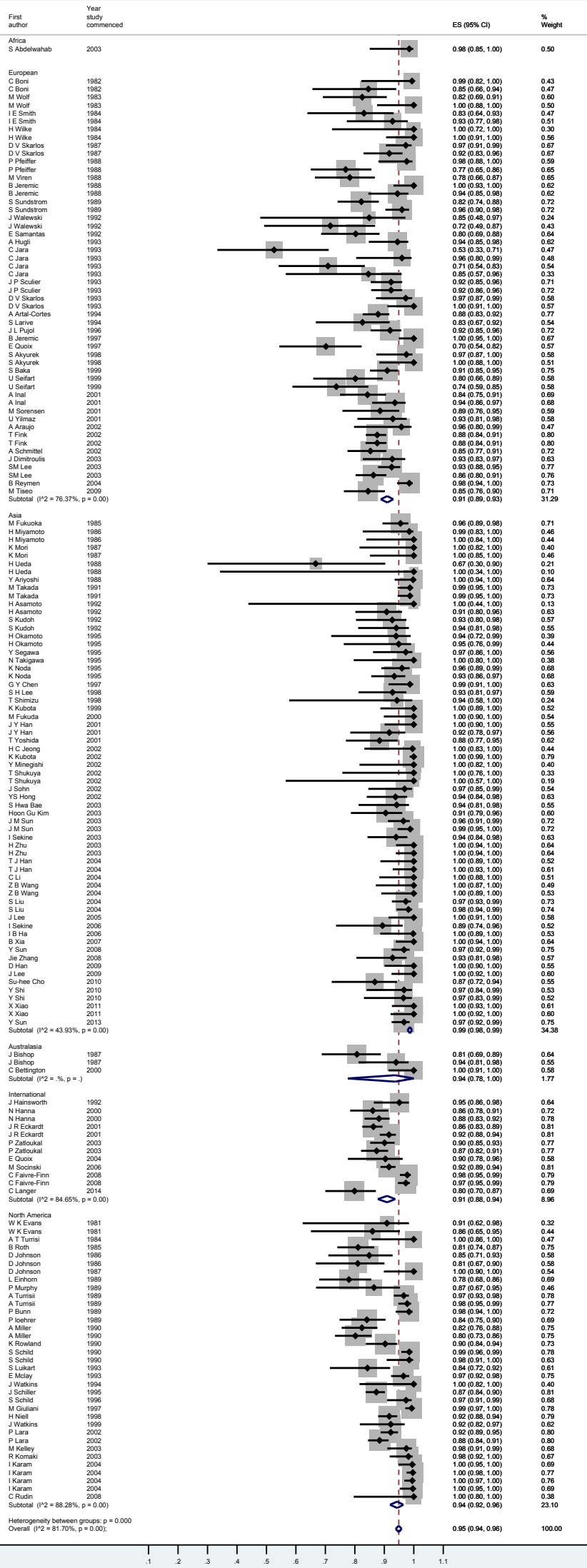




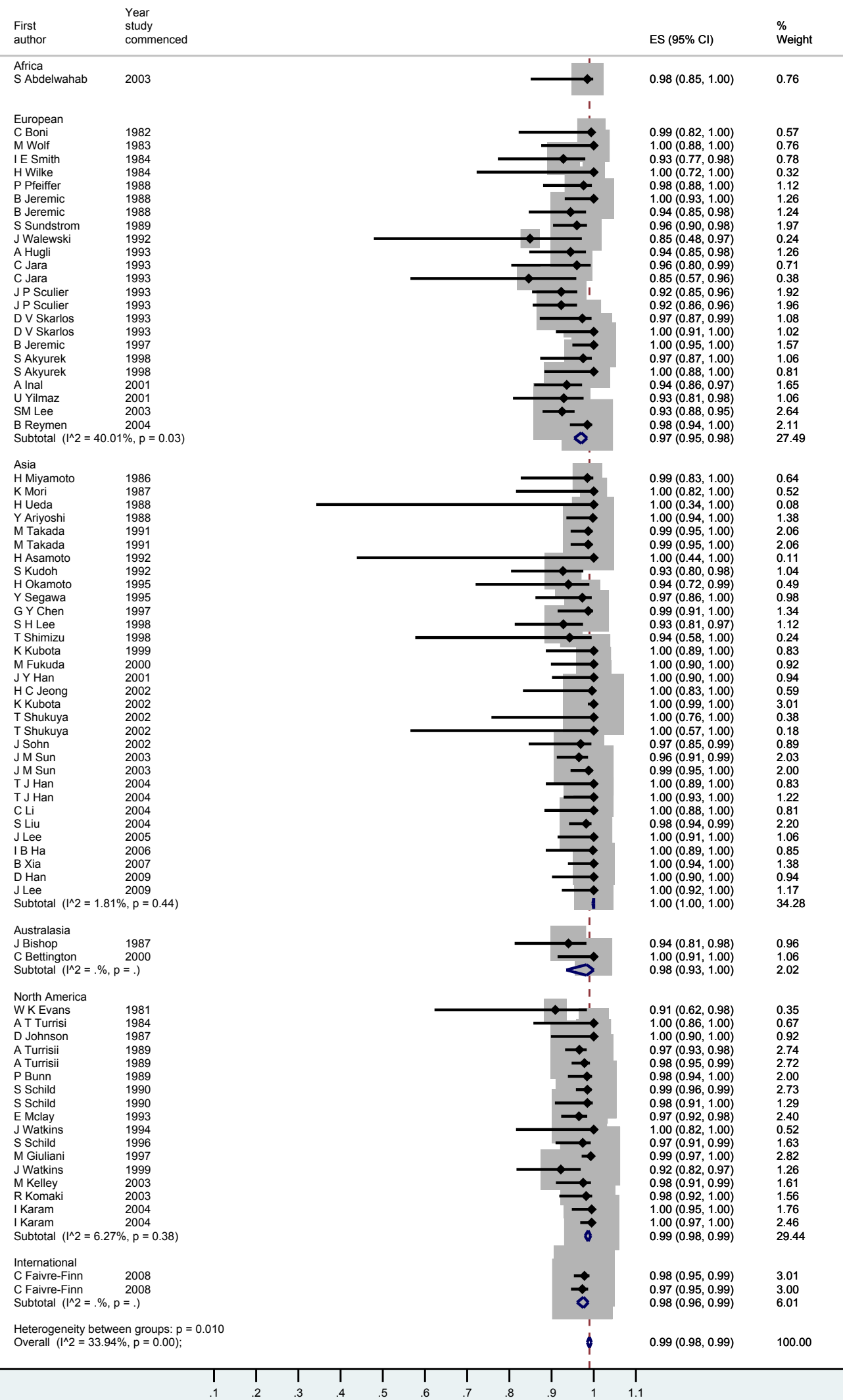
90 day survival after chemotherapy by quality score

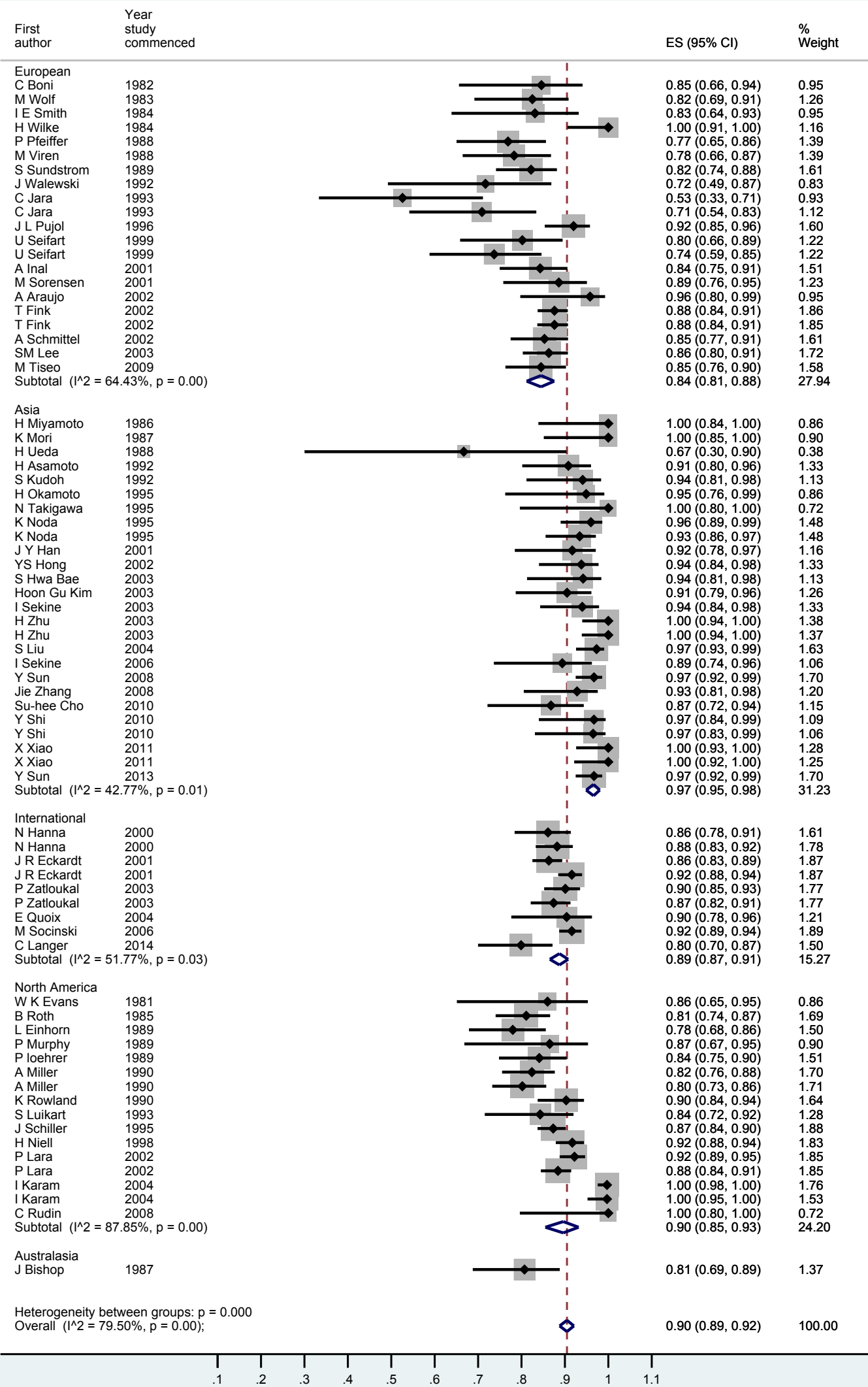


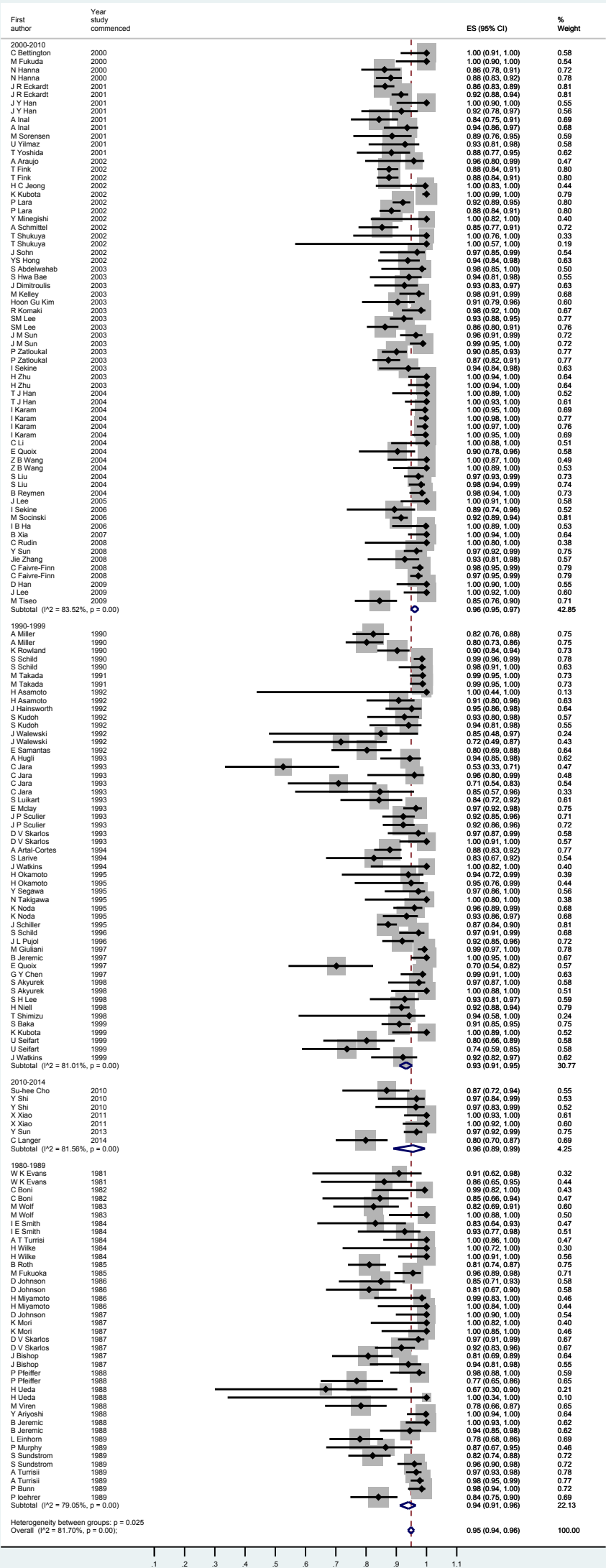




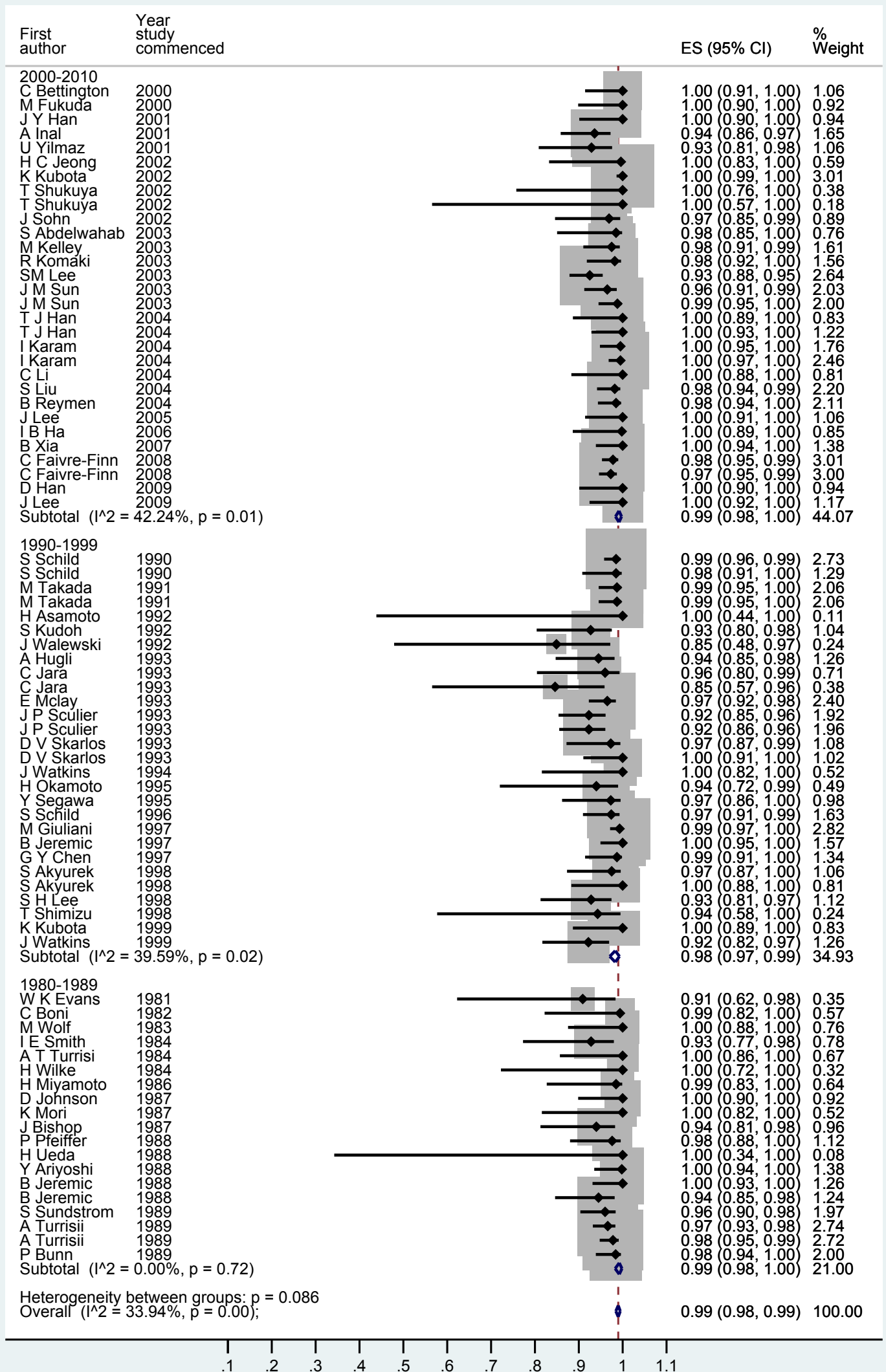
90 day survival after chemotherapy by region

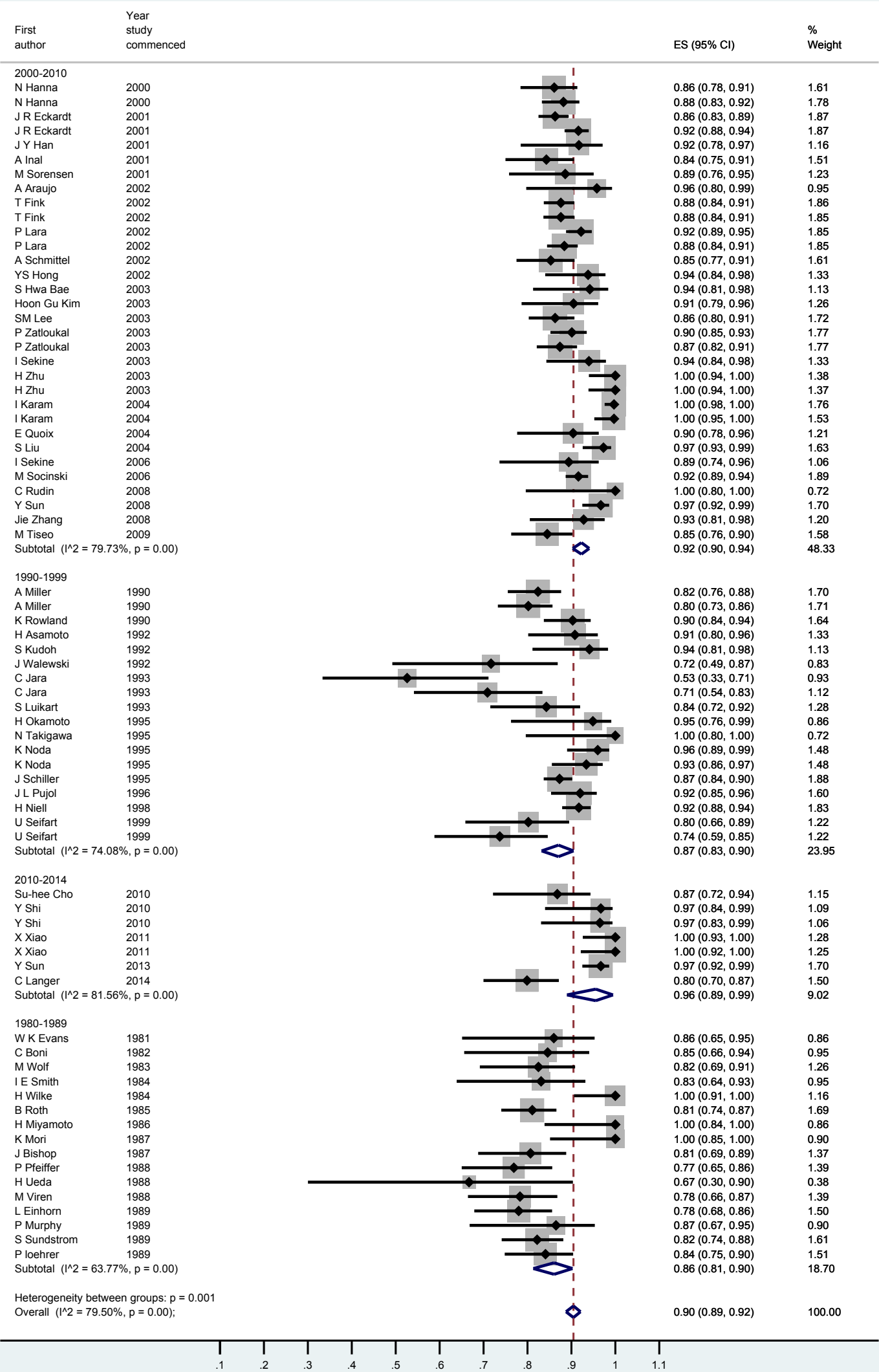






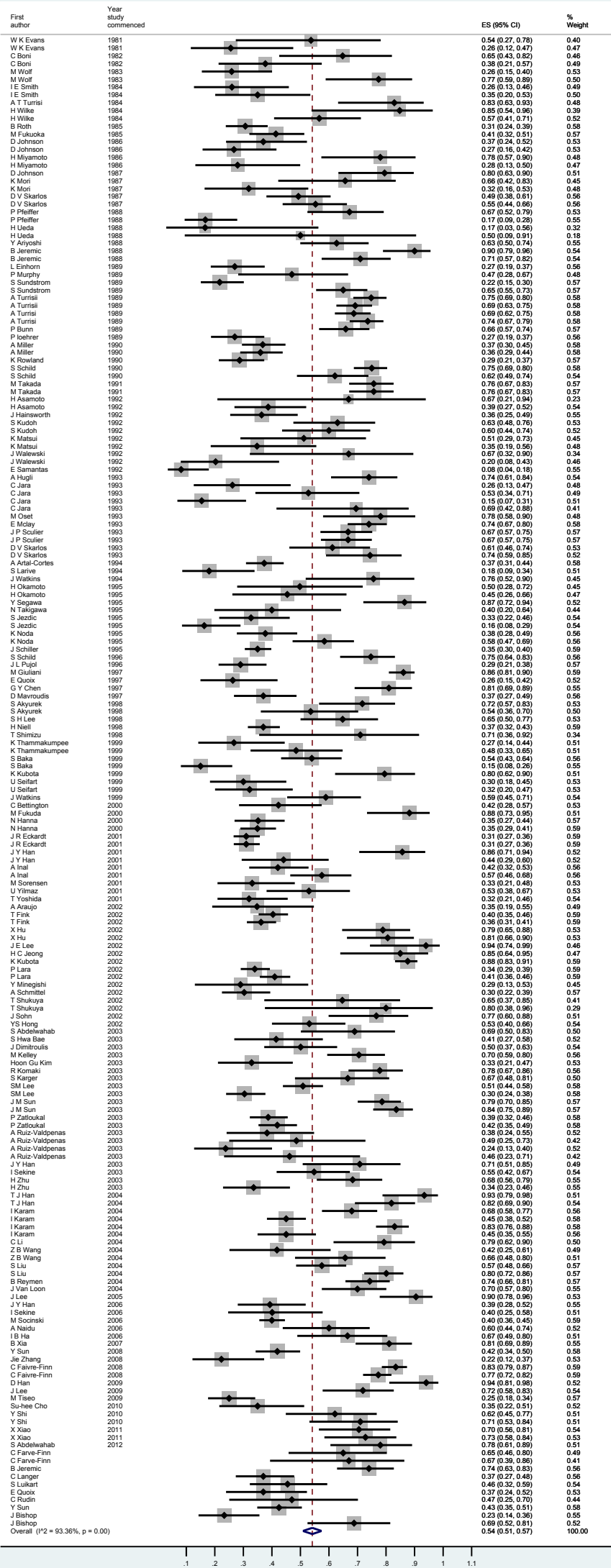
90 day survival after chemotherapy by study year

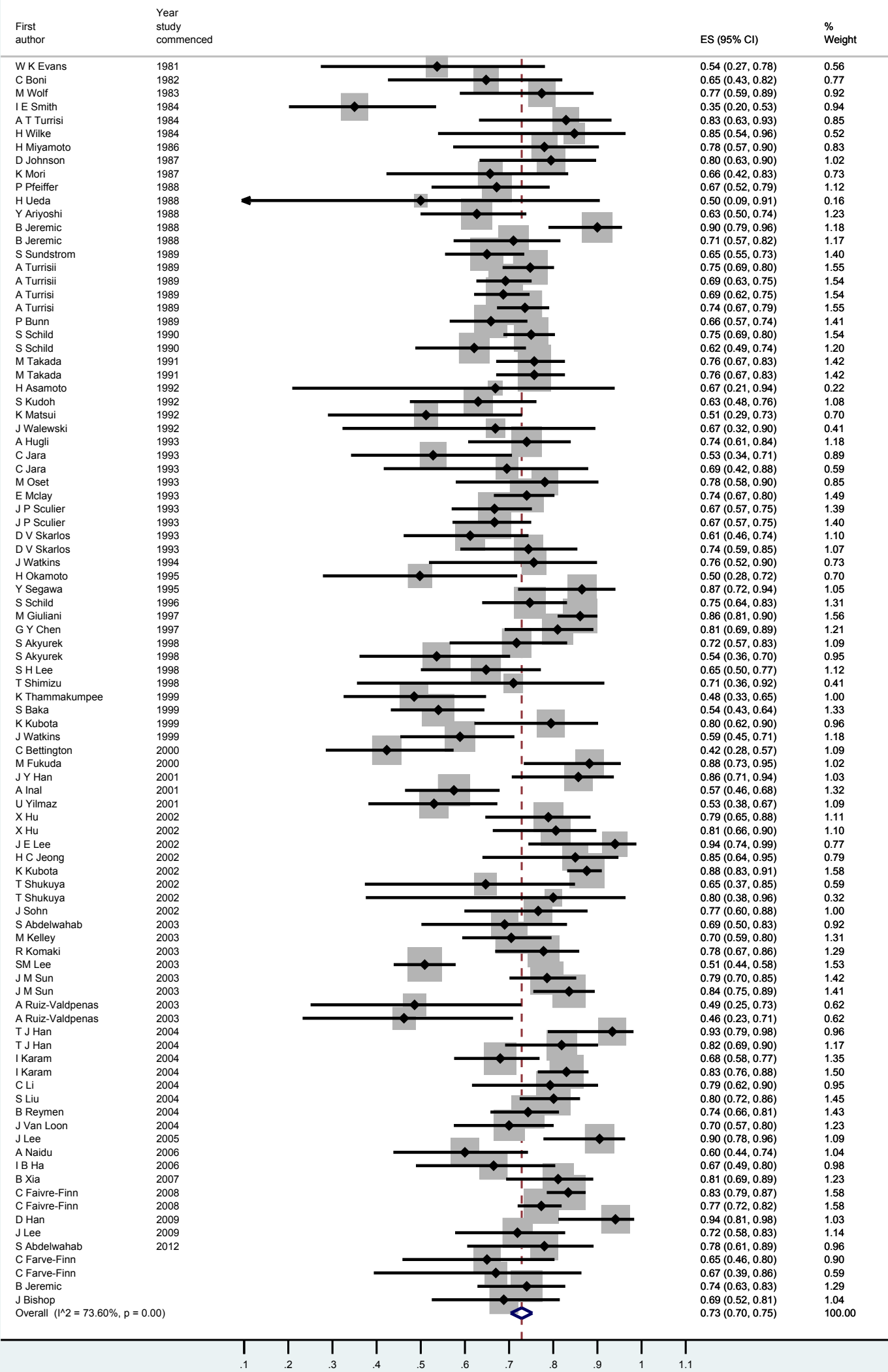




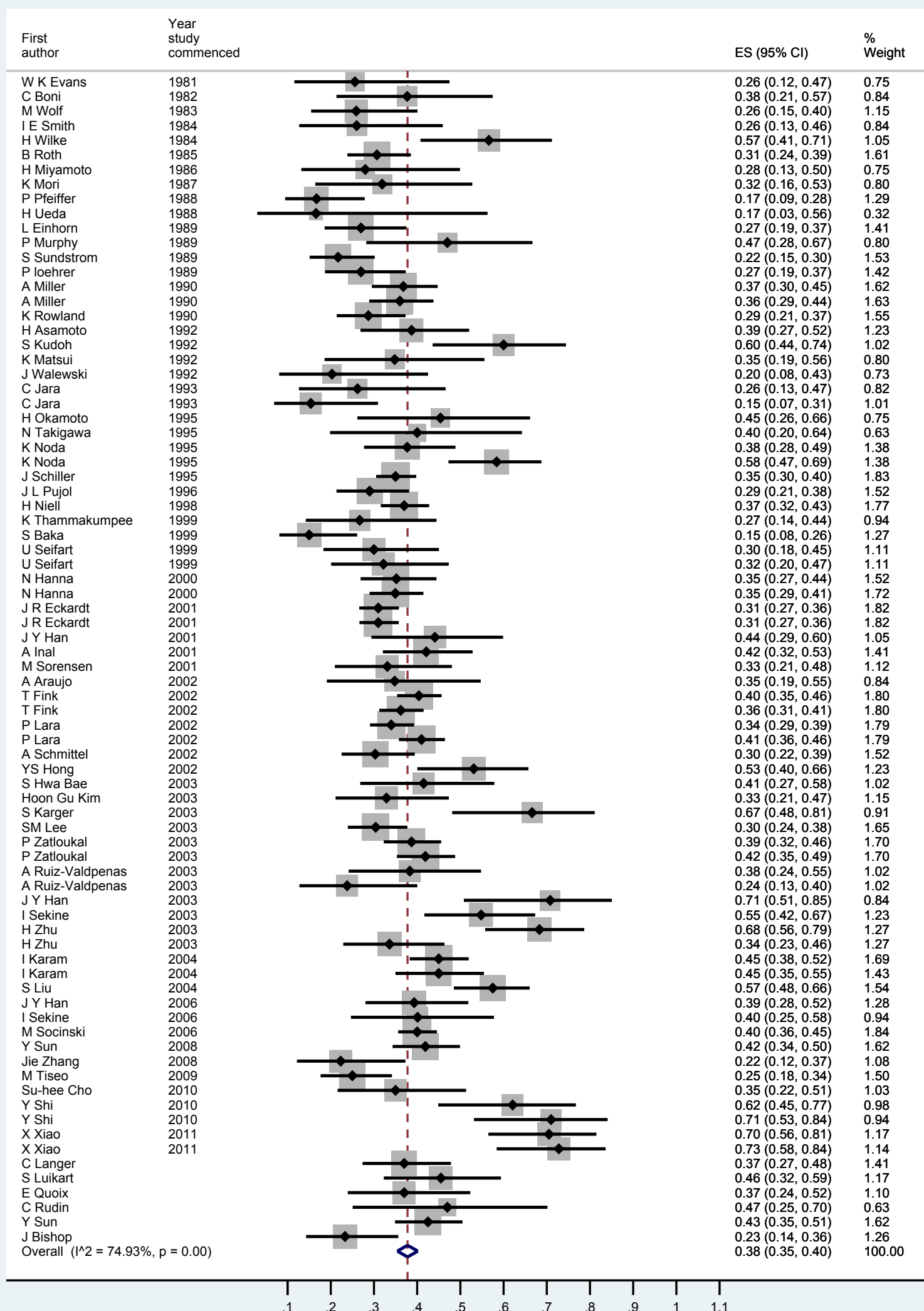
Proportion of 90 day survival in extensive stage by study year

1-year survival

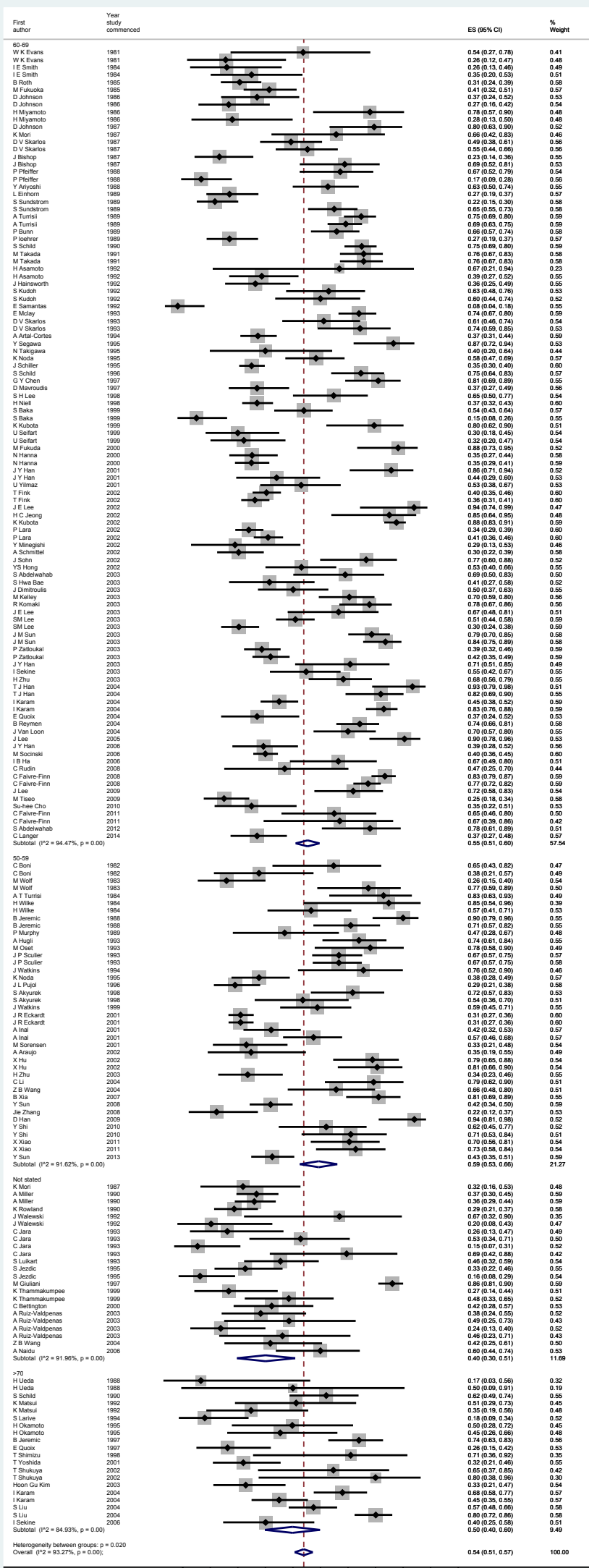




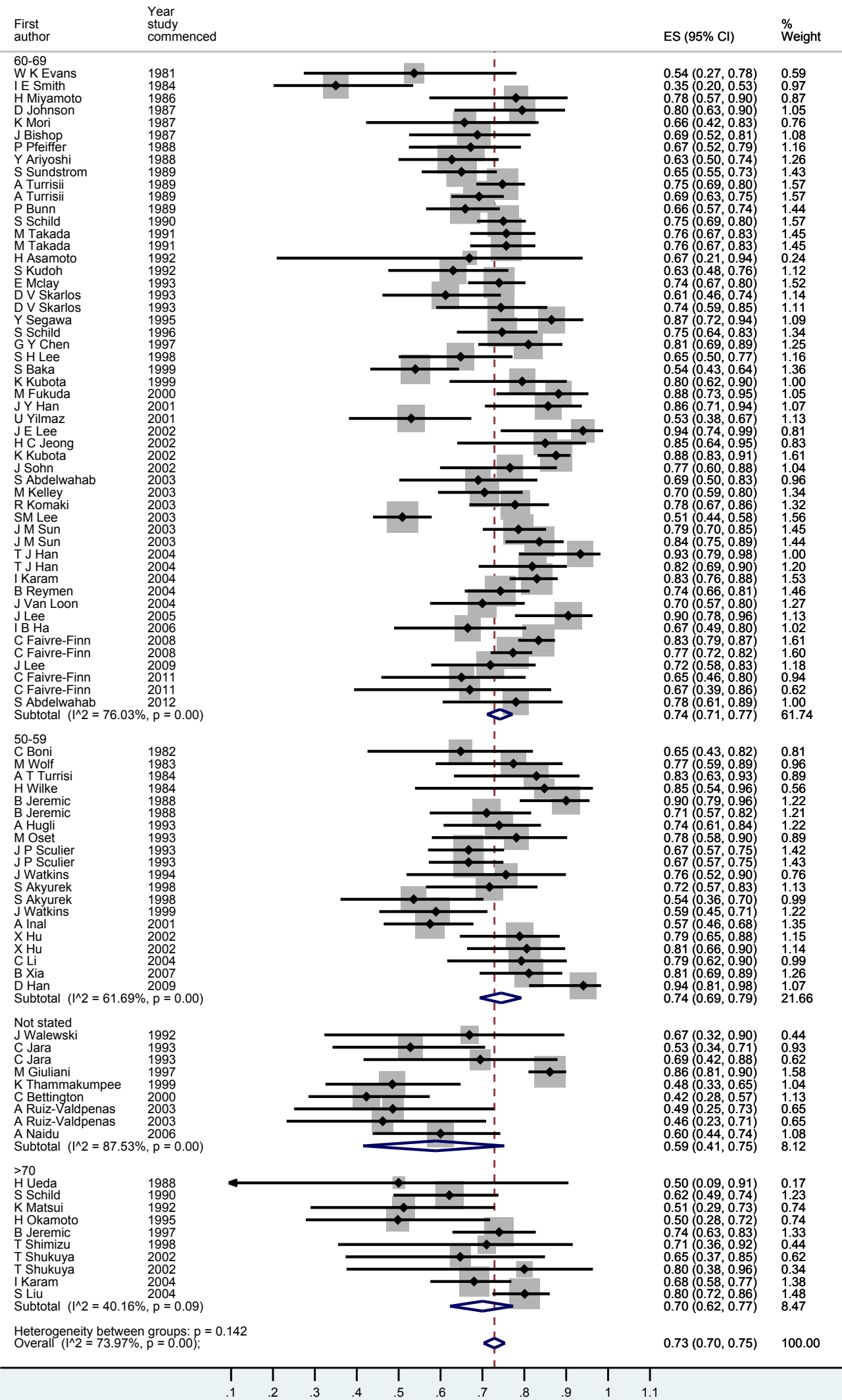
1 year survival after chemotherapy in limited stage



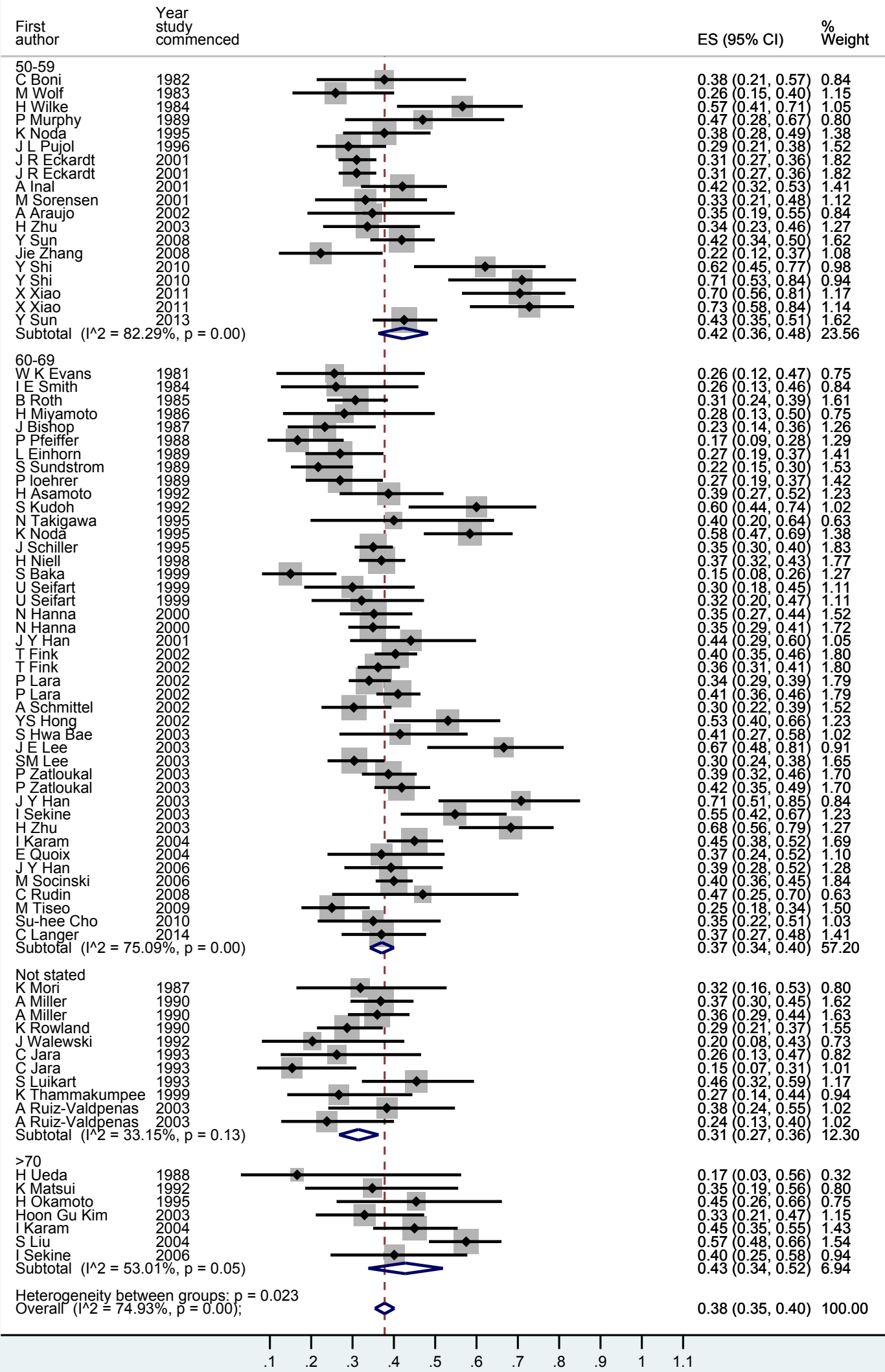
1 year survival after chemotherapy in extensive stage



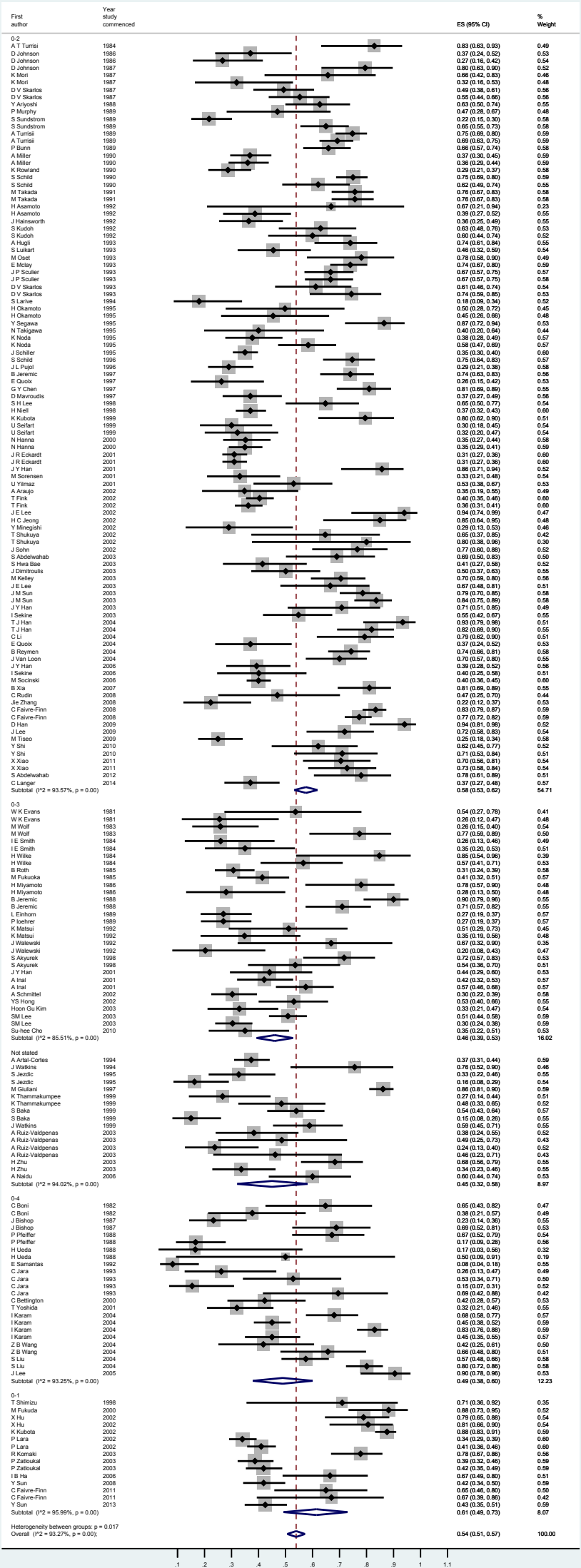
Proportion of 1 year survival by median participant age

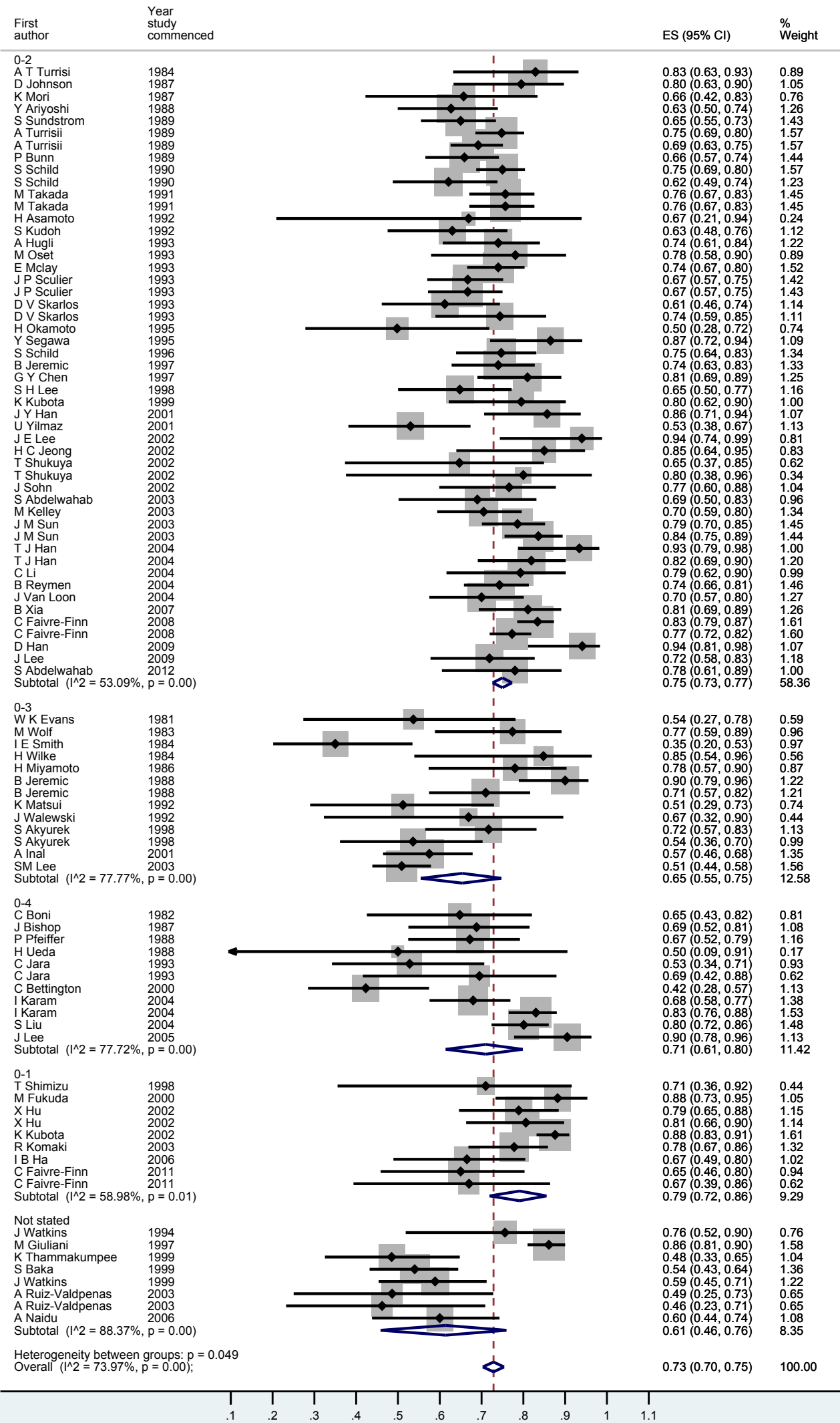


Proportion of 1 year survival in limited stage by median participant age

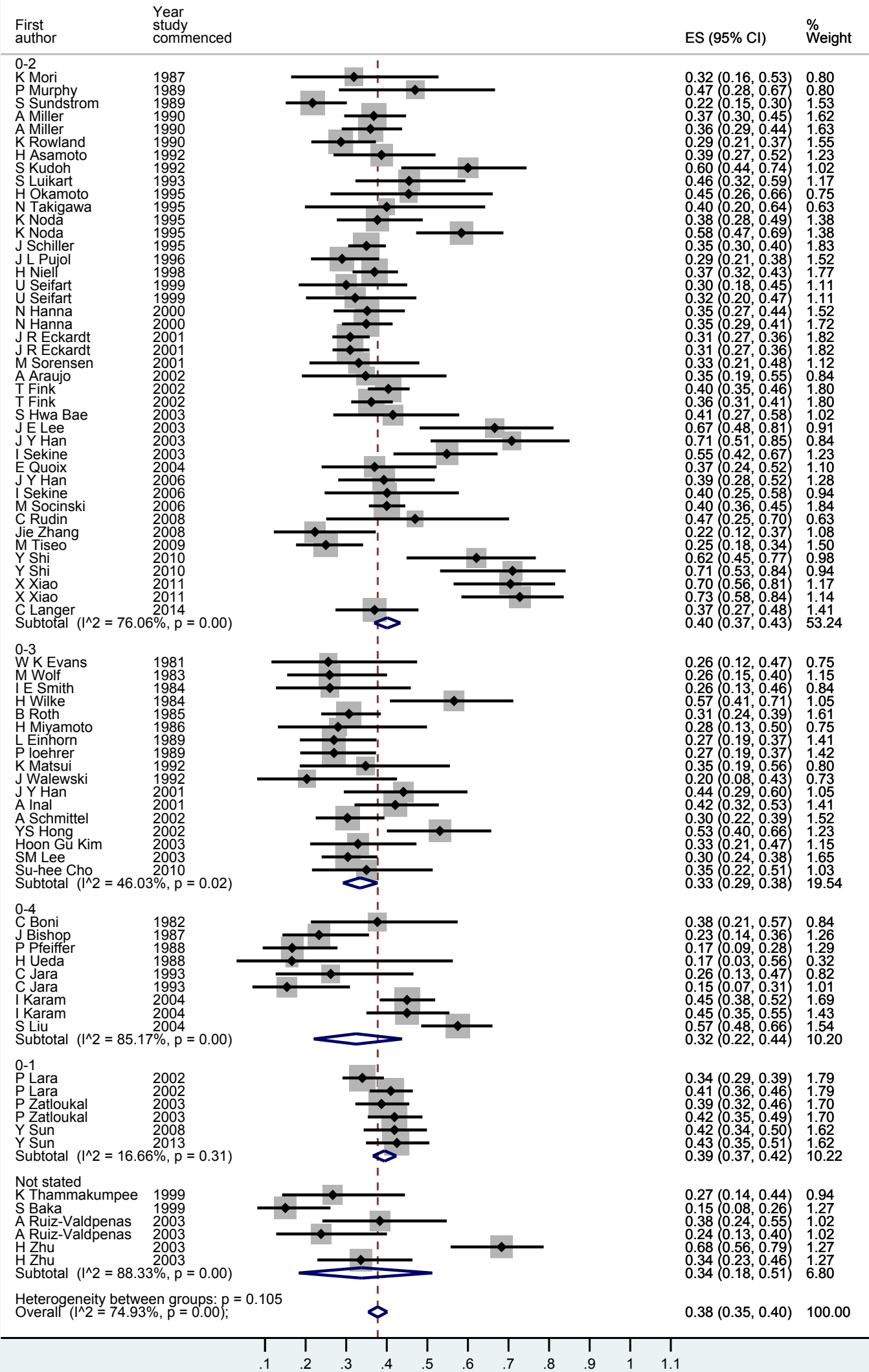


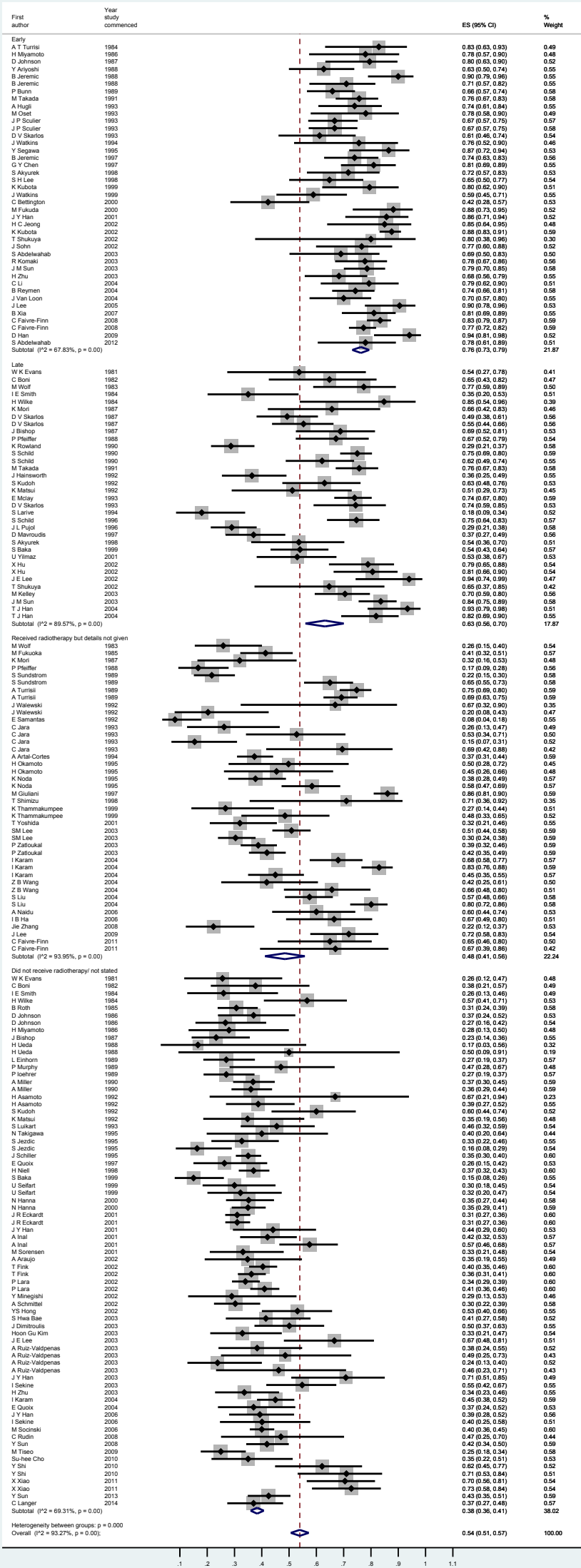
Proportion of 1 year survival in extensive stage by median participant age



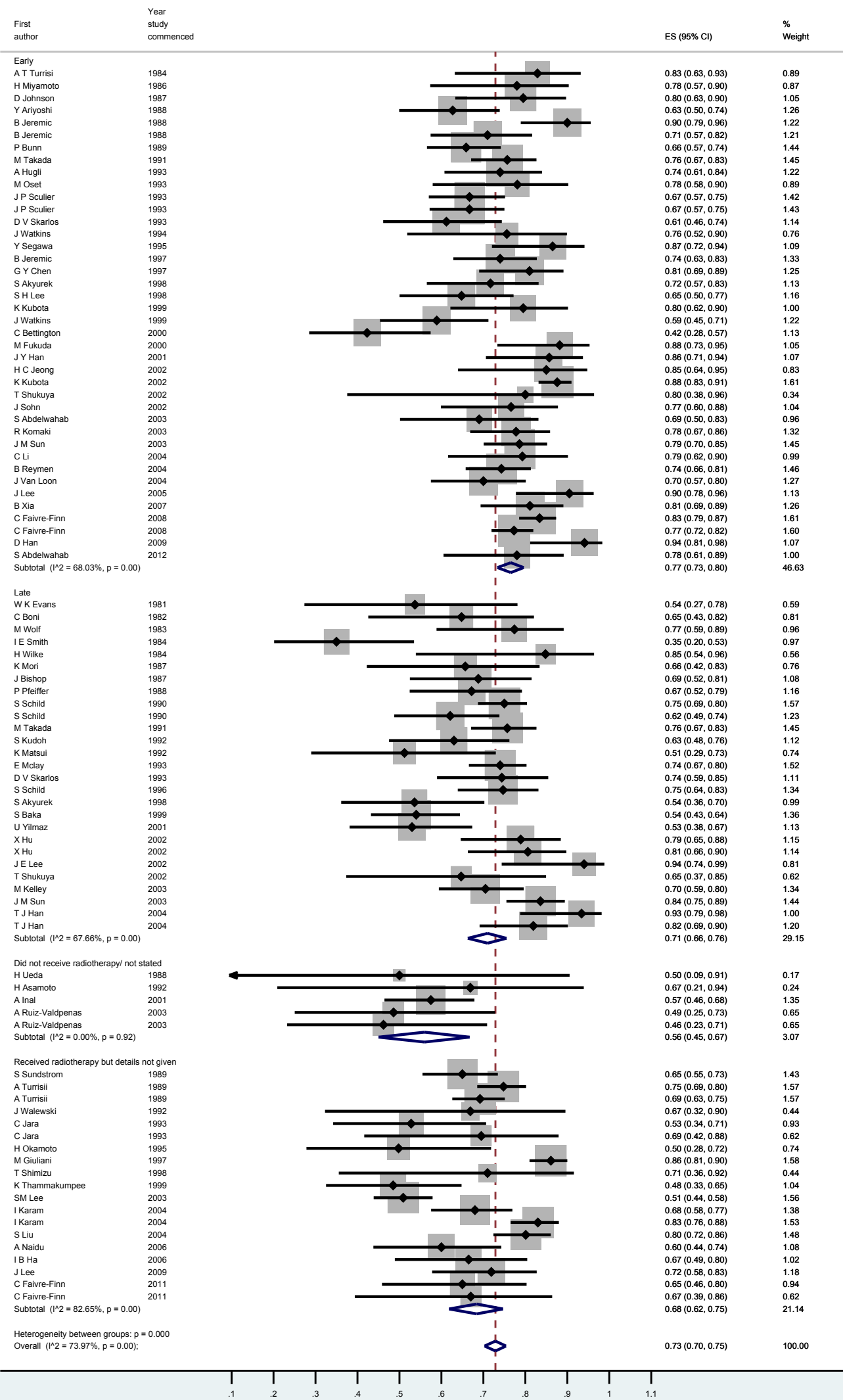


Proportion of 1 year survival in limited stage by PS

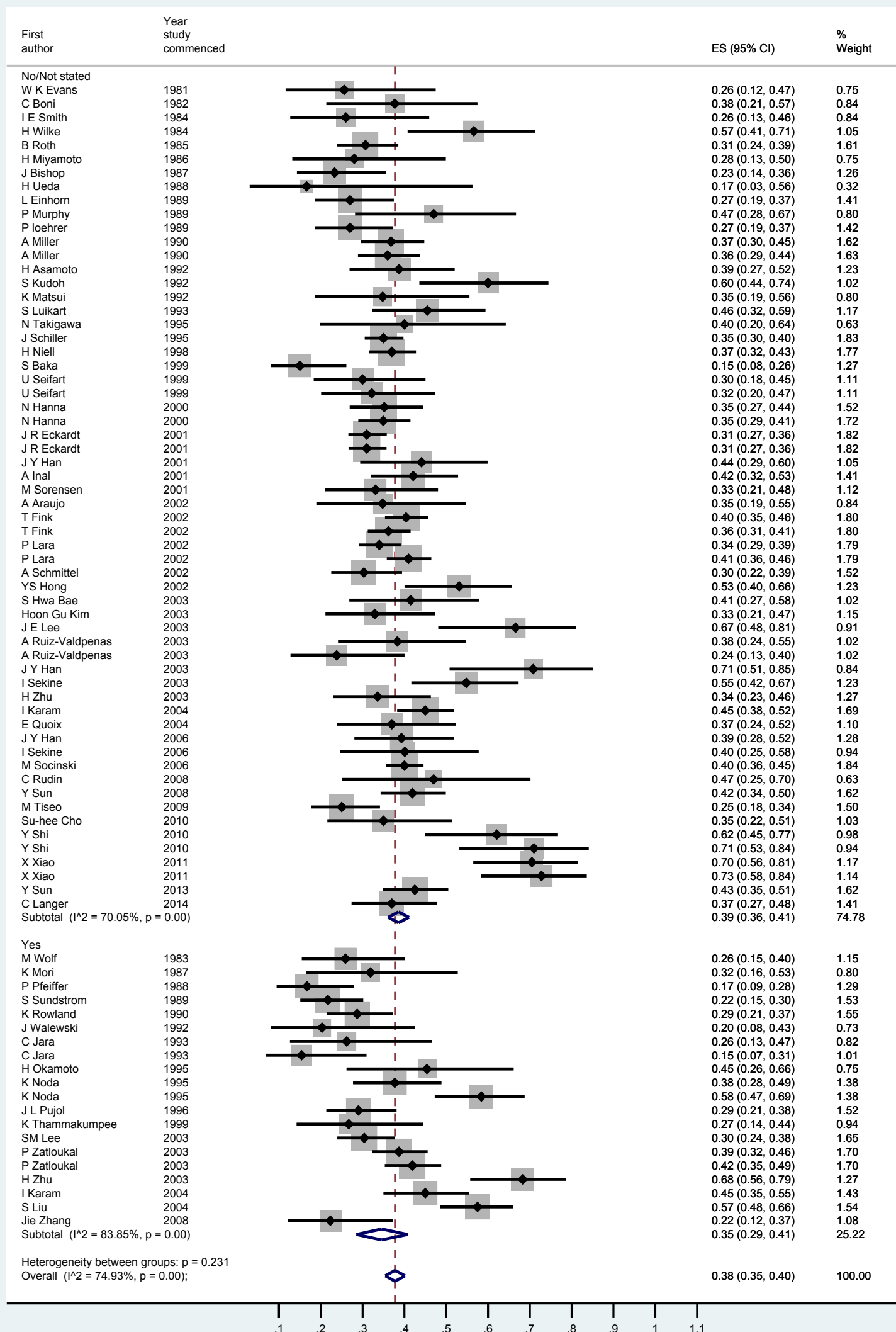




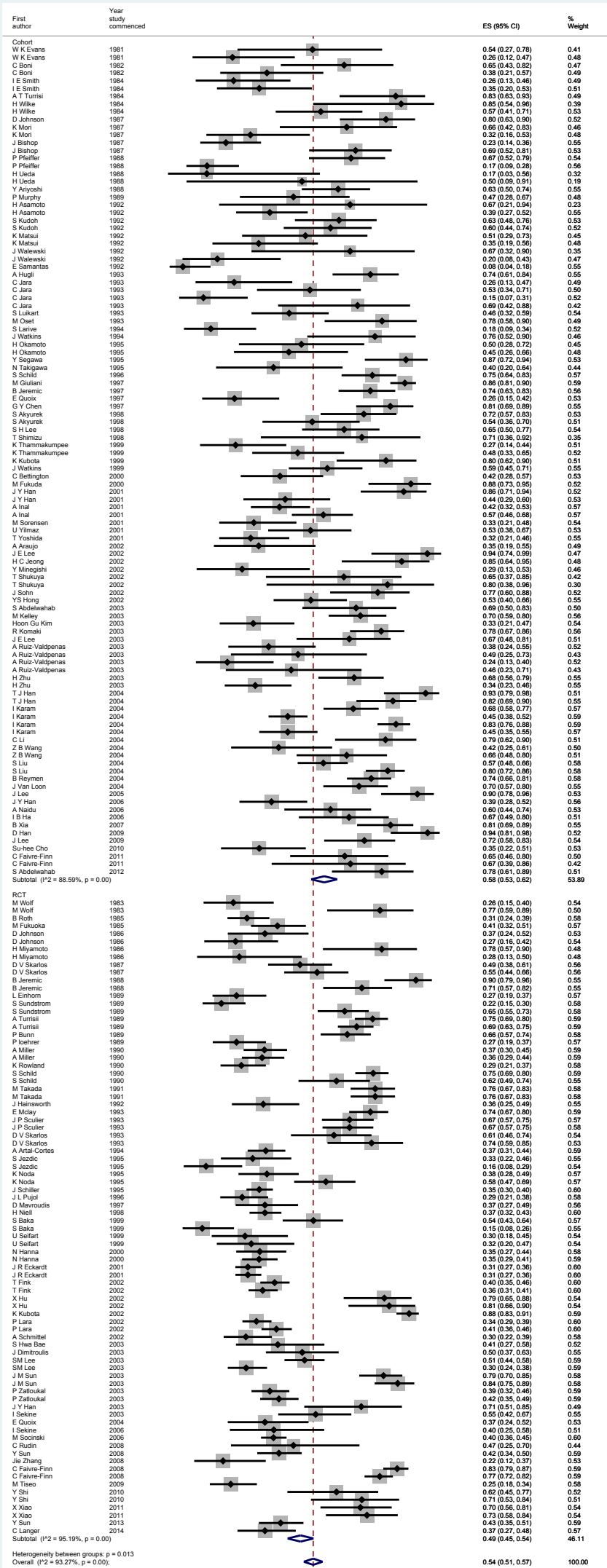
Proportion of 1 year survival by radiotherapy



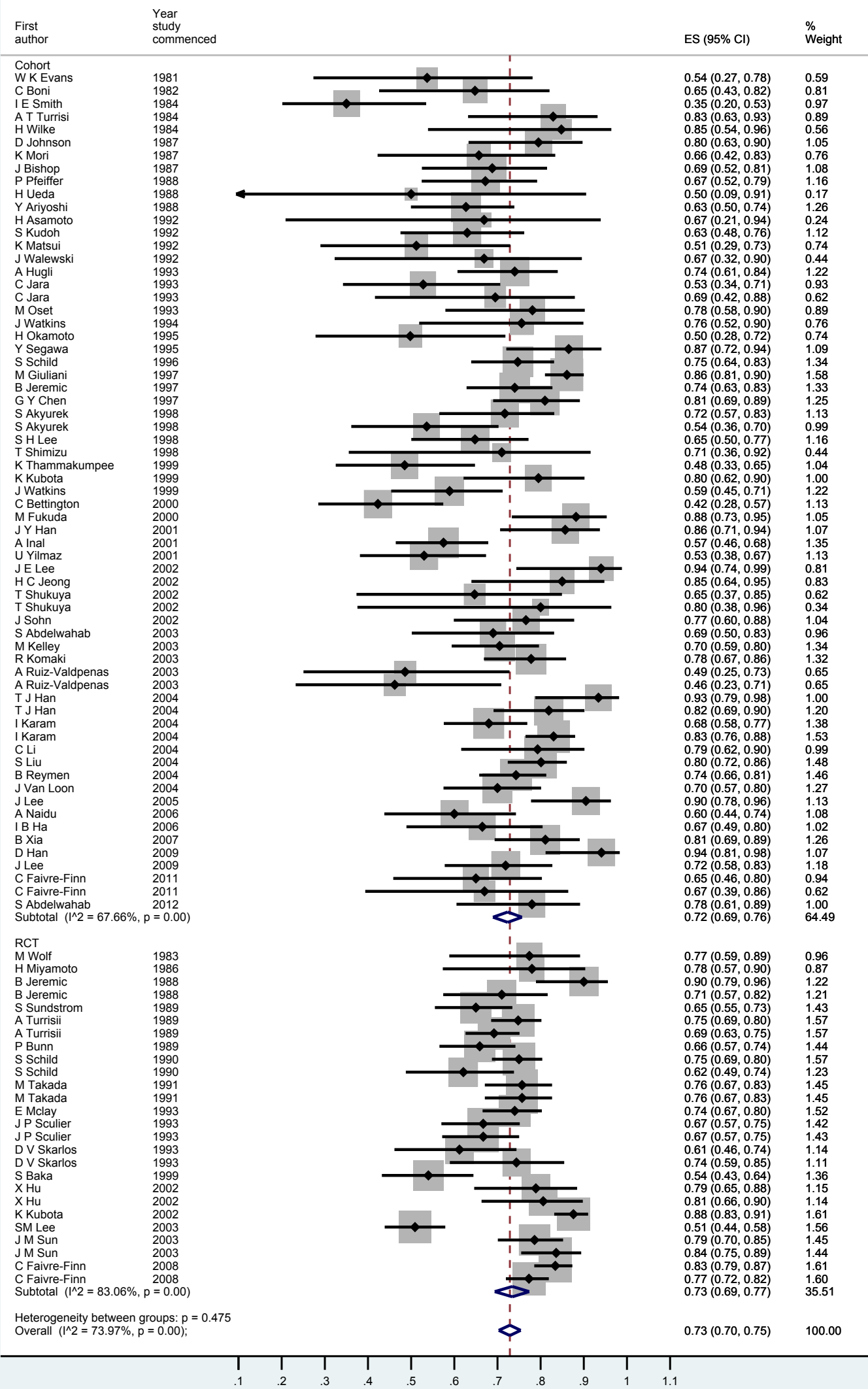
Proportion of 1 year survival in limited stage by radiotherapy

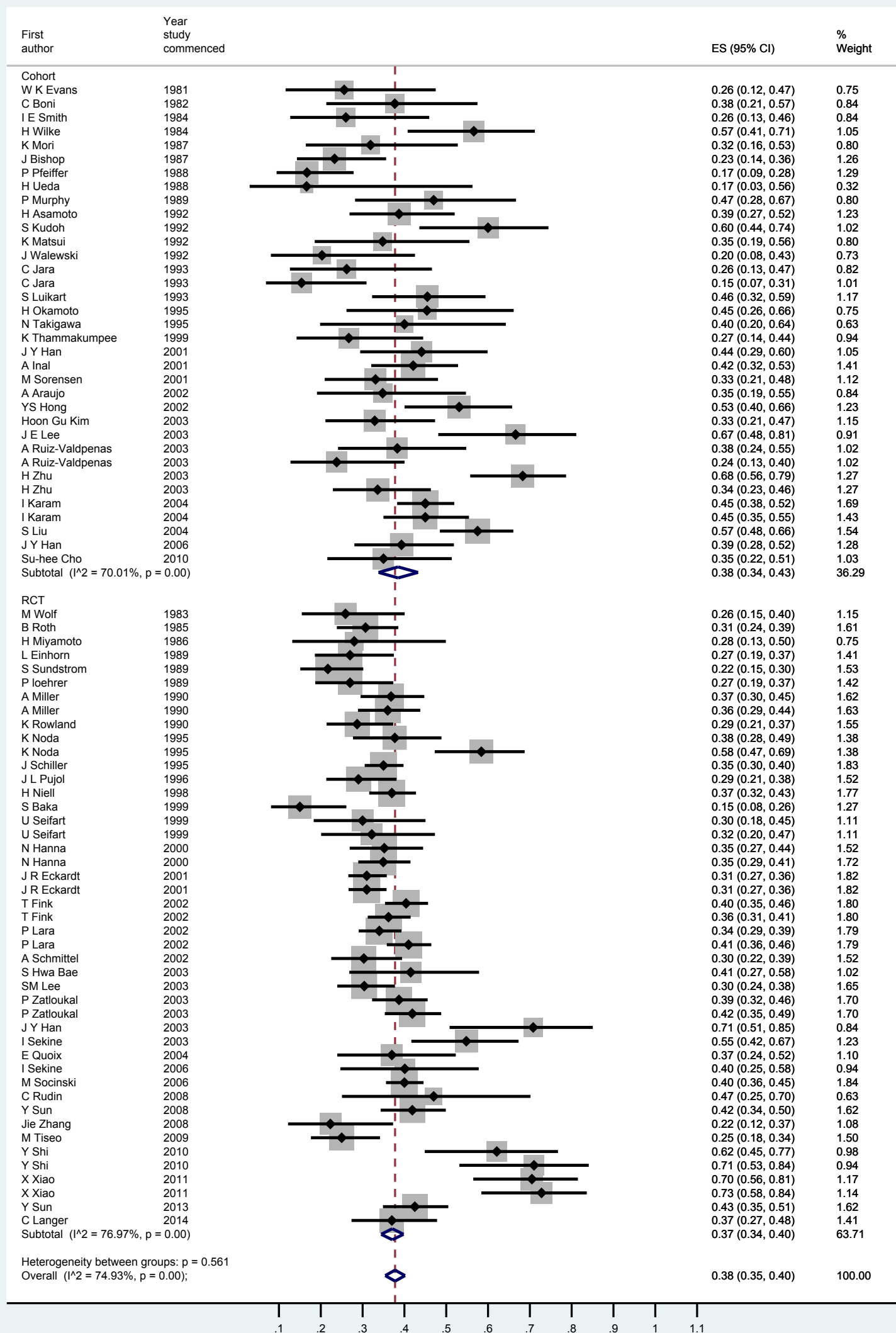


Proportion of 1 year survival in extensive stage by radiotherapy

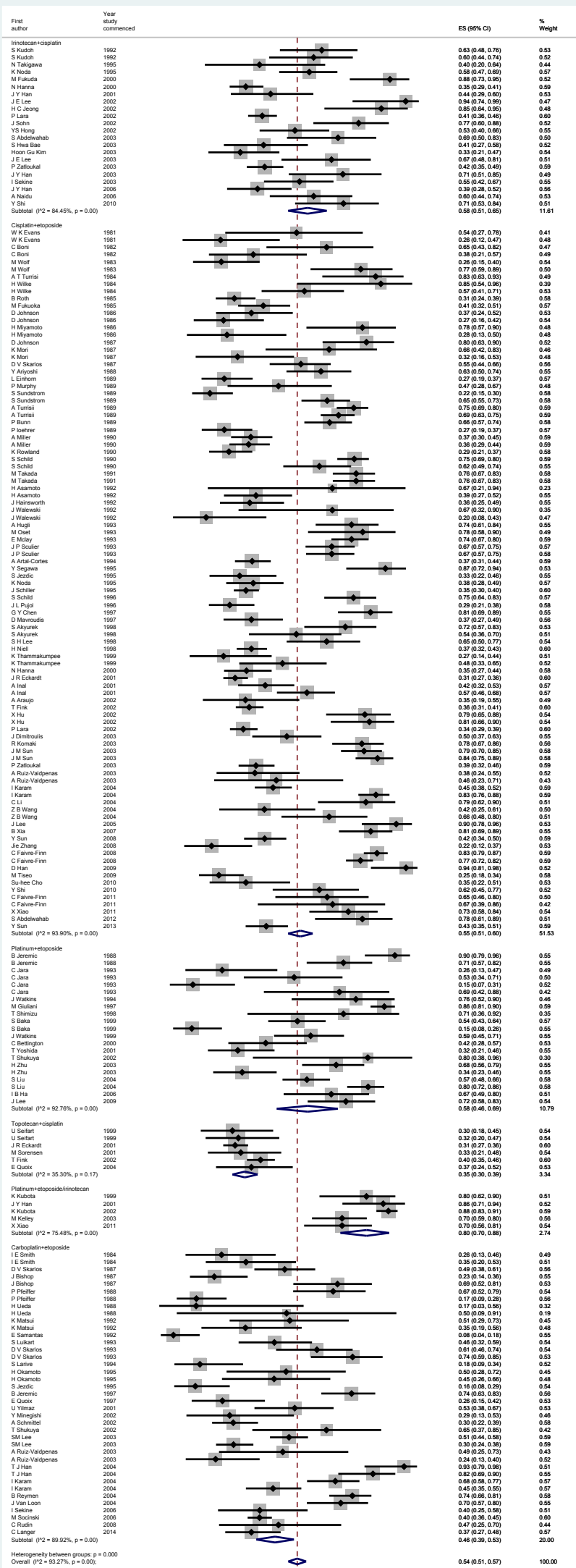


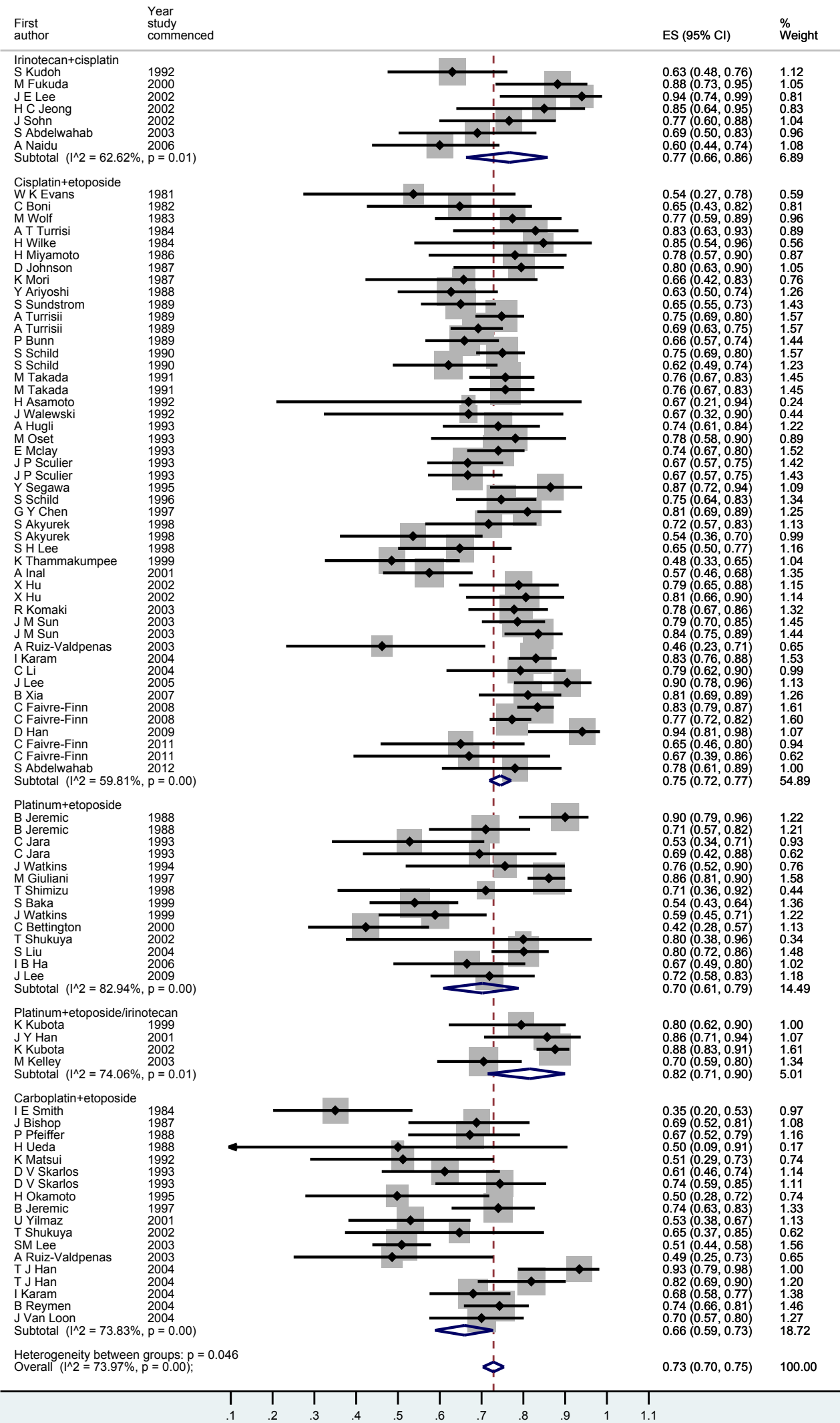
1 year survival after chemotherapy by study design



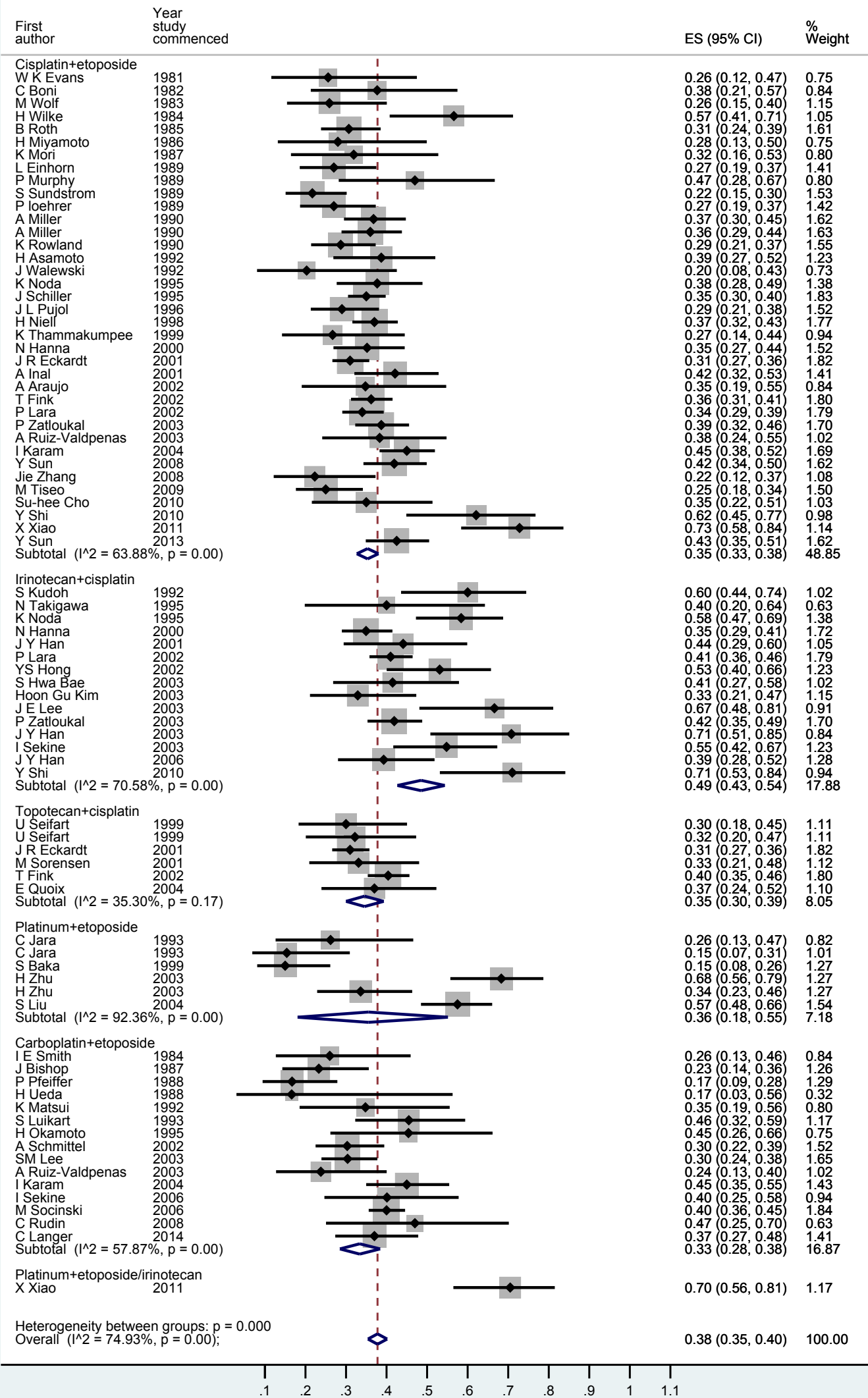


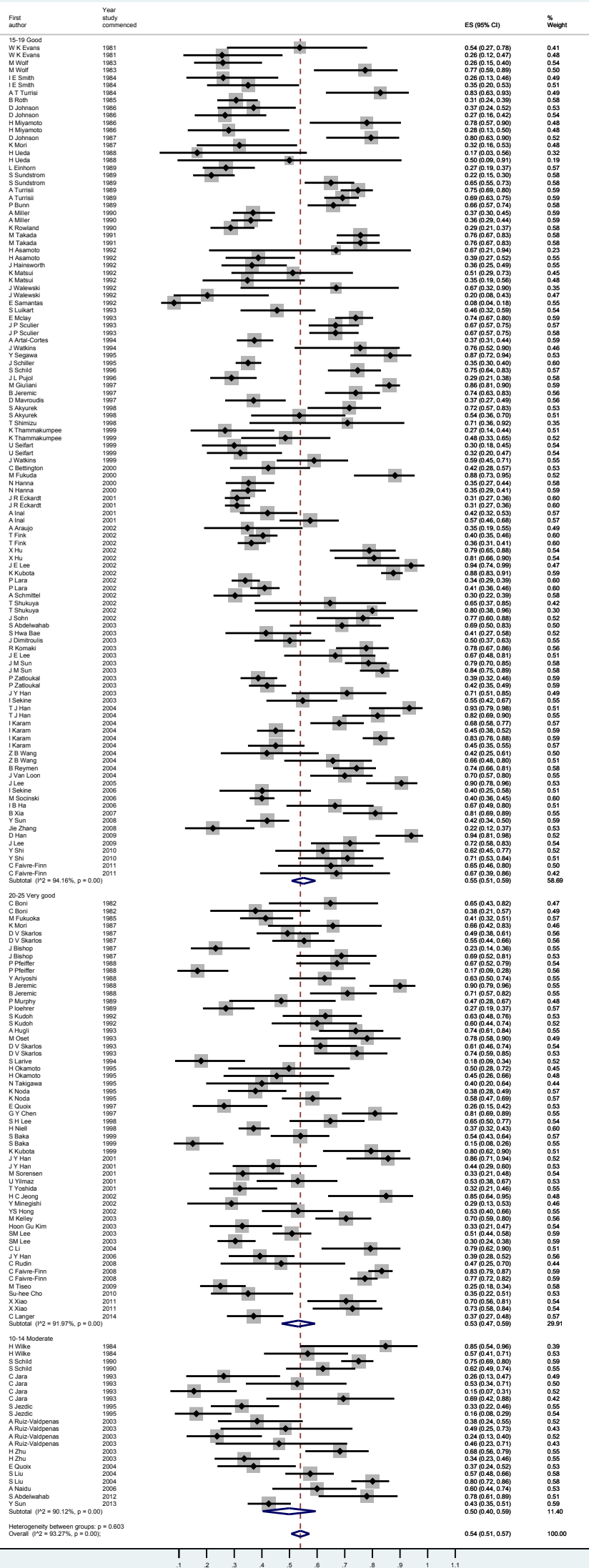
Proportion of 1 year survival in extensive stage by study design



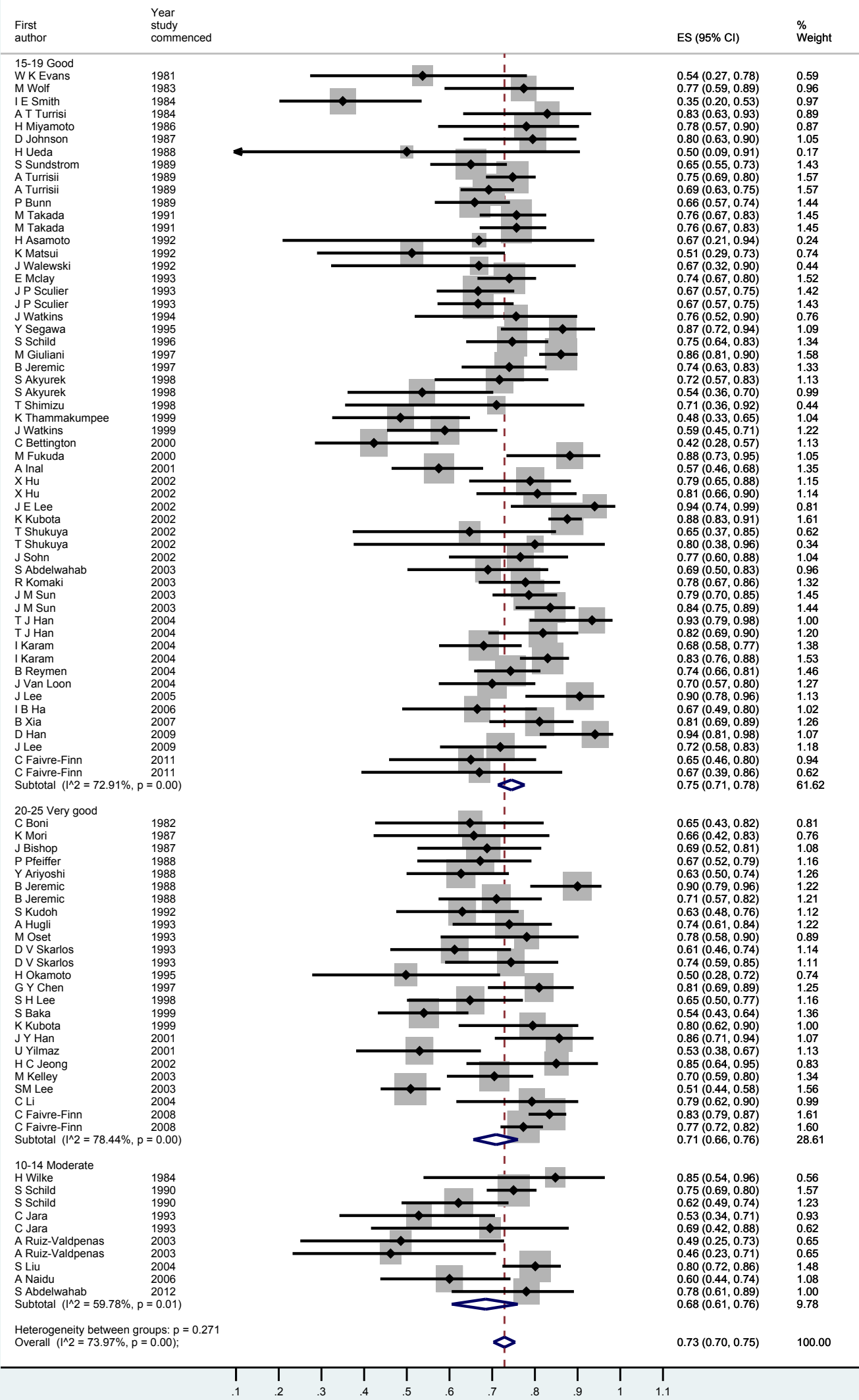


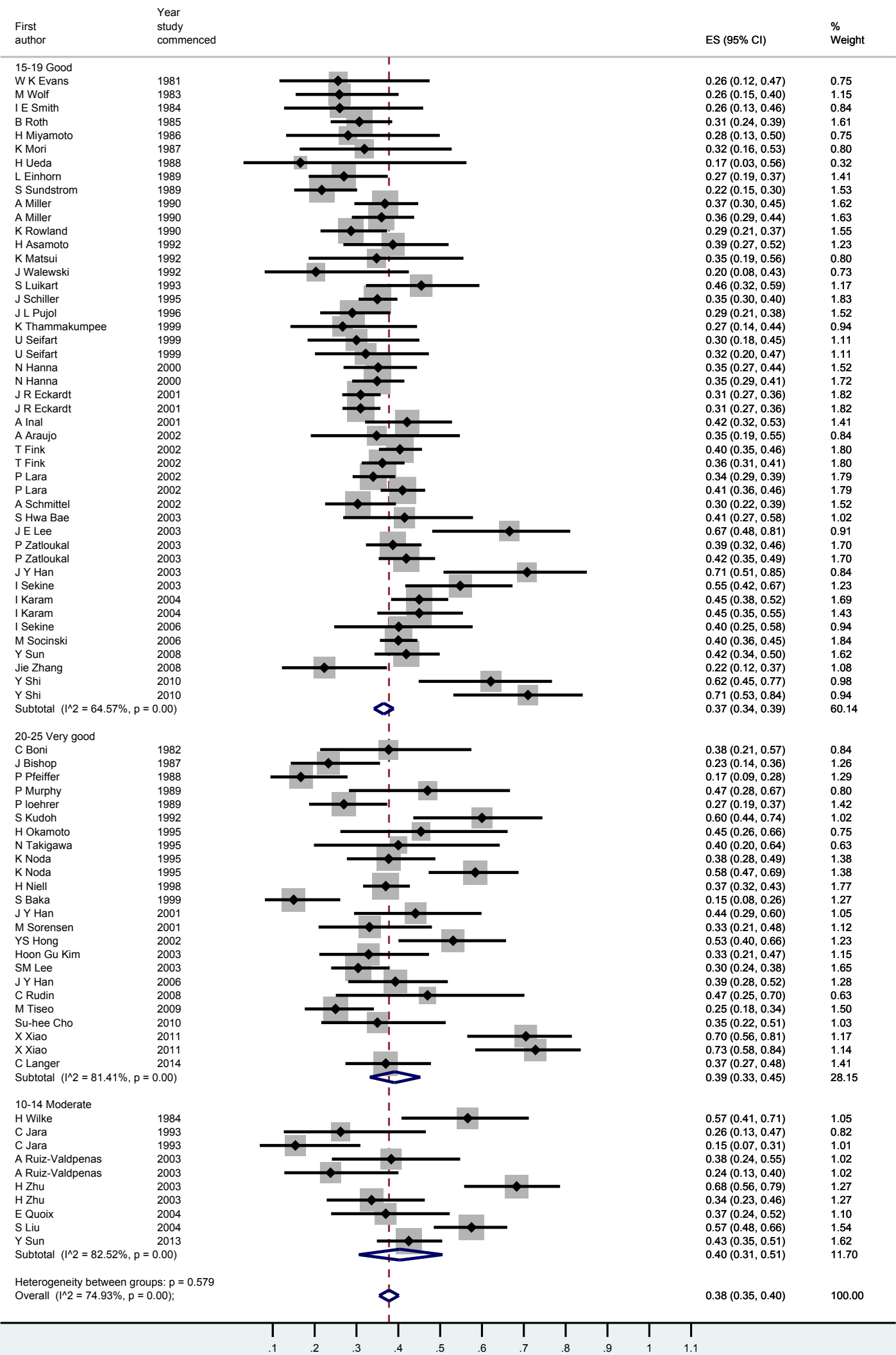
Proportion of 1 year survival in limited stage by drug



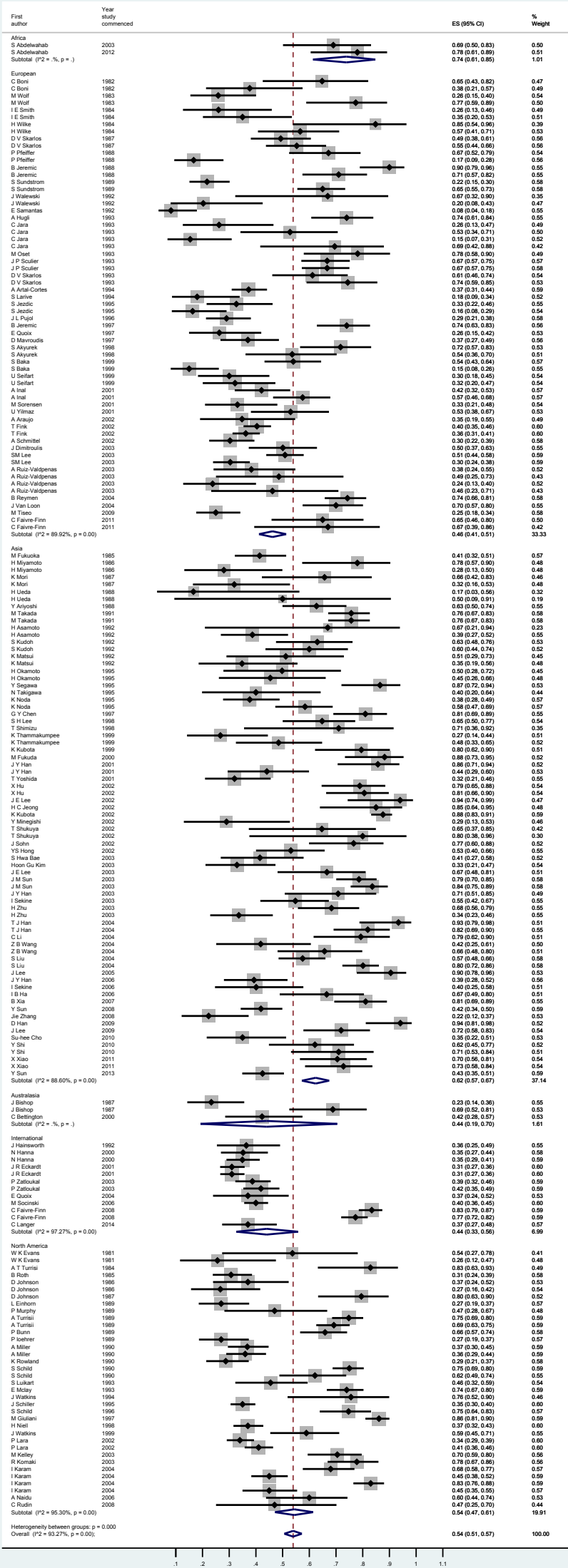


1 year survival after chemotherapy by quality score

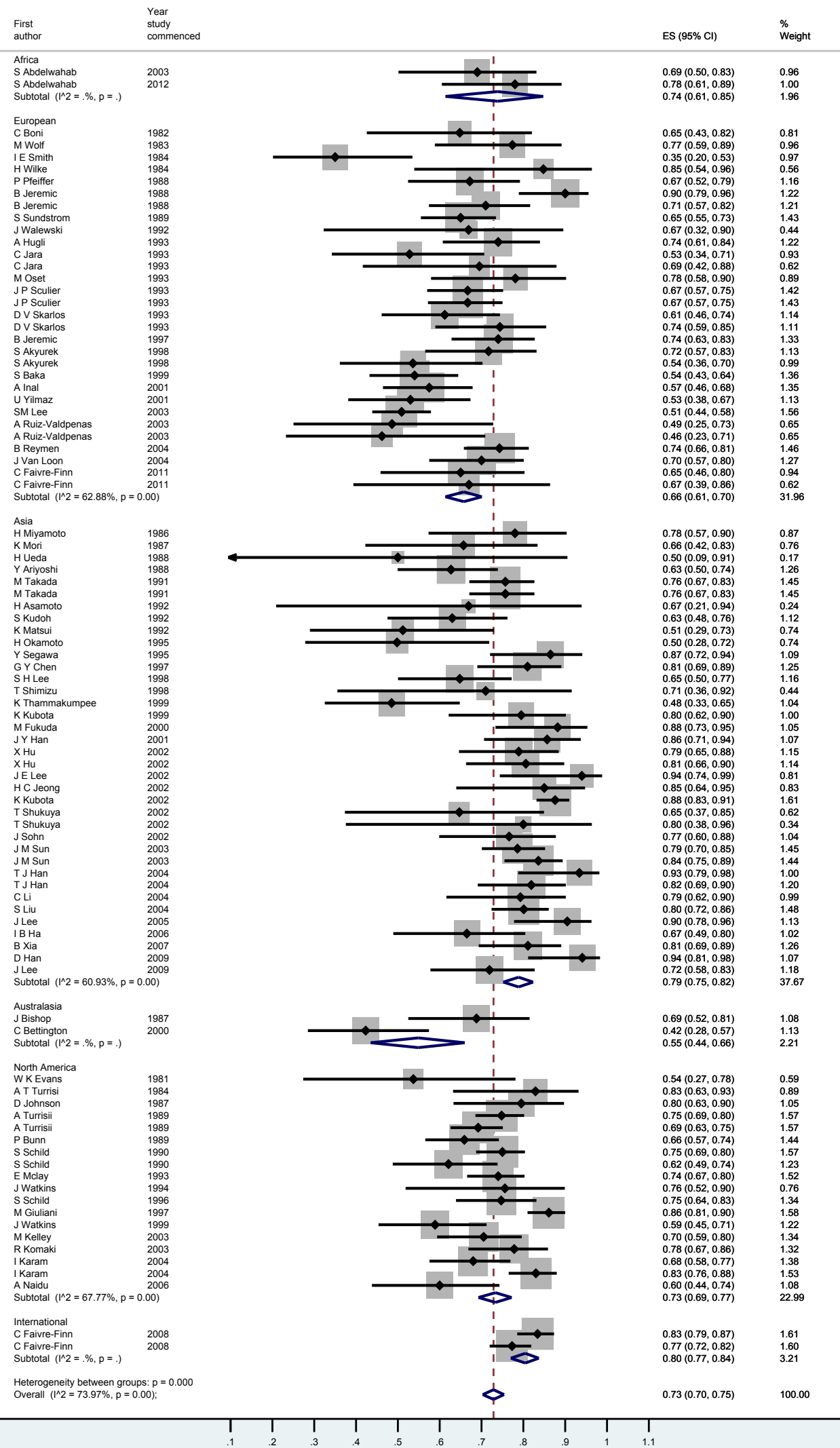




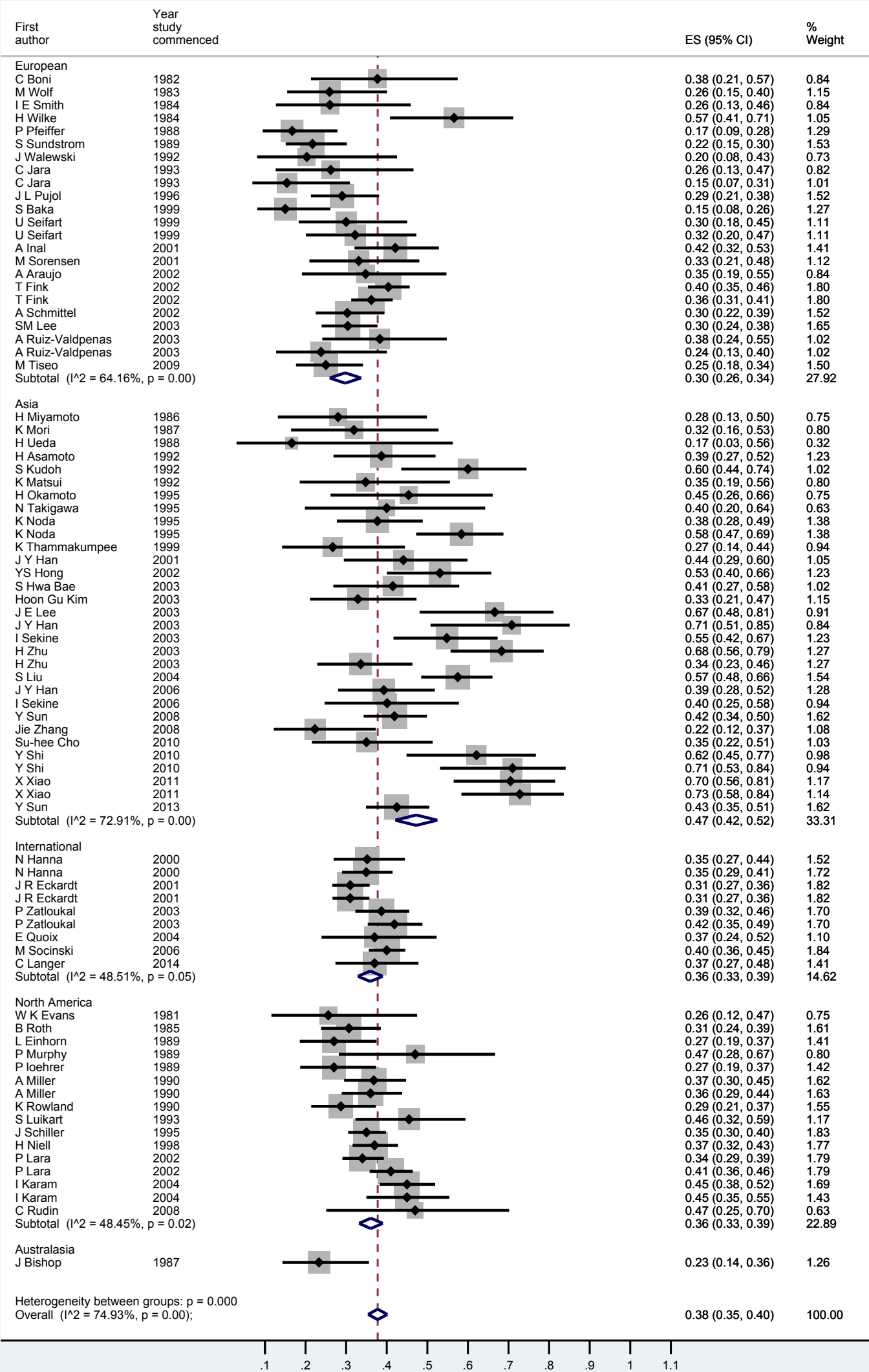
Proportion of 1 year survival in extensive stage by quality score

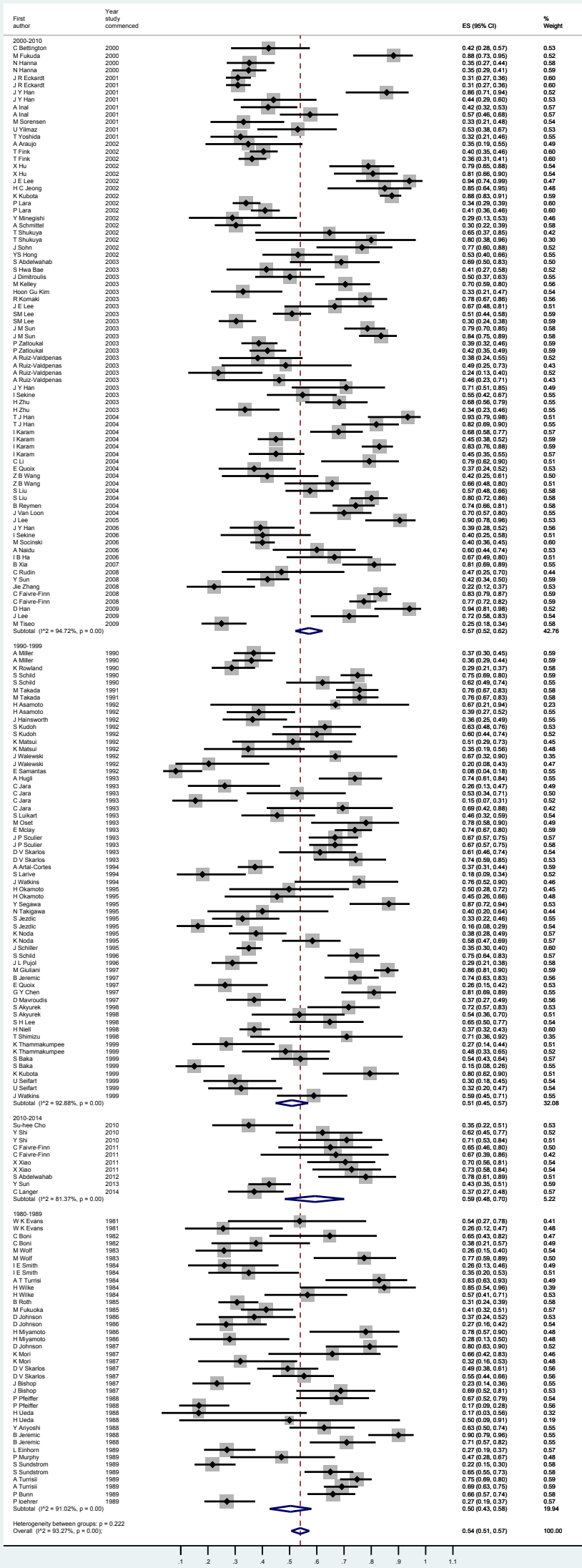


1 year survival after chemotherapy by region

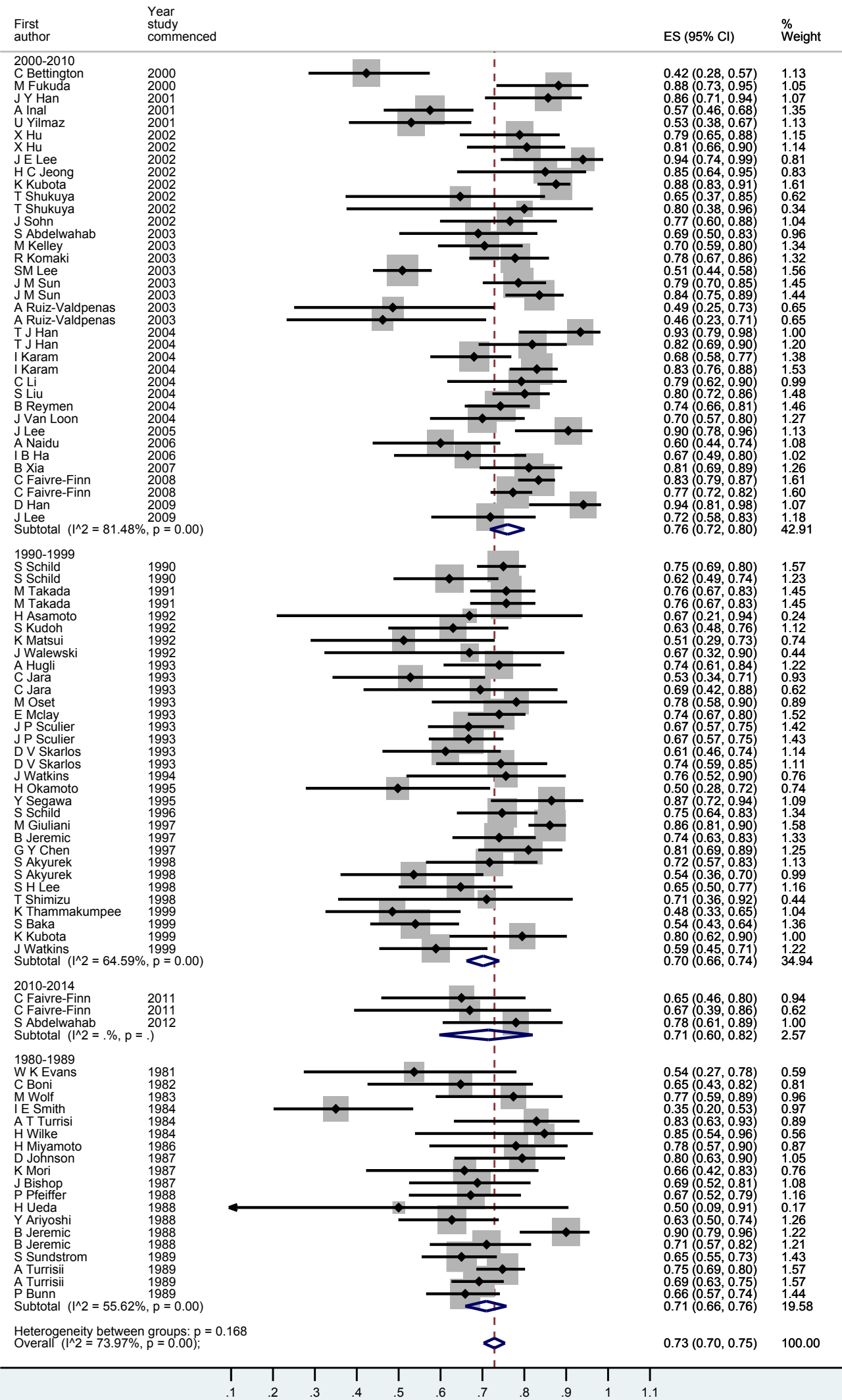


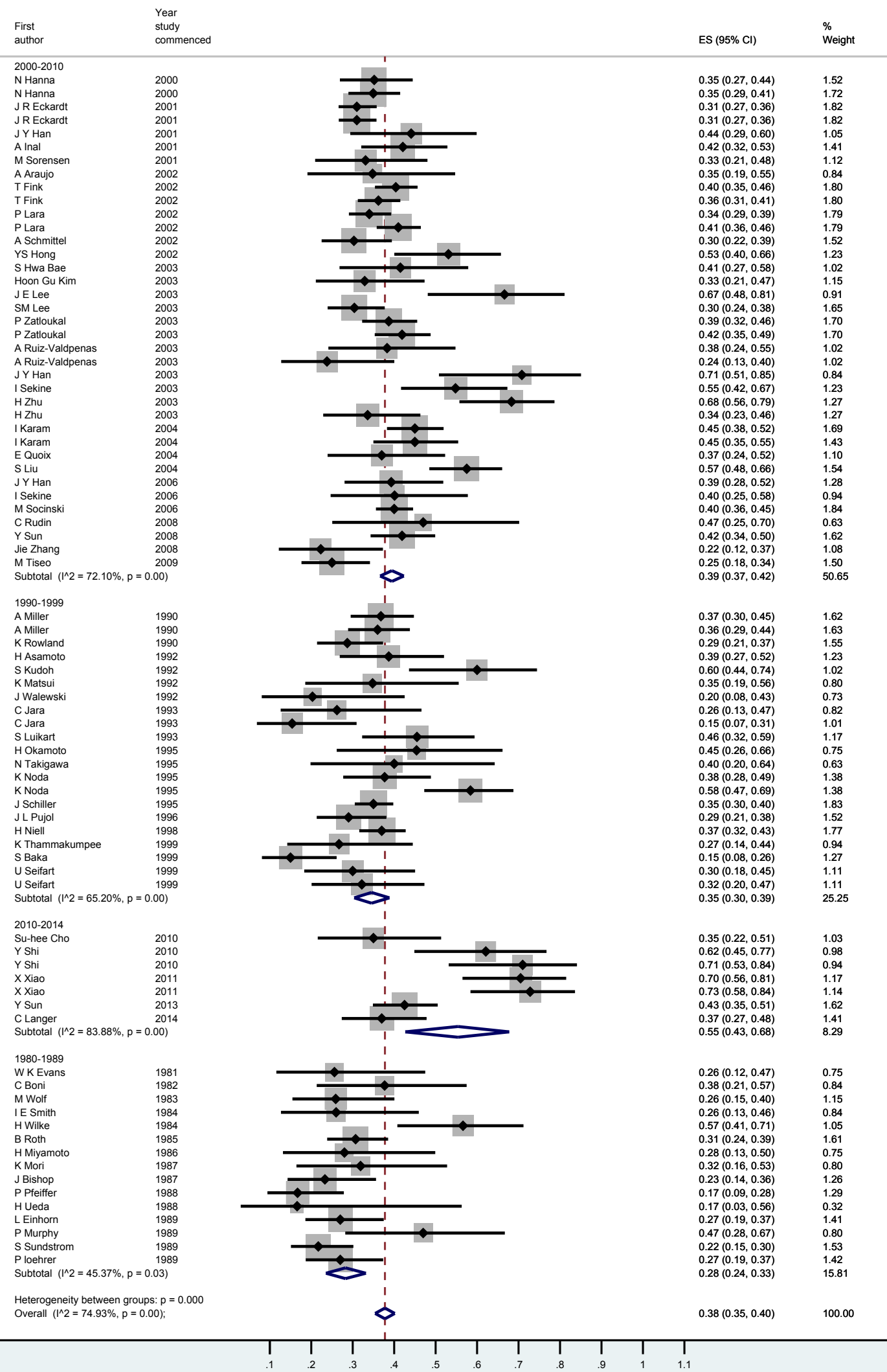
Proportion of 1 year survival in limited stage by region





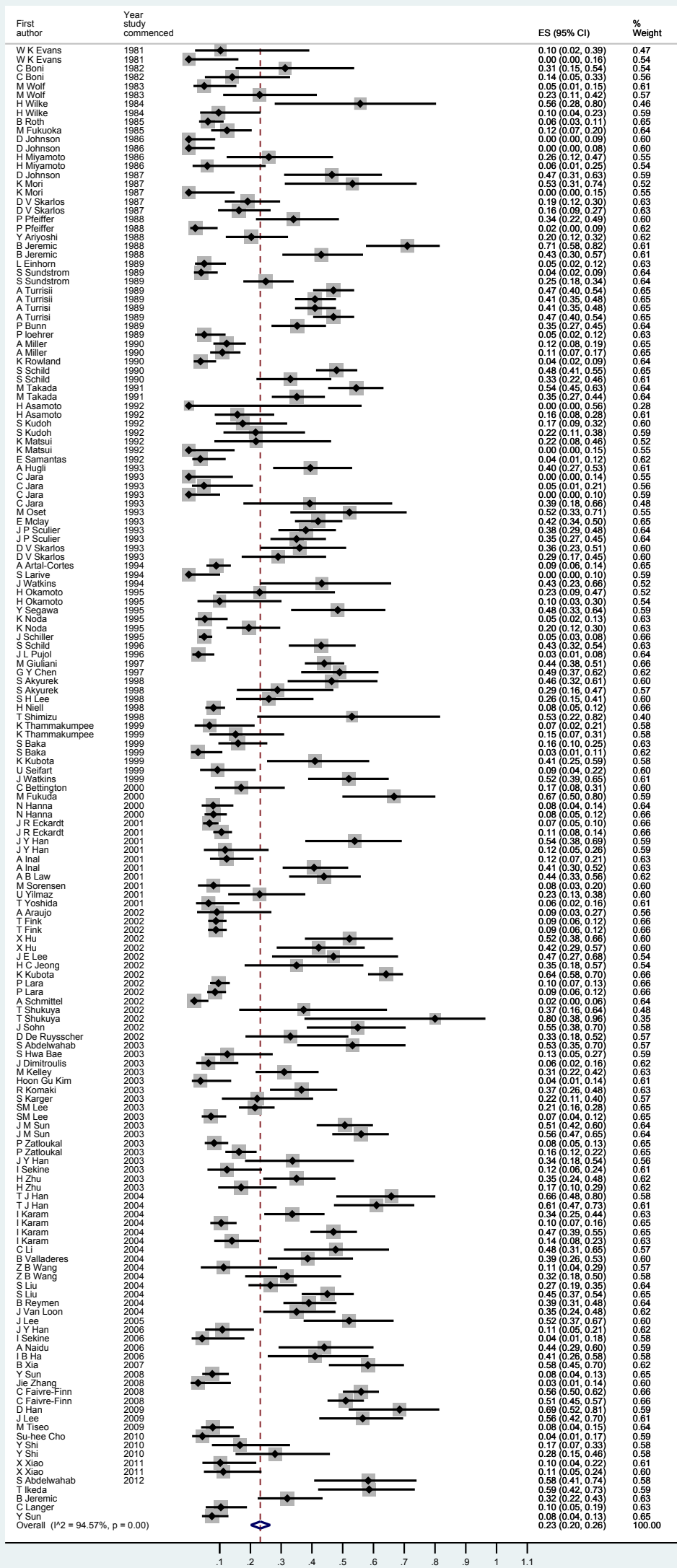
1 year survival after chemotherapy by study year

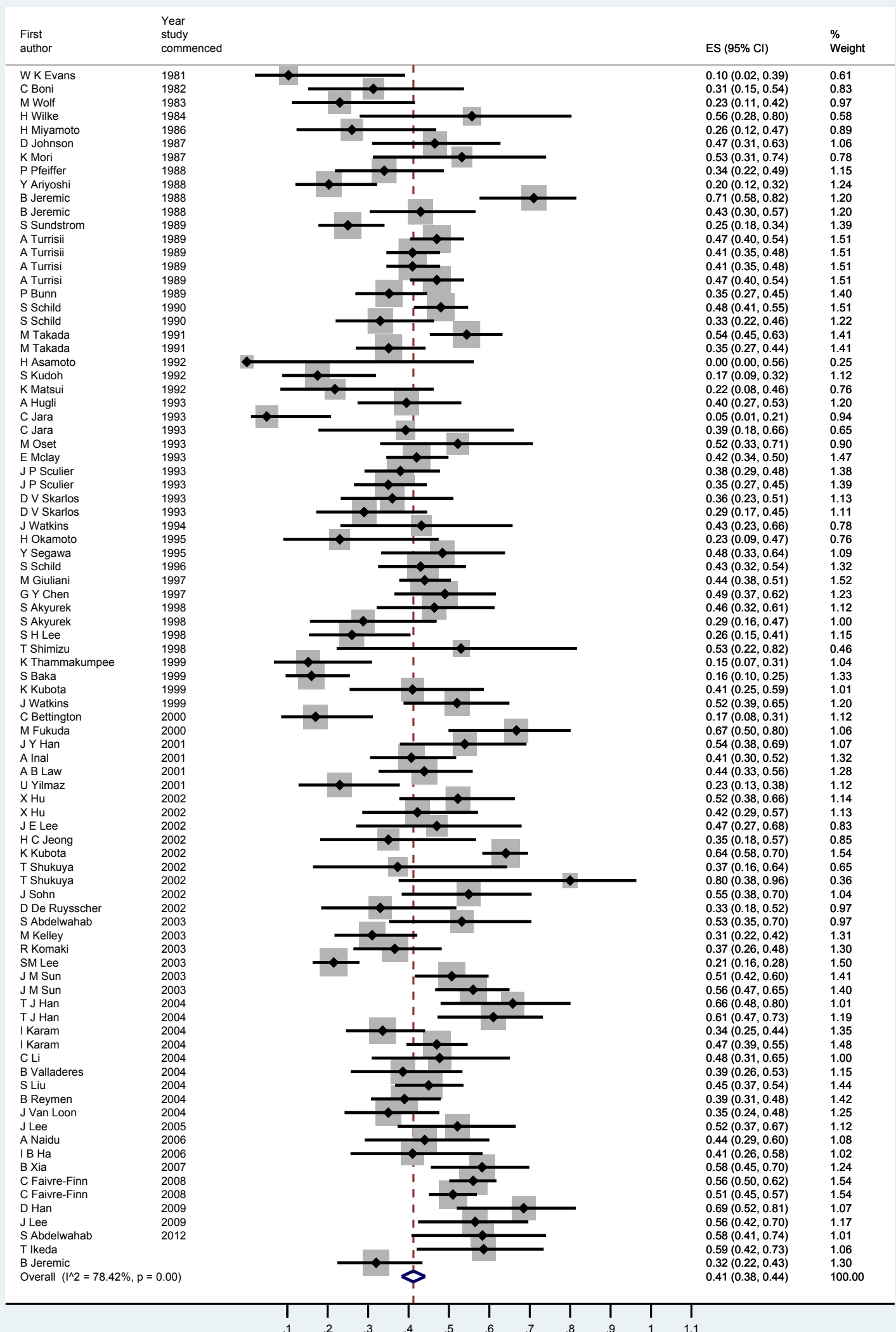




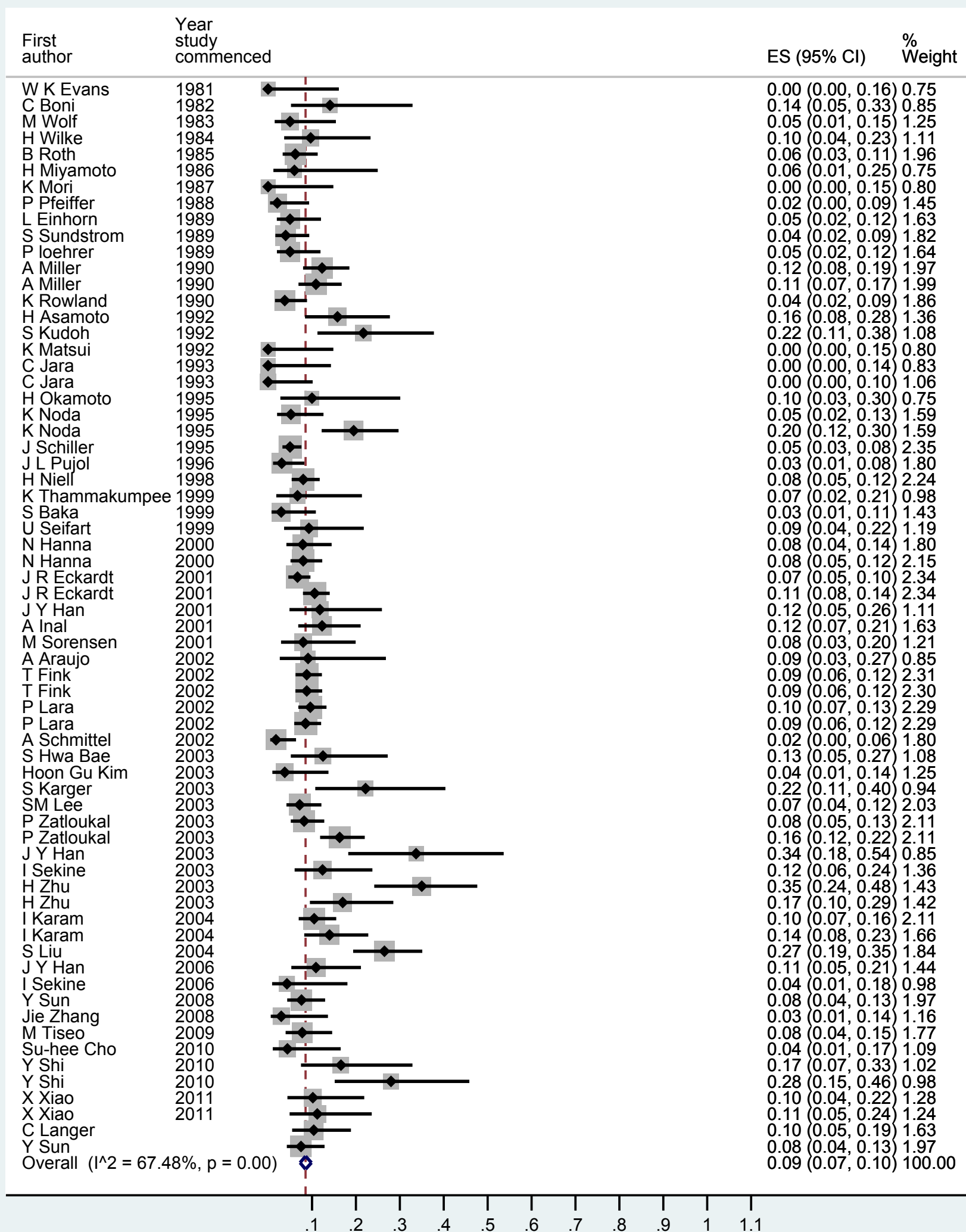
Proportion of 1 year survival in extensive stage by study year

2-year survival

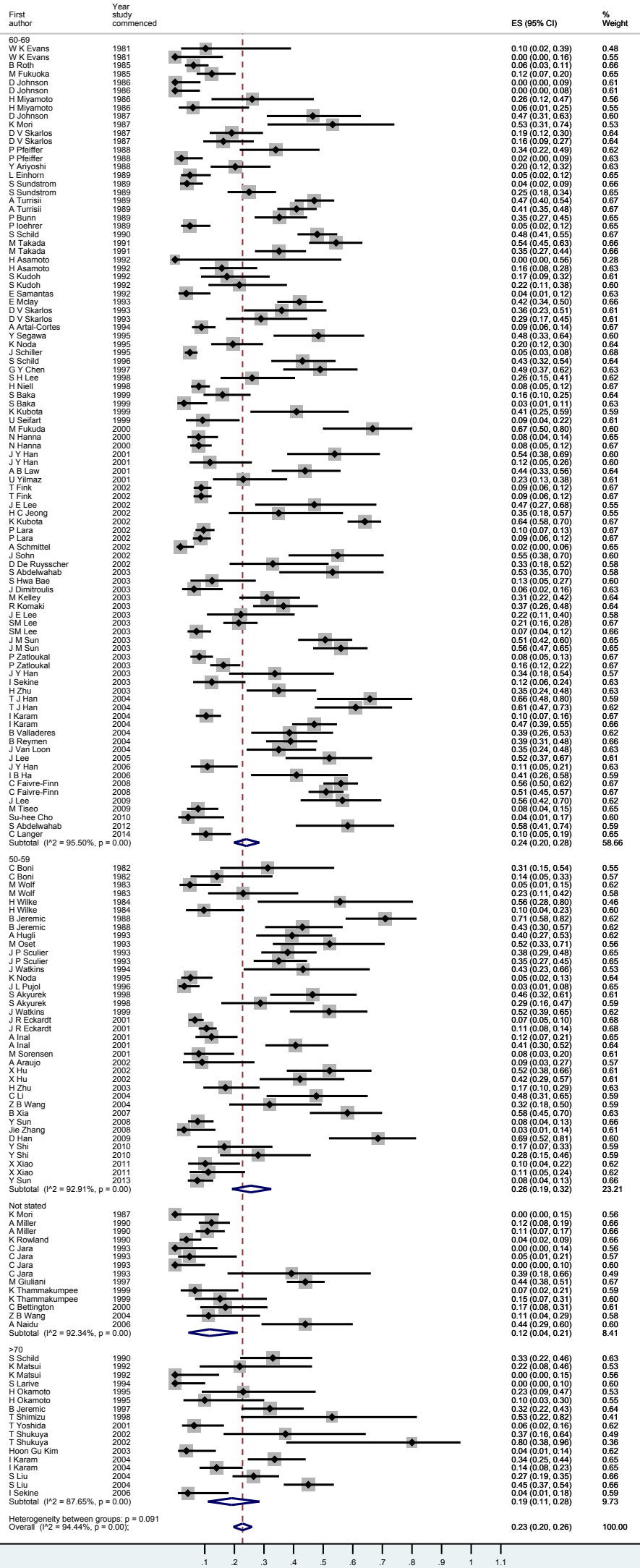




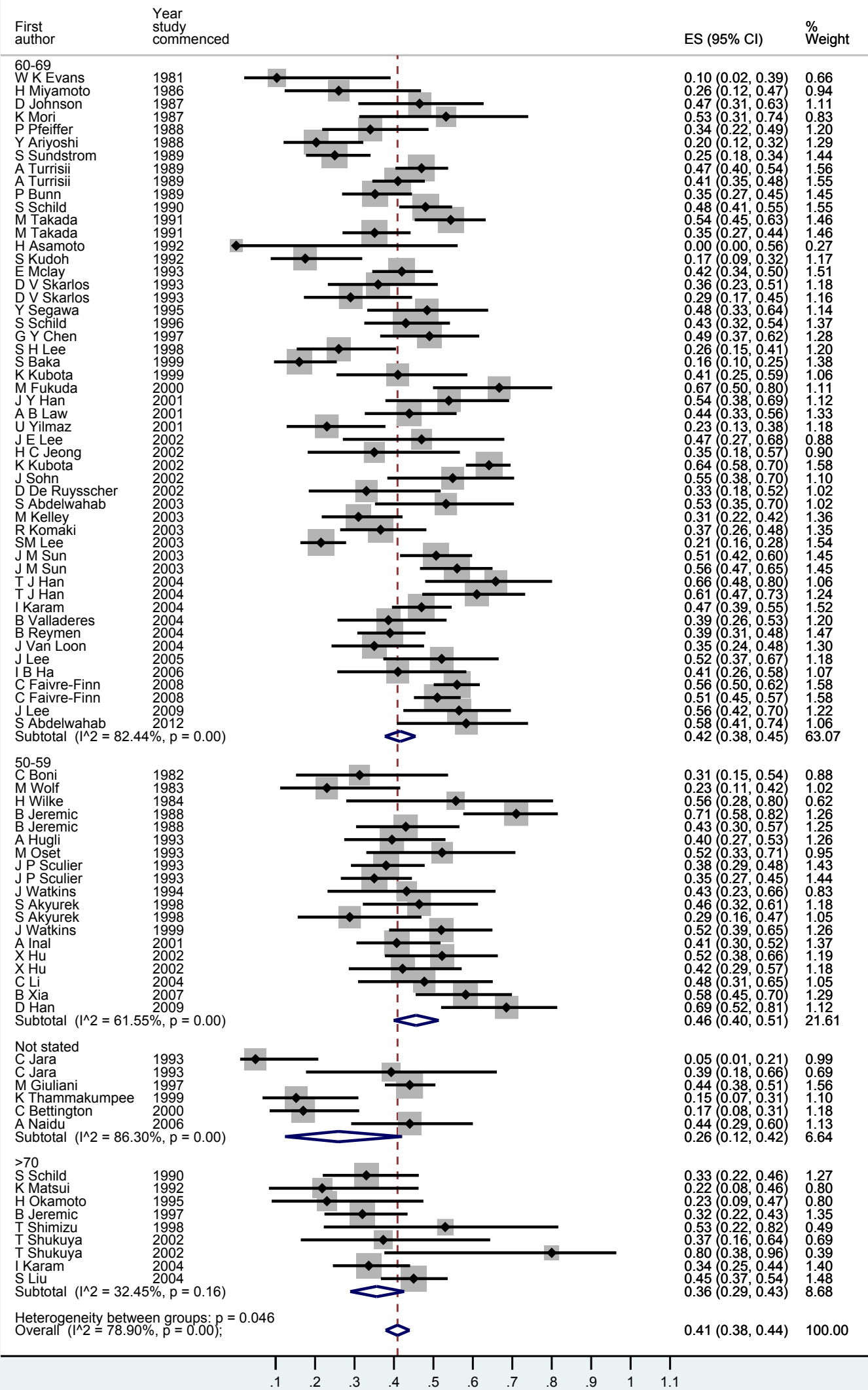
2 year survival after chemotherapy in limited stage



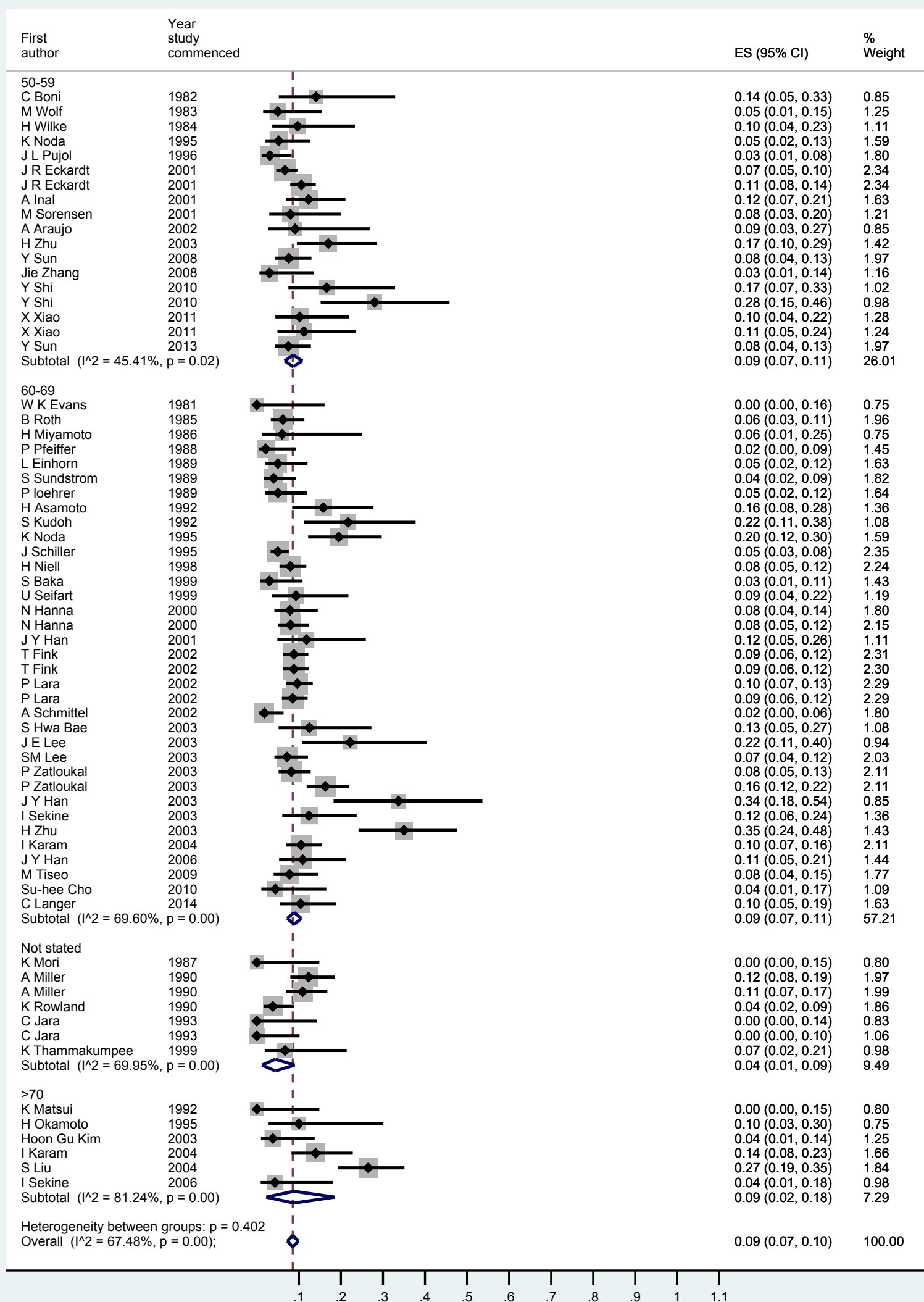
2 year survival after chemotherapy in extensive stage



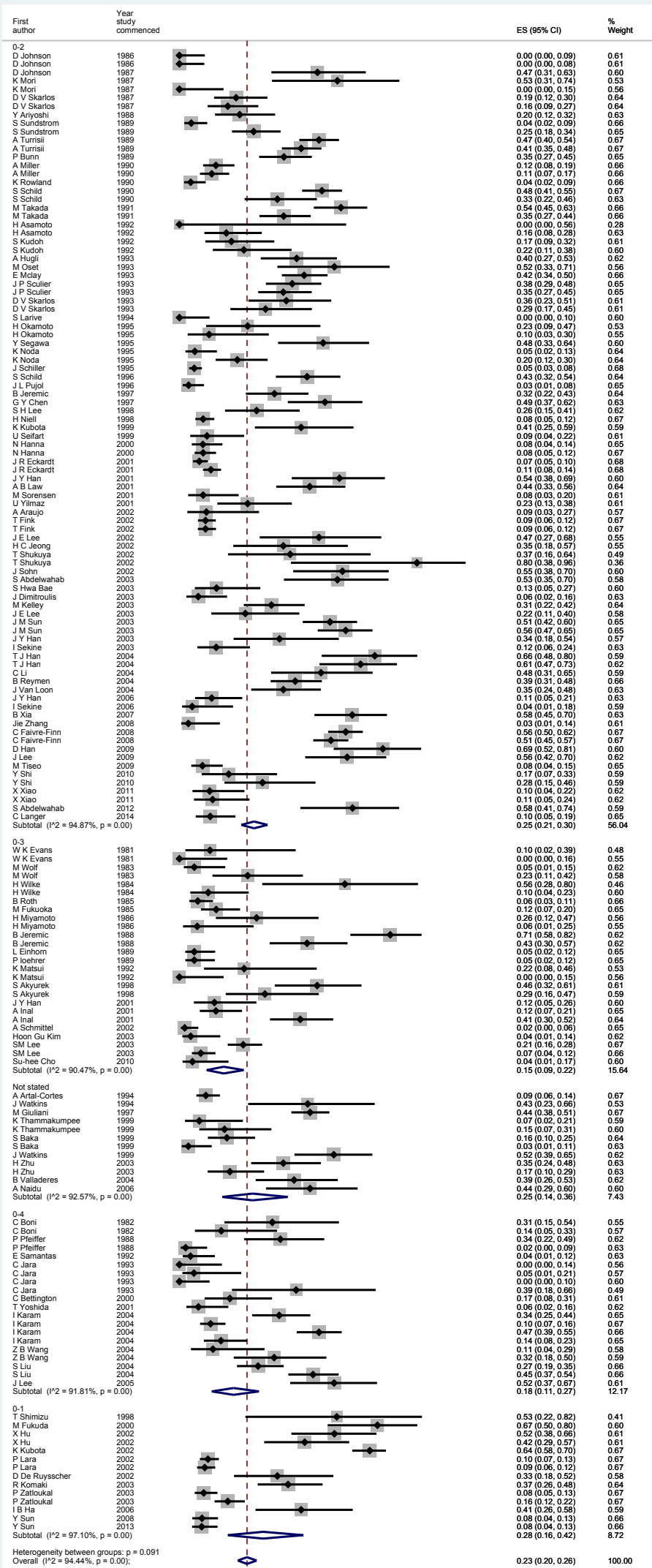
Proportion of 2 year survival by median participant age

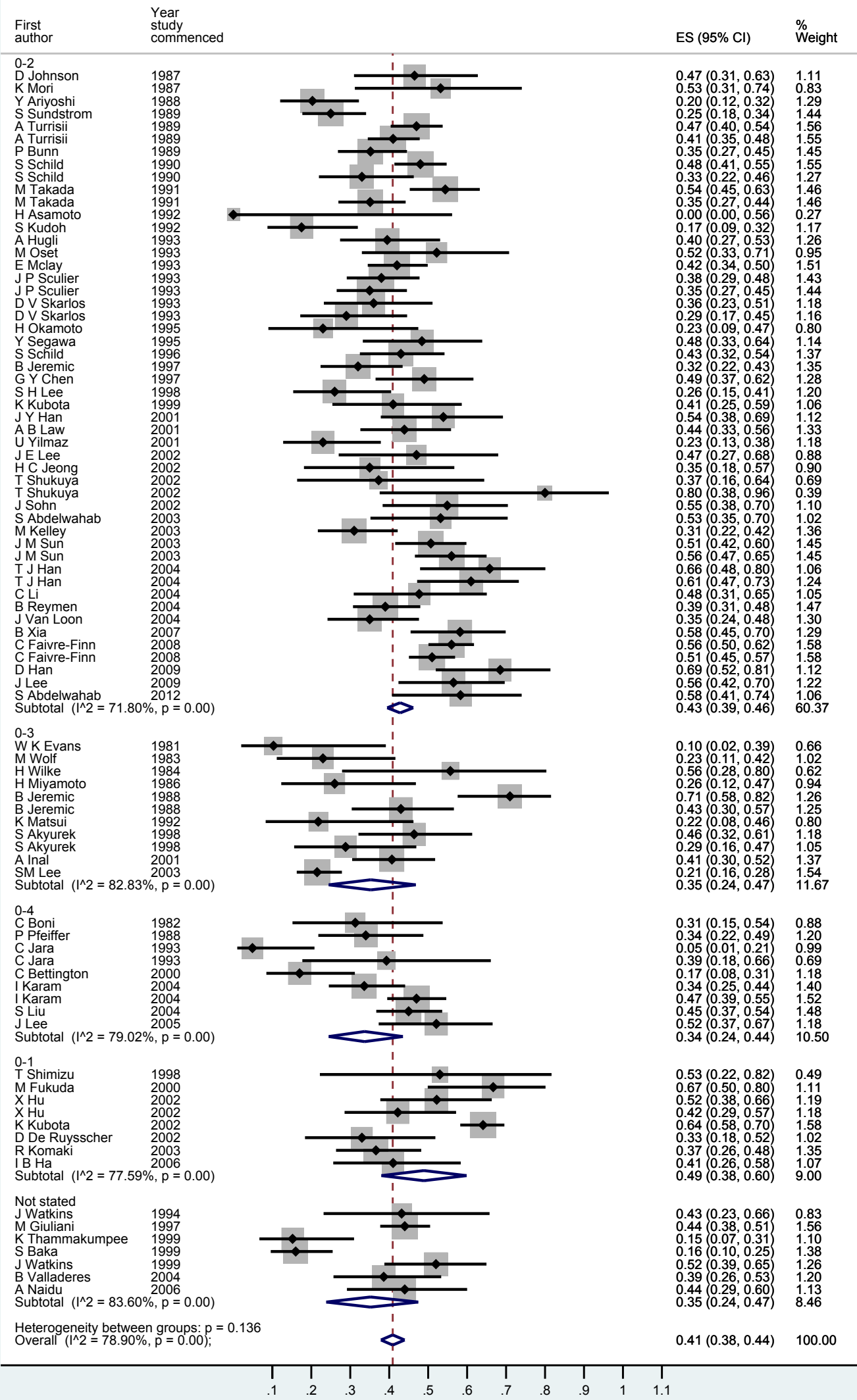


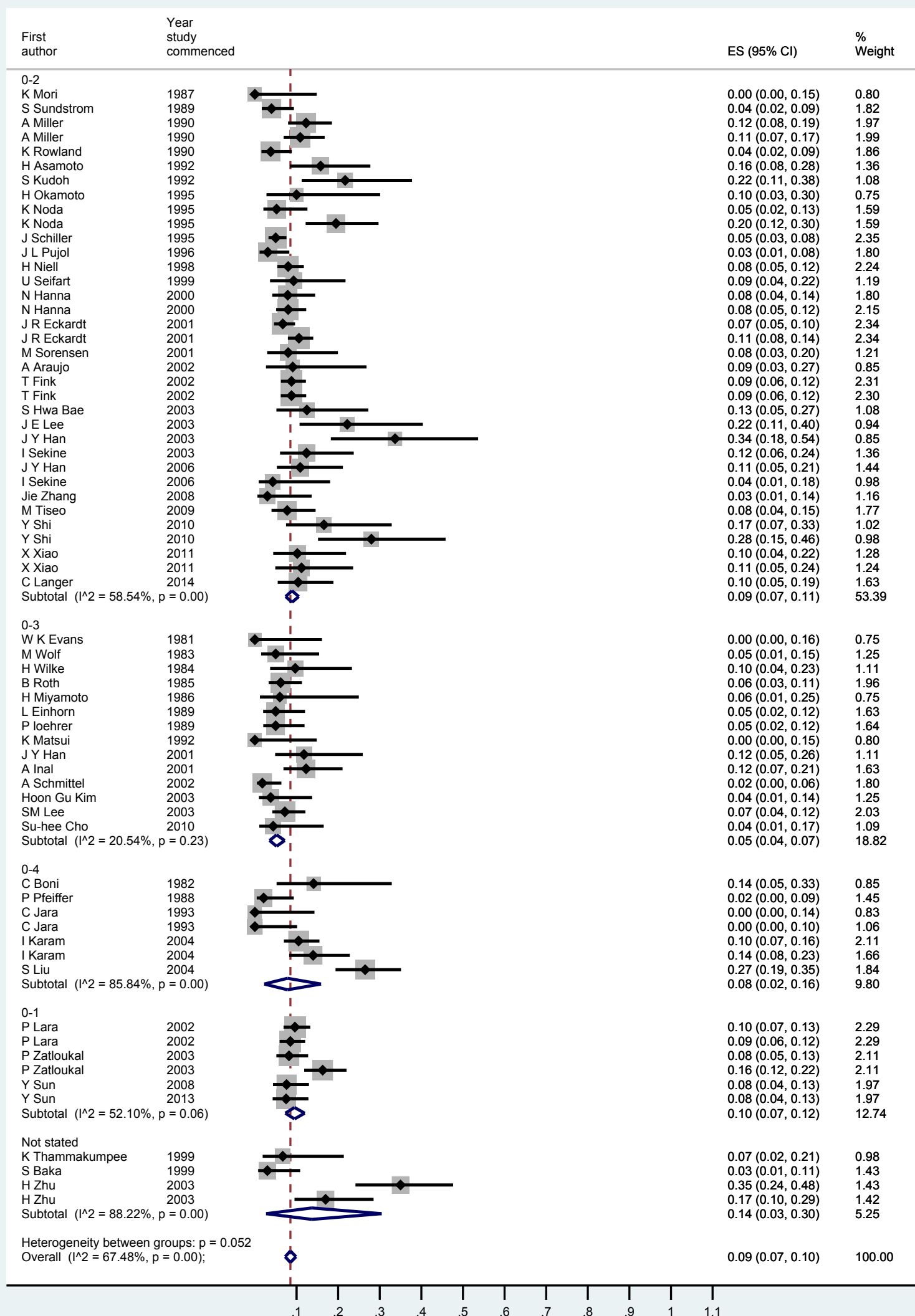
Proportion of 2 year survival in limited stage by median participant age

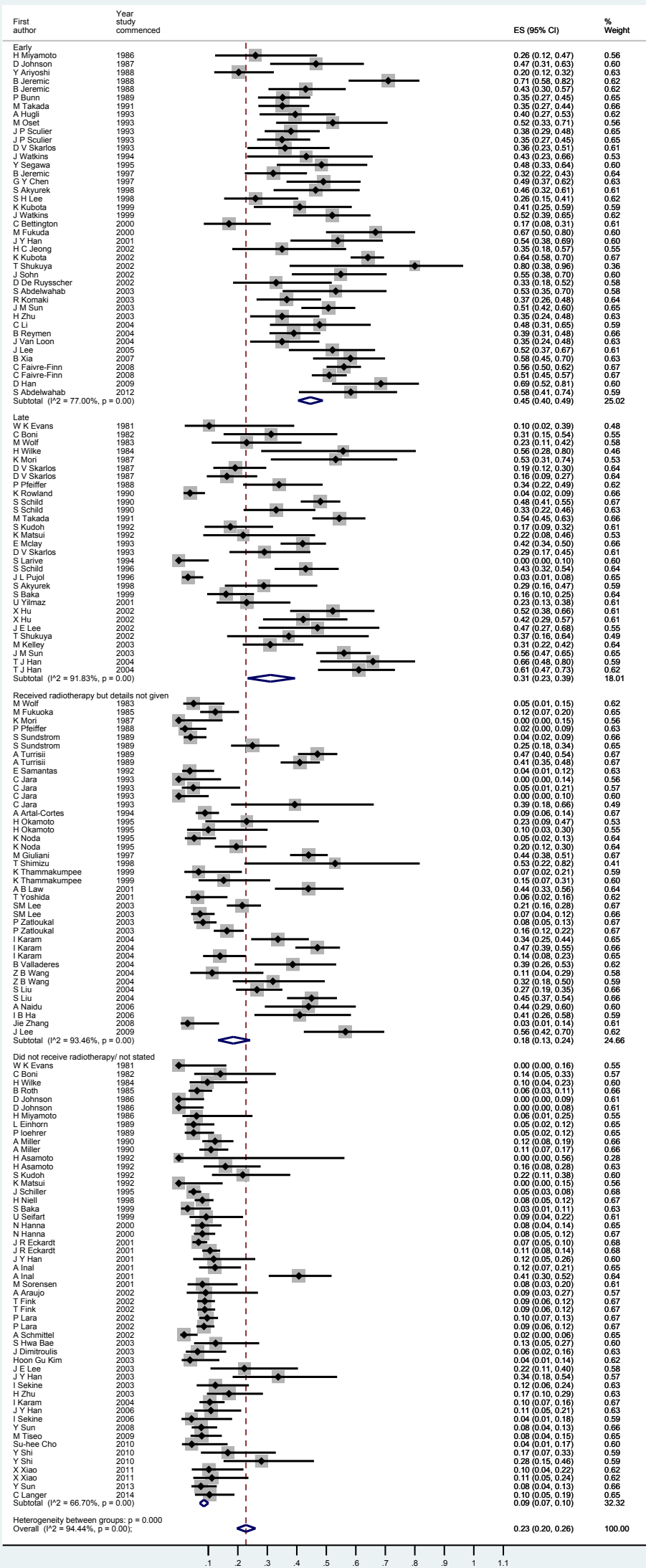


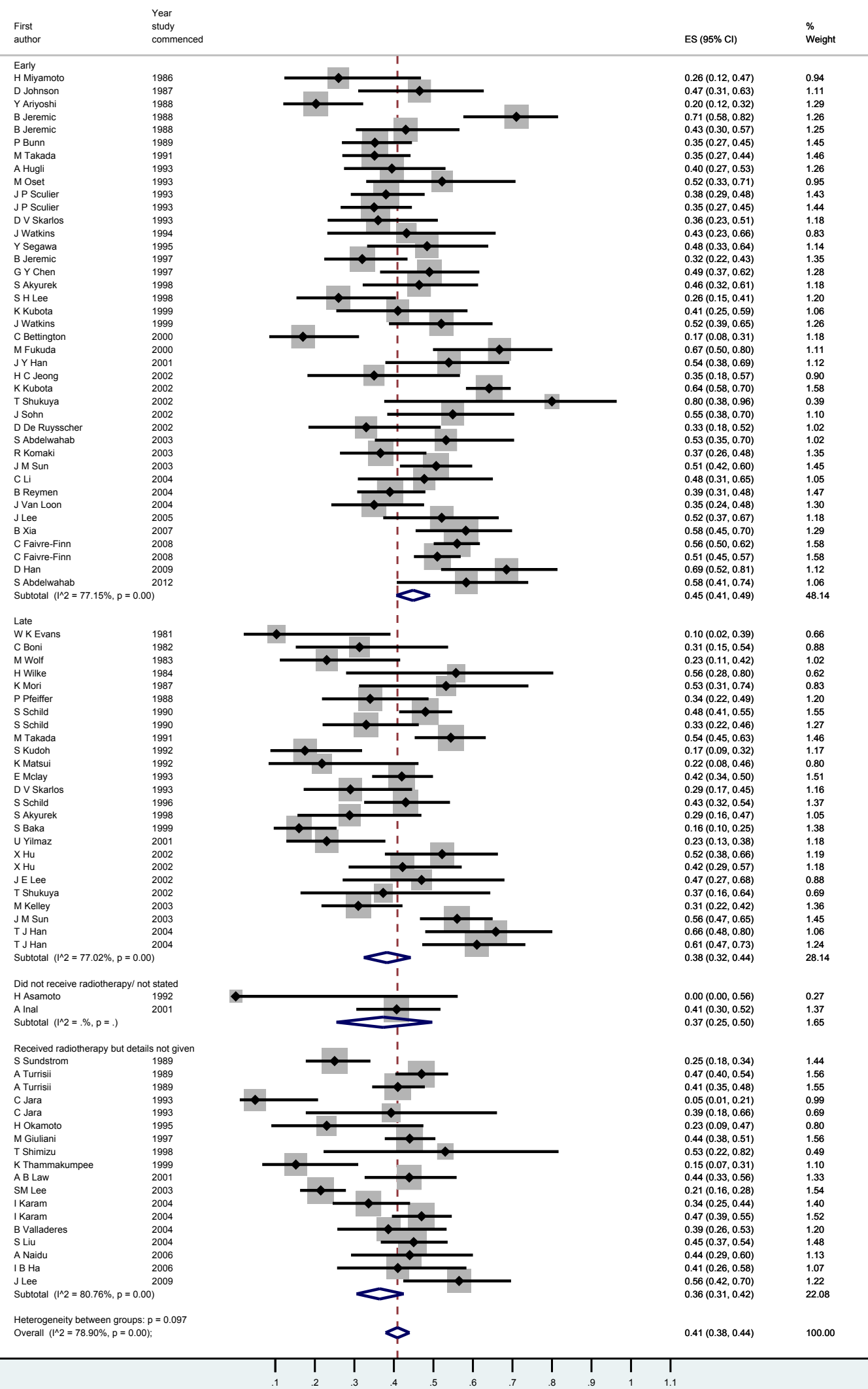
Proportion of 2 year survival in extensive stage by median participant age

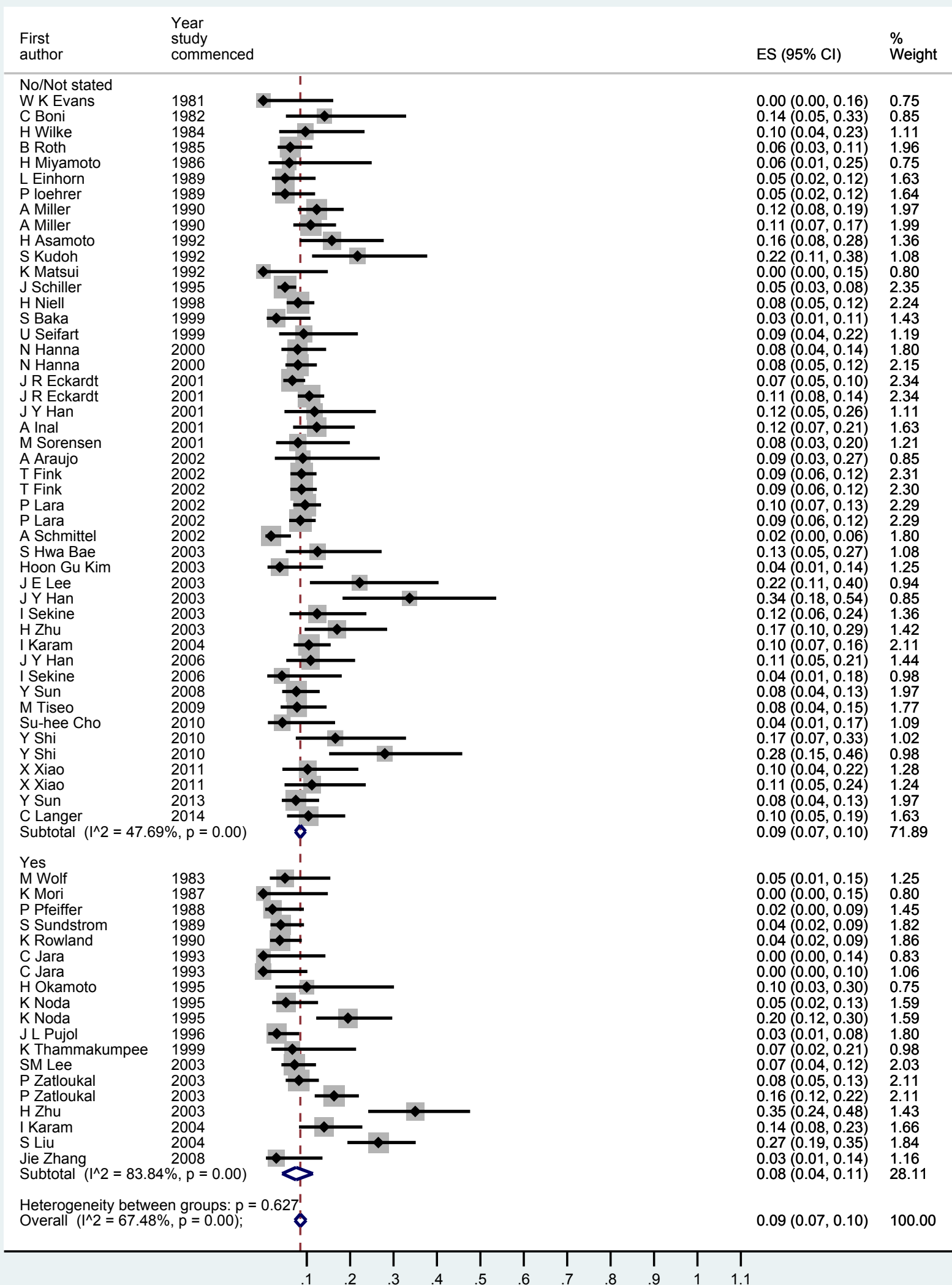




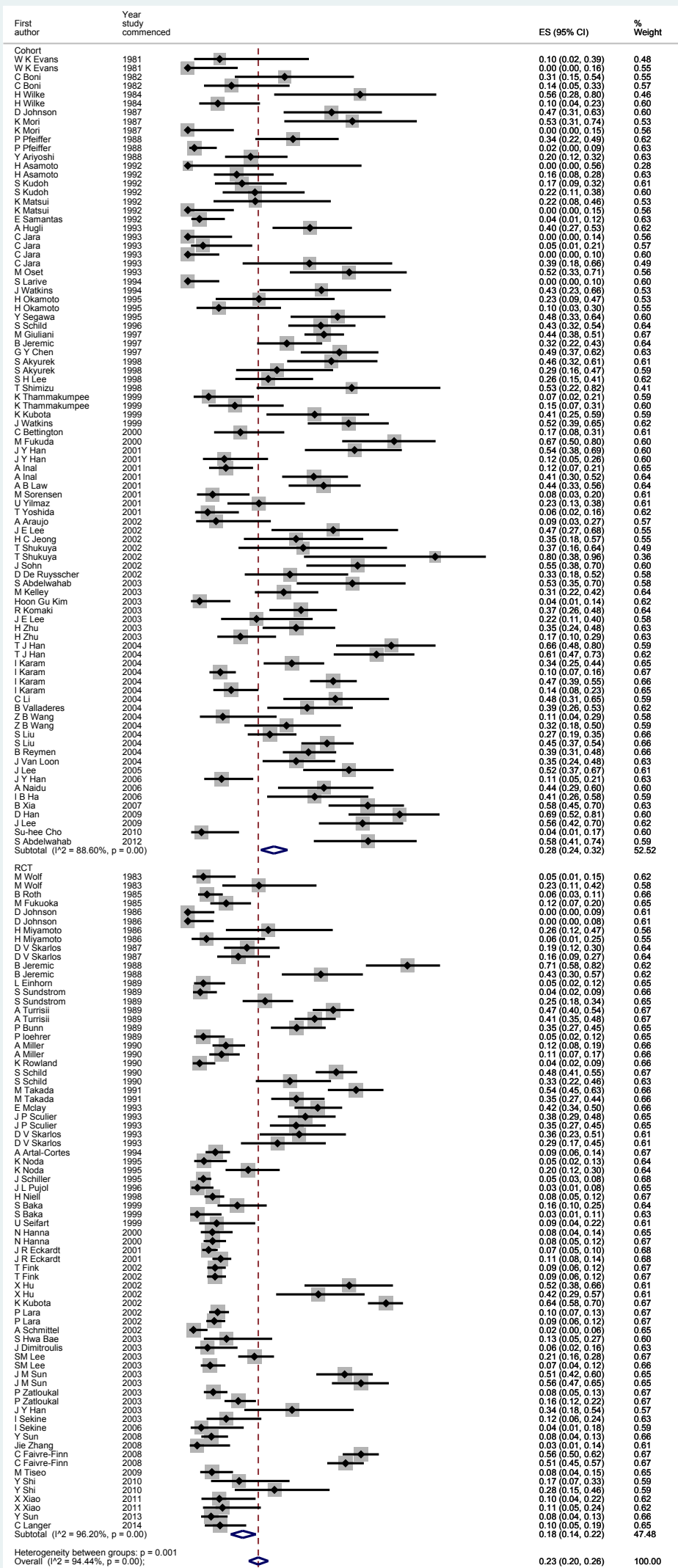




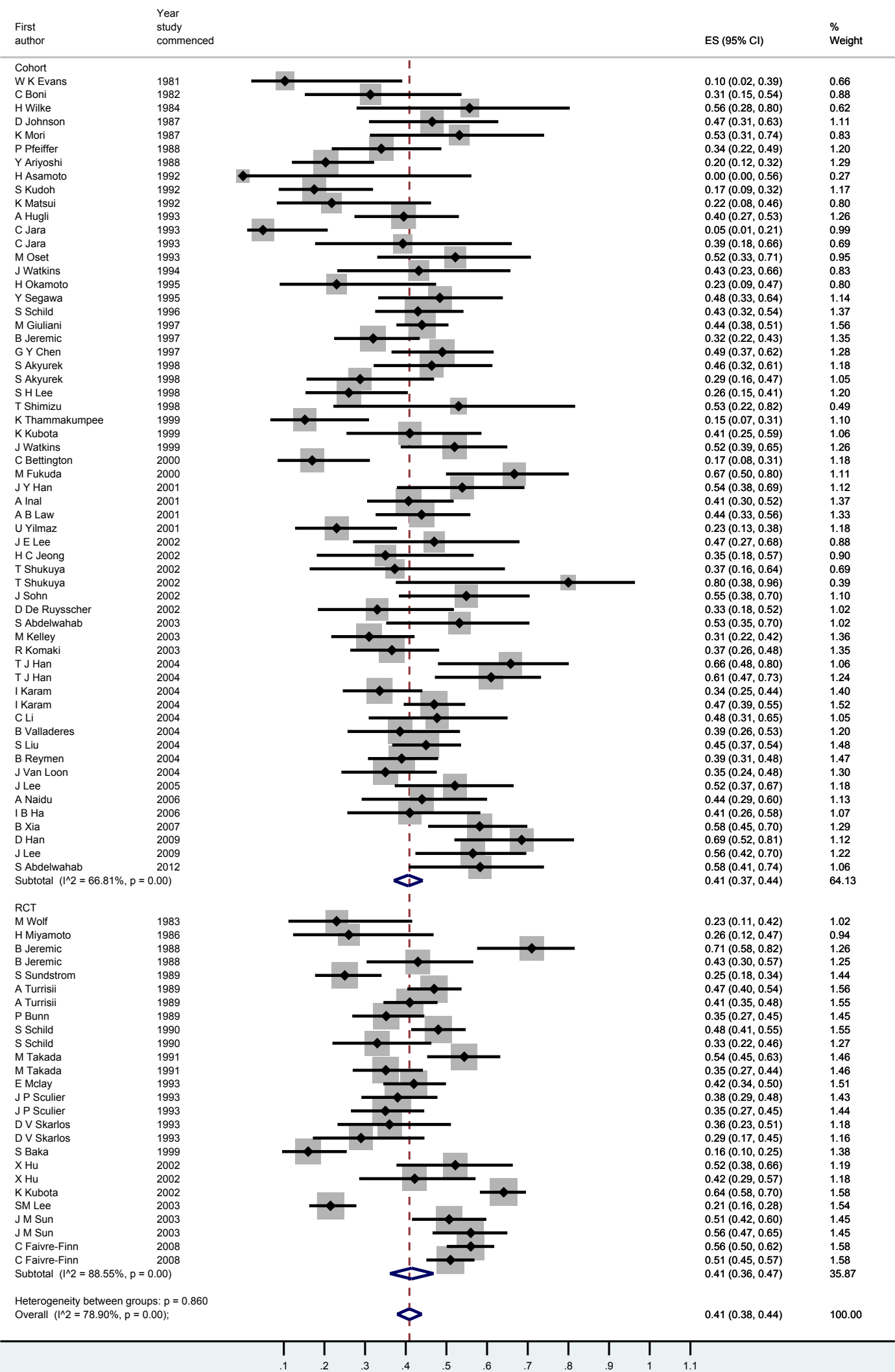


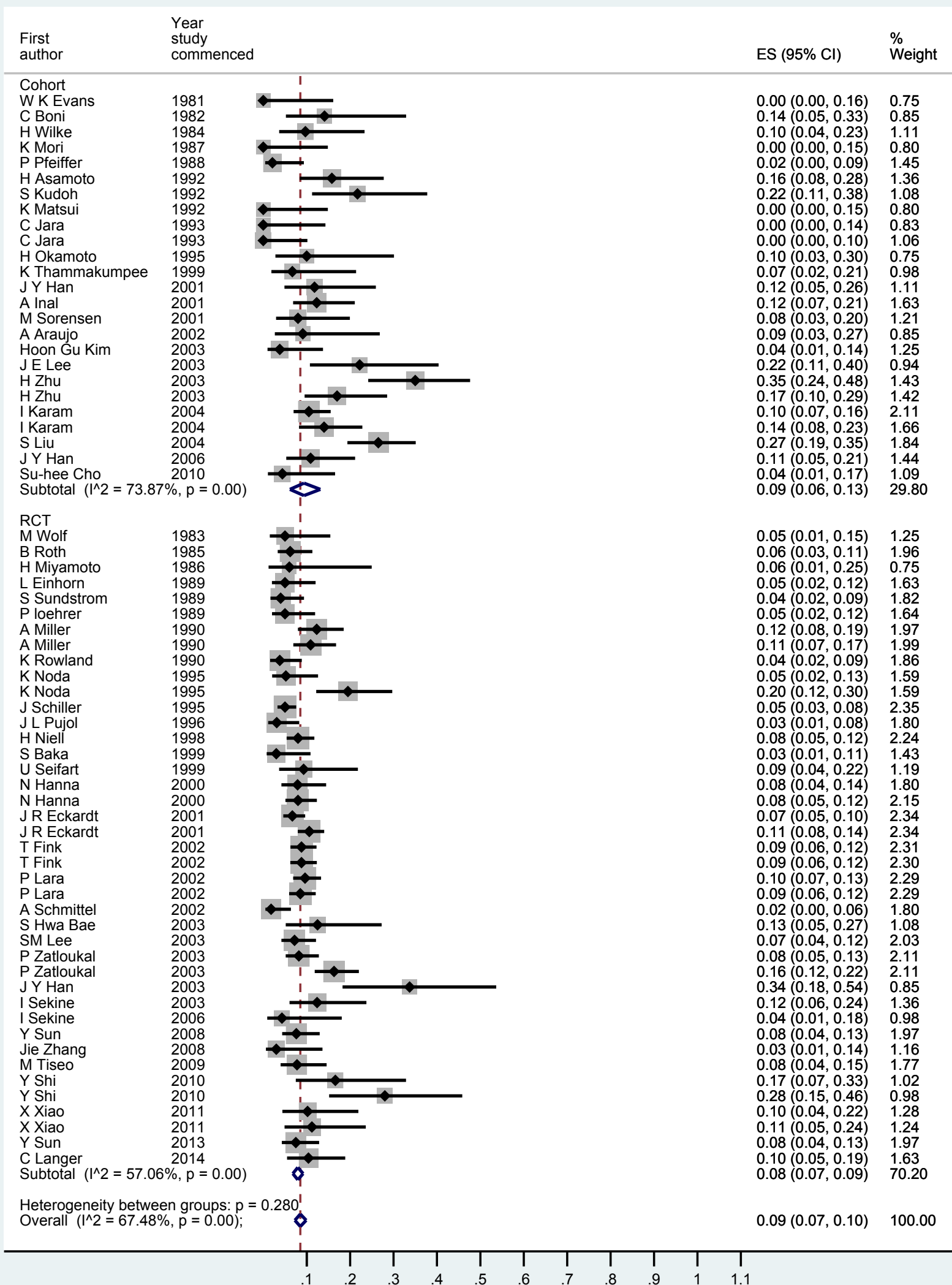


Proportion of 2 year survival in extensive stage by radiotherapy

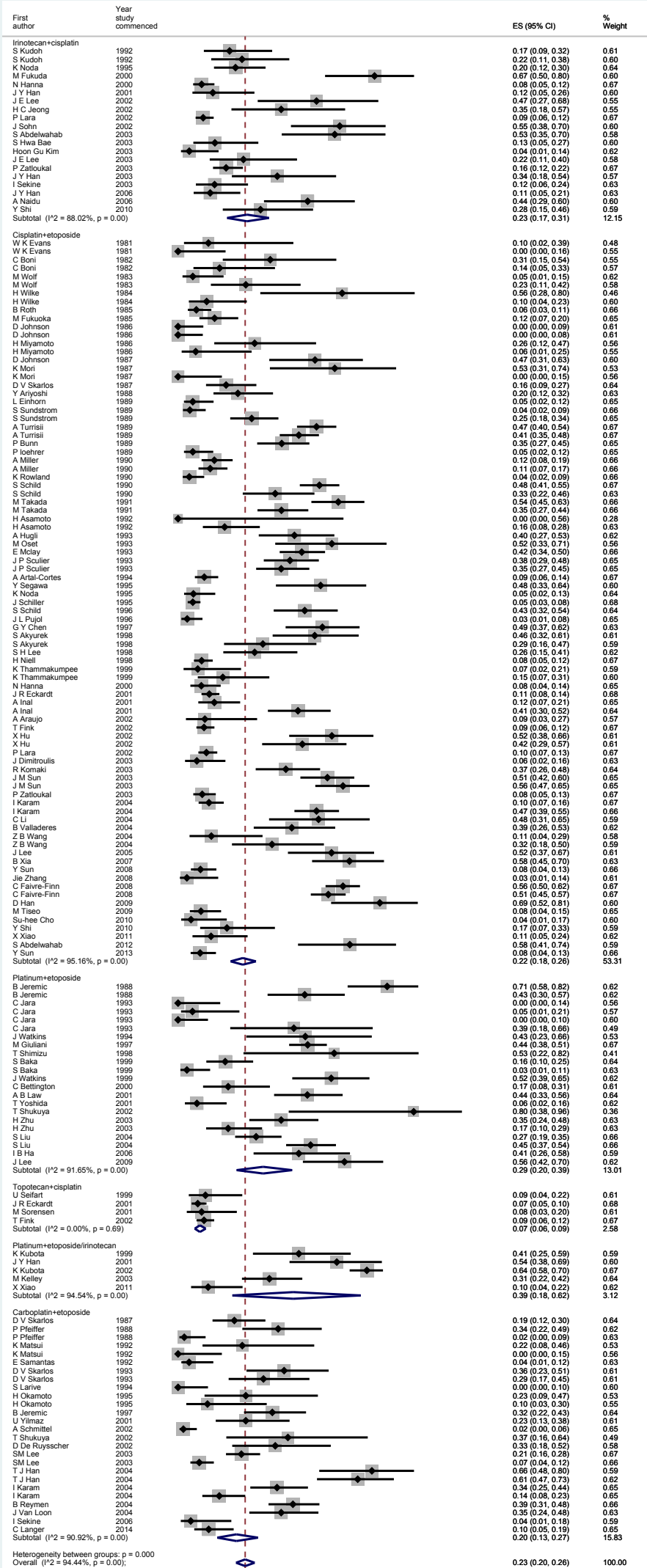


2 year survival after chemotherapy by study design

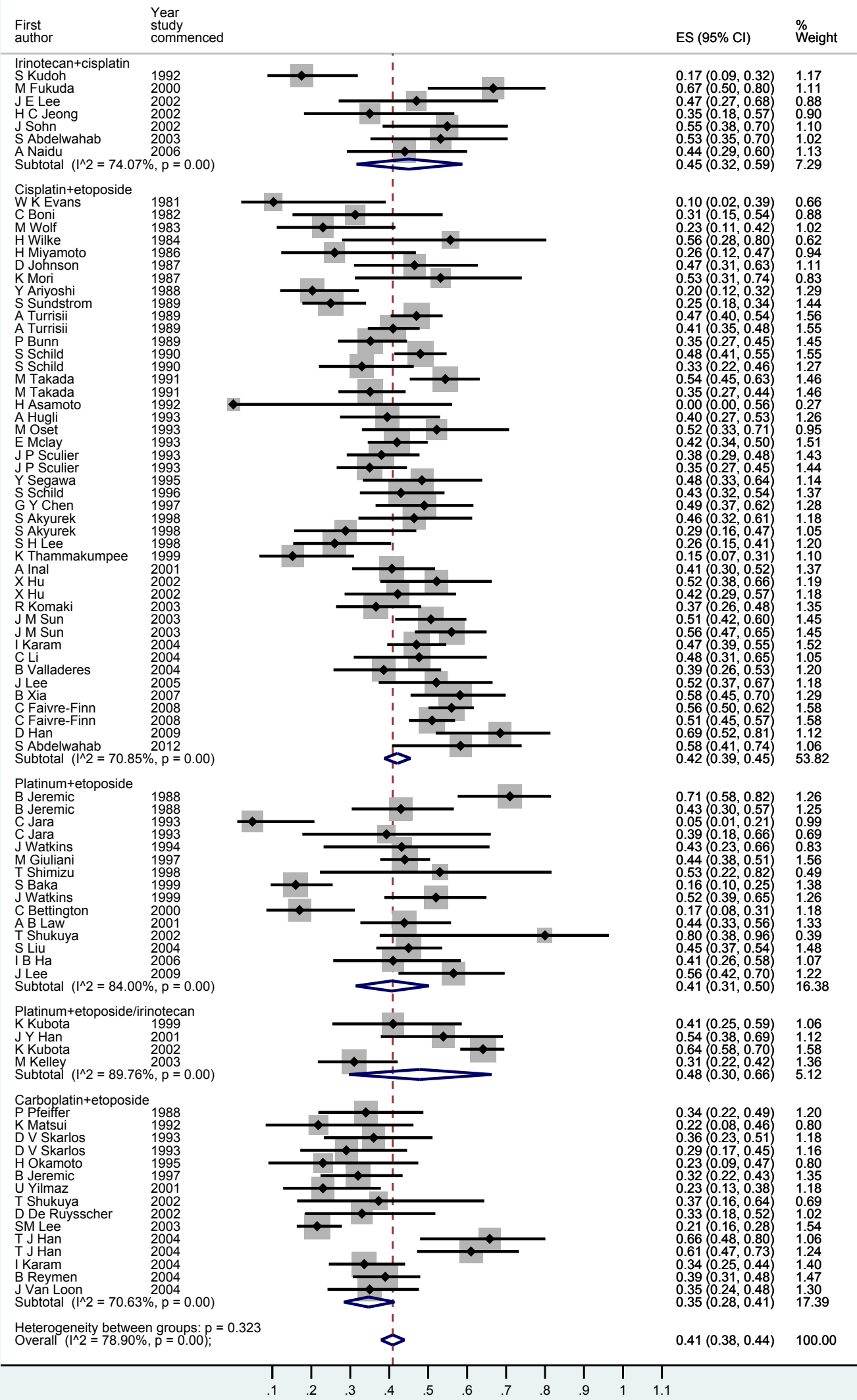


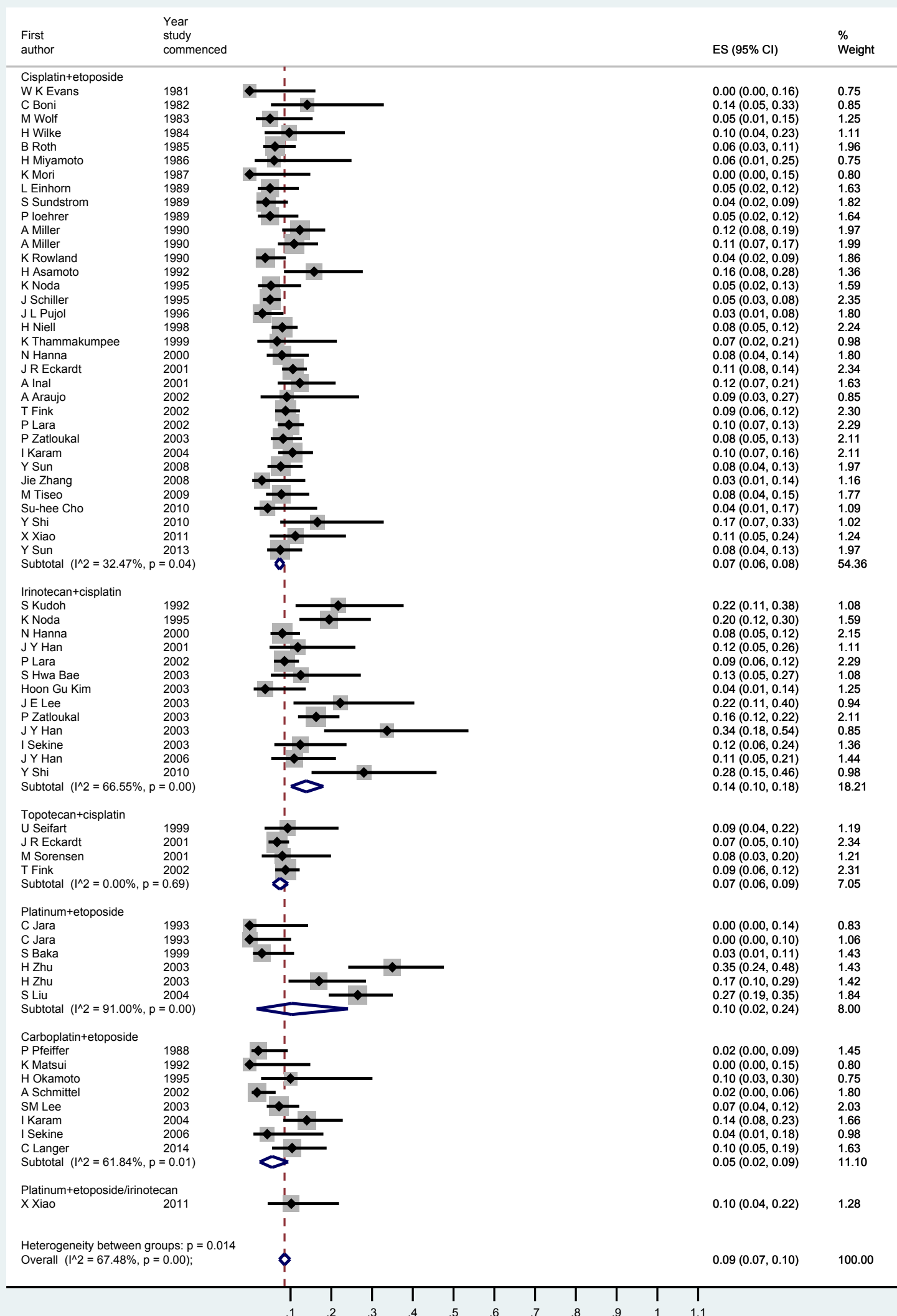


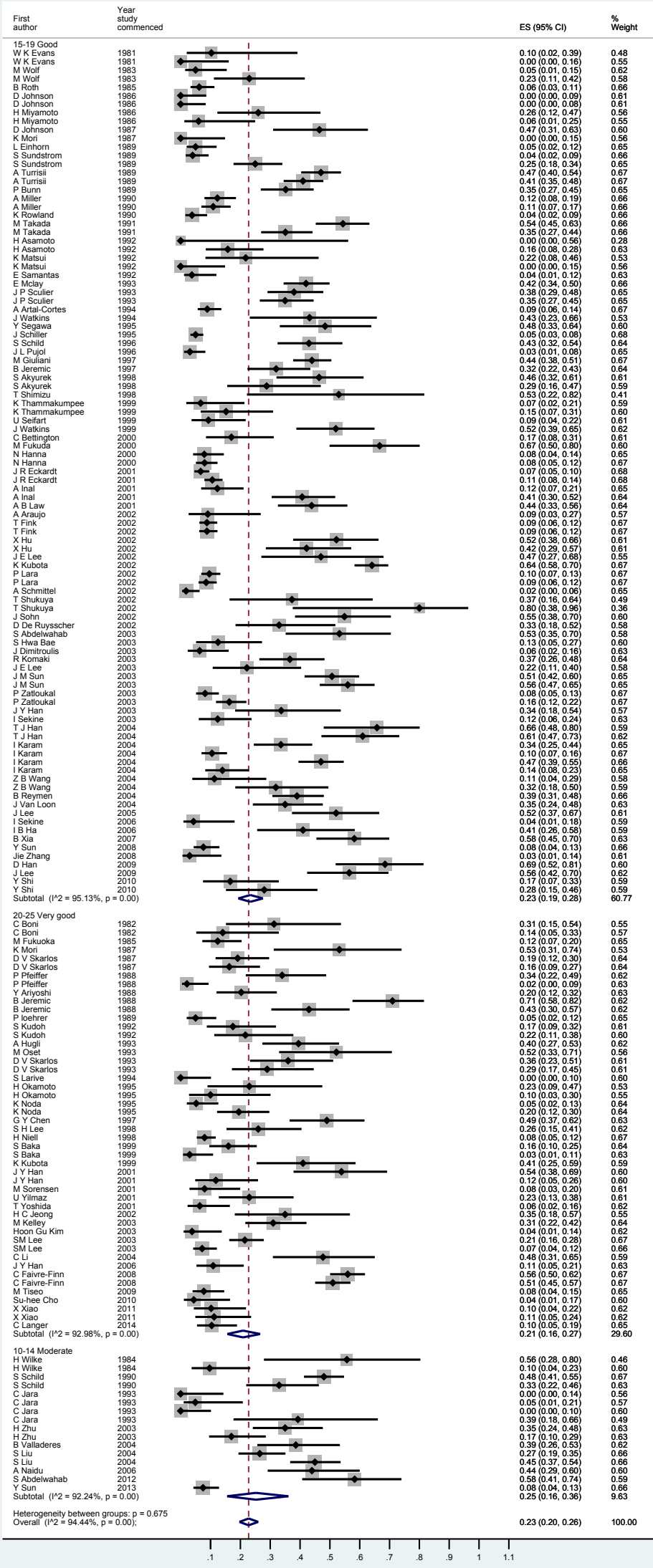
Proportion of 2 year survival in extensive stage by study design



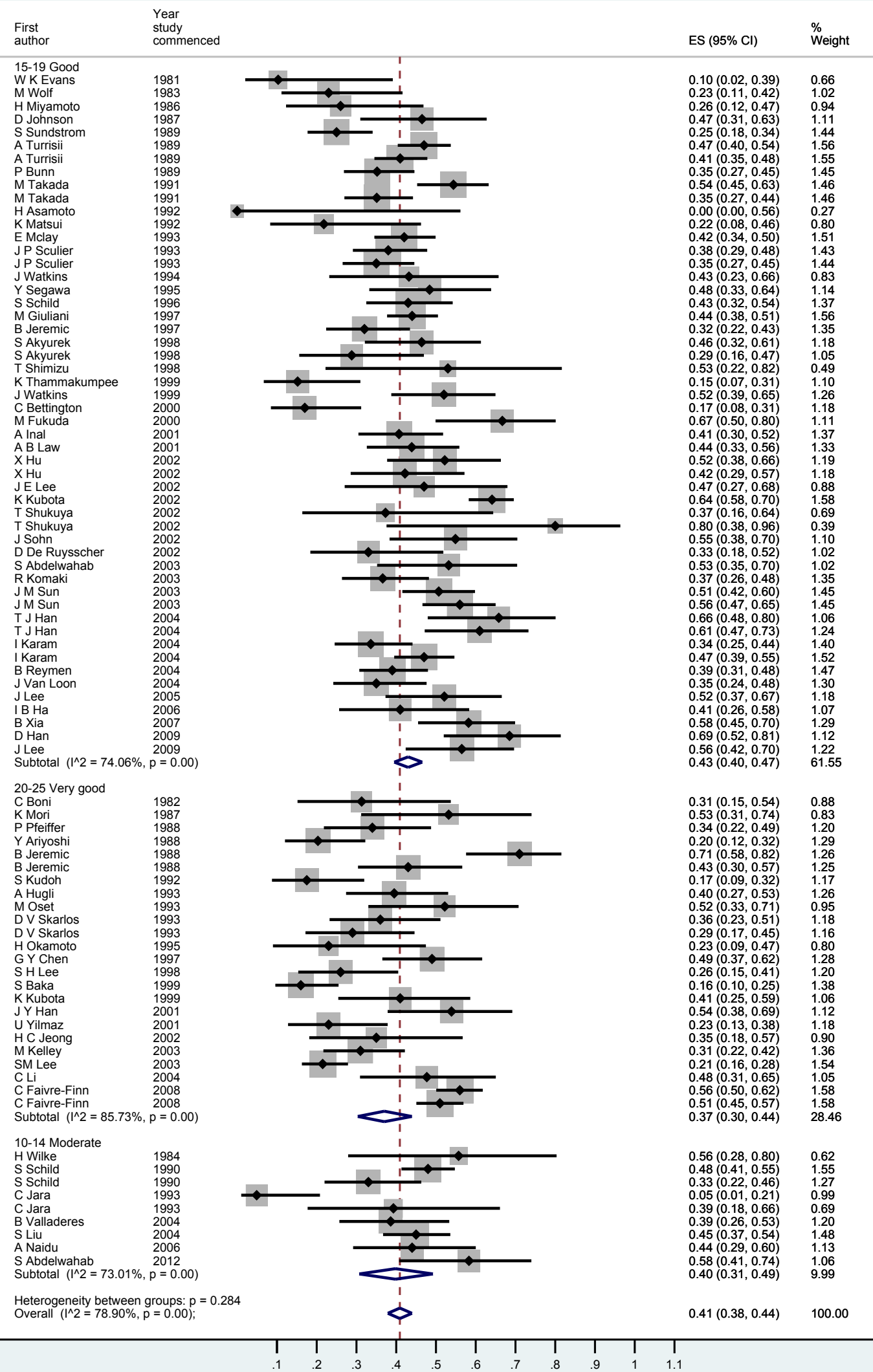
2 year survival after chemotherapy by drug

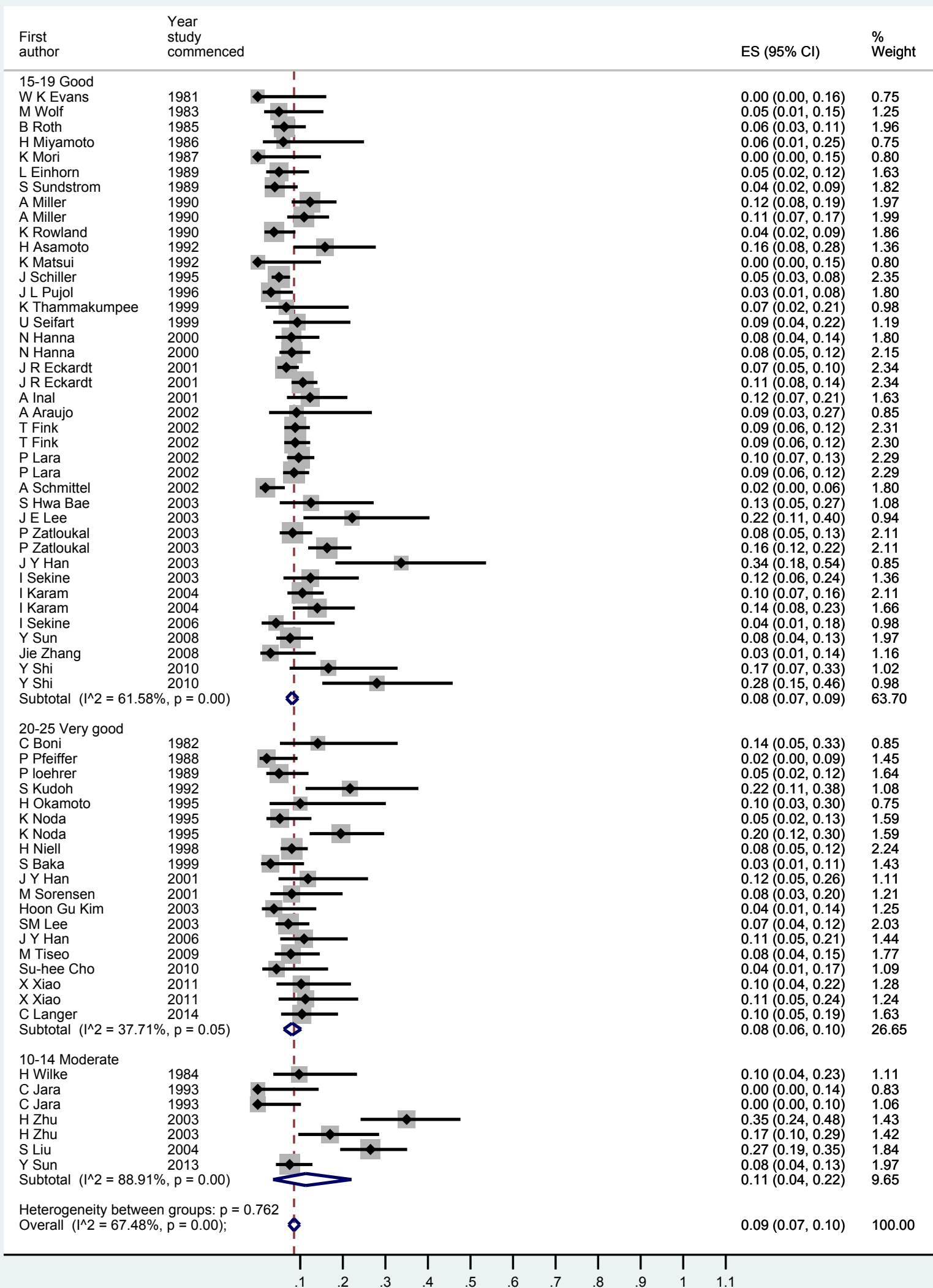




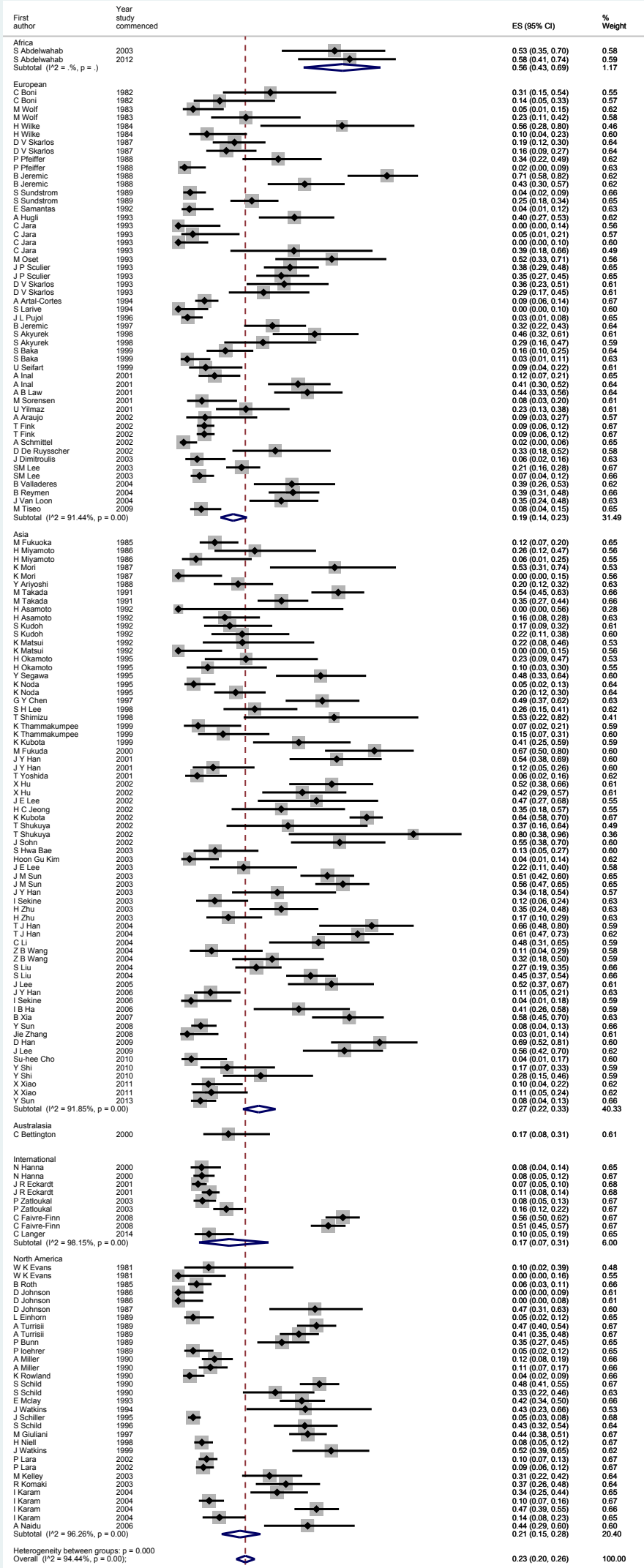


2 year survival after chemotherapy by quality score

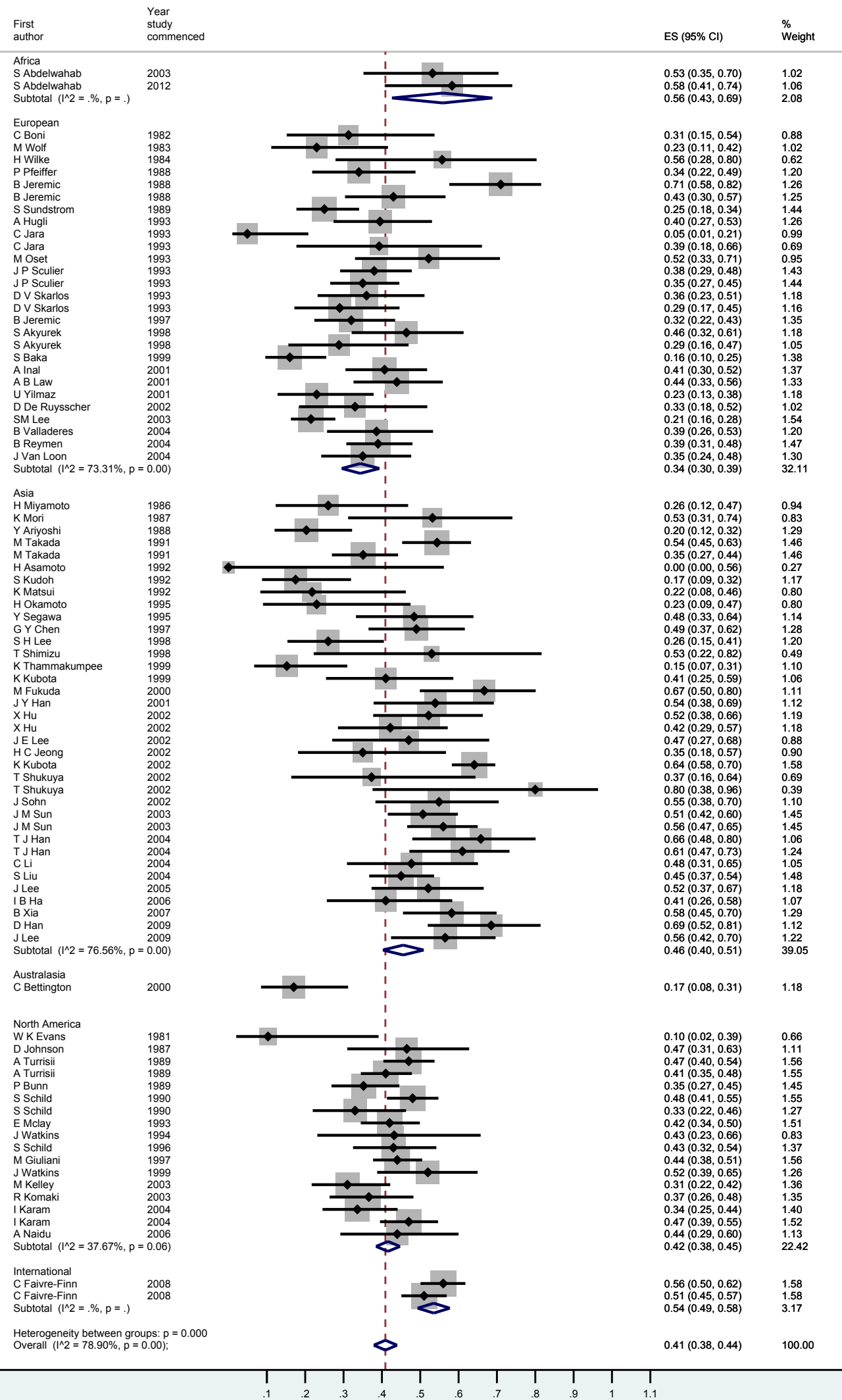


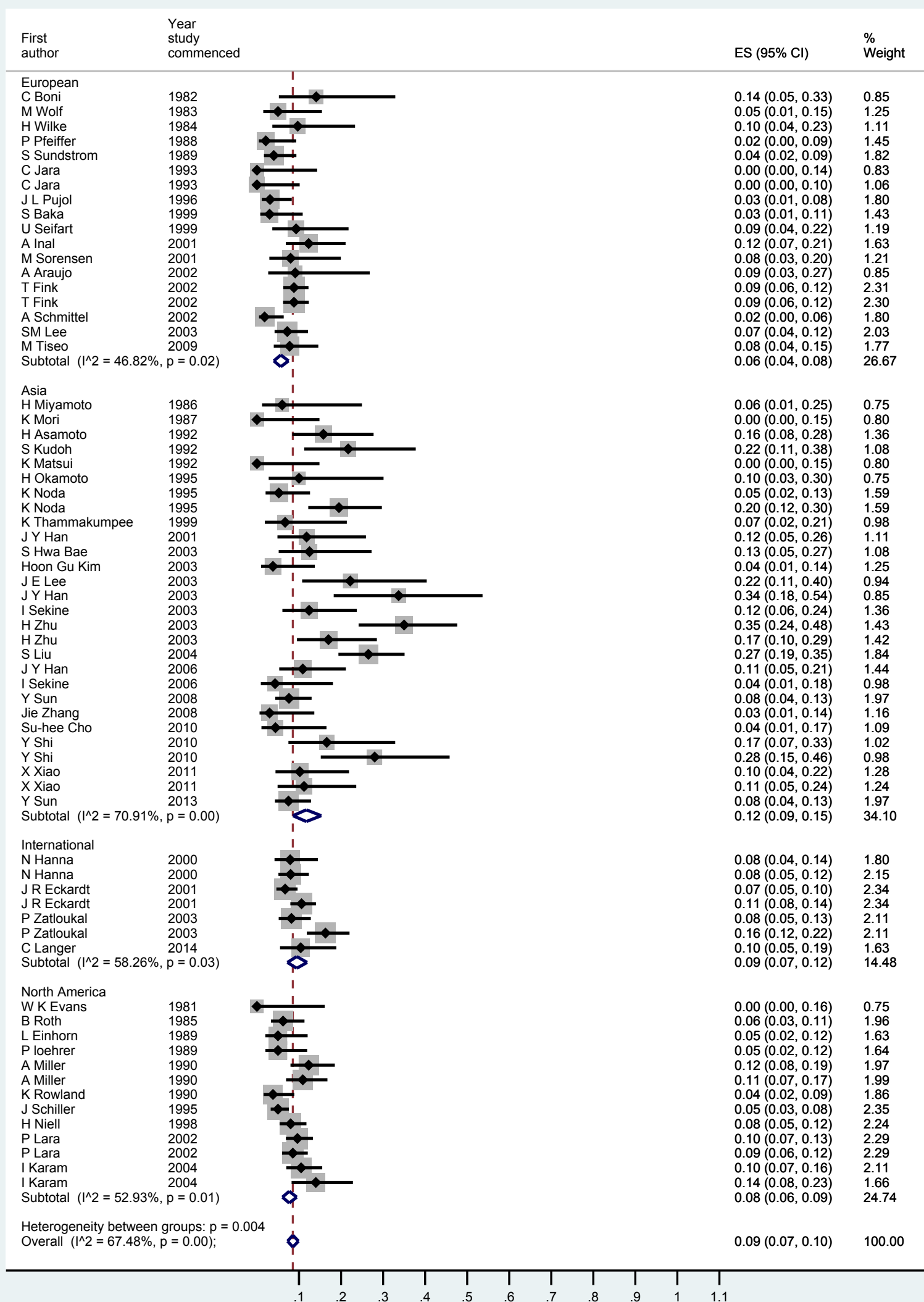


Proportion of 2 year survival in extensive stage by quality score

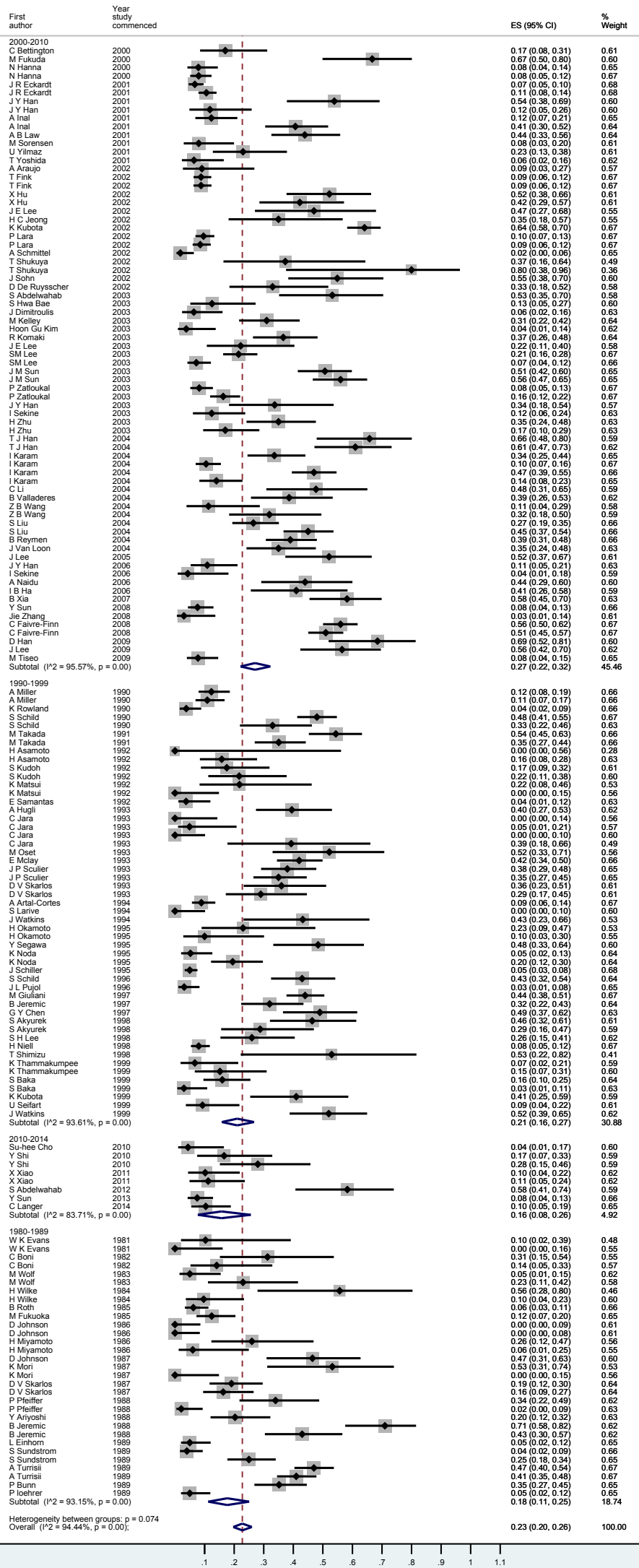


2 year survival after chemotherapy by region

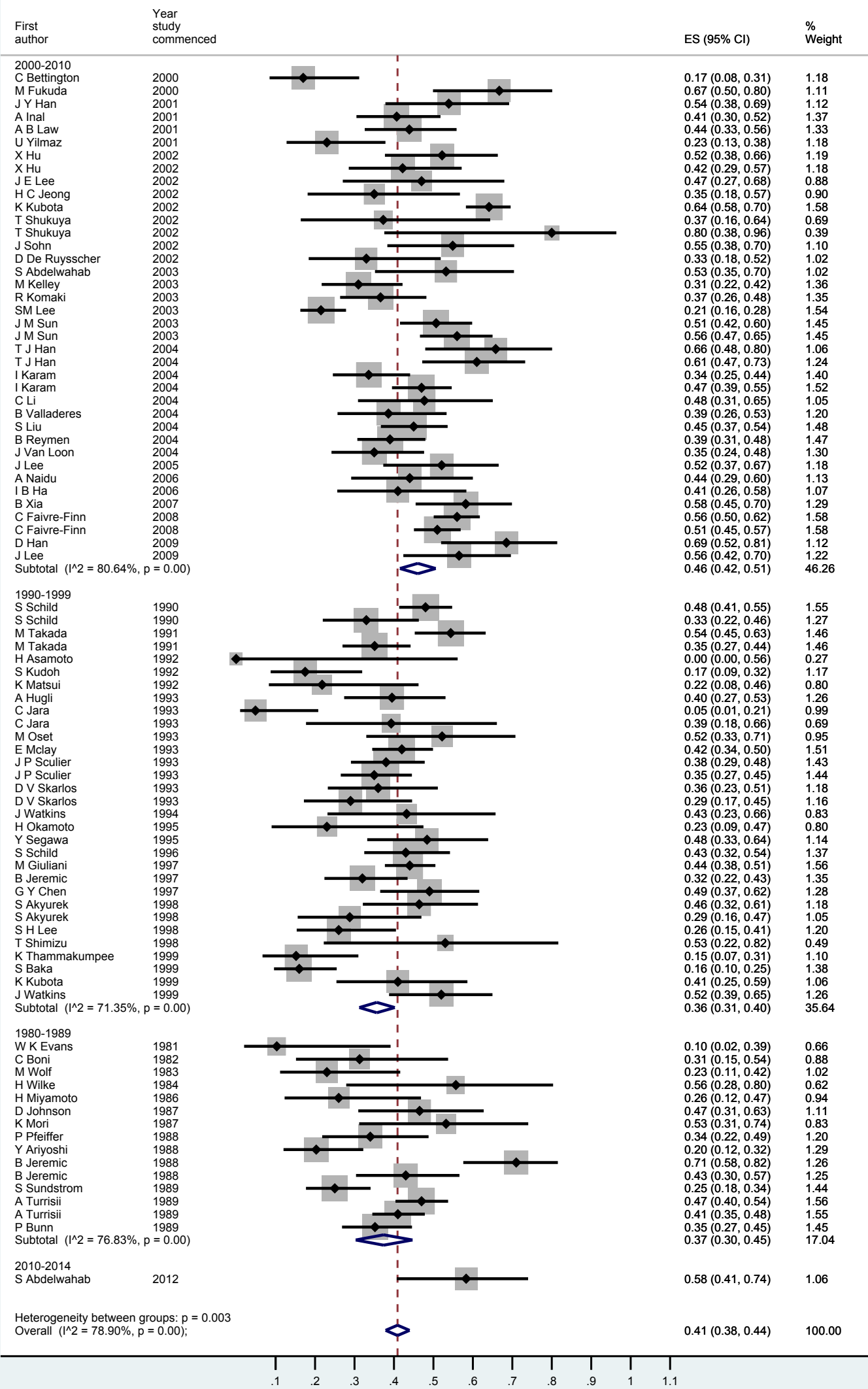


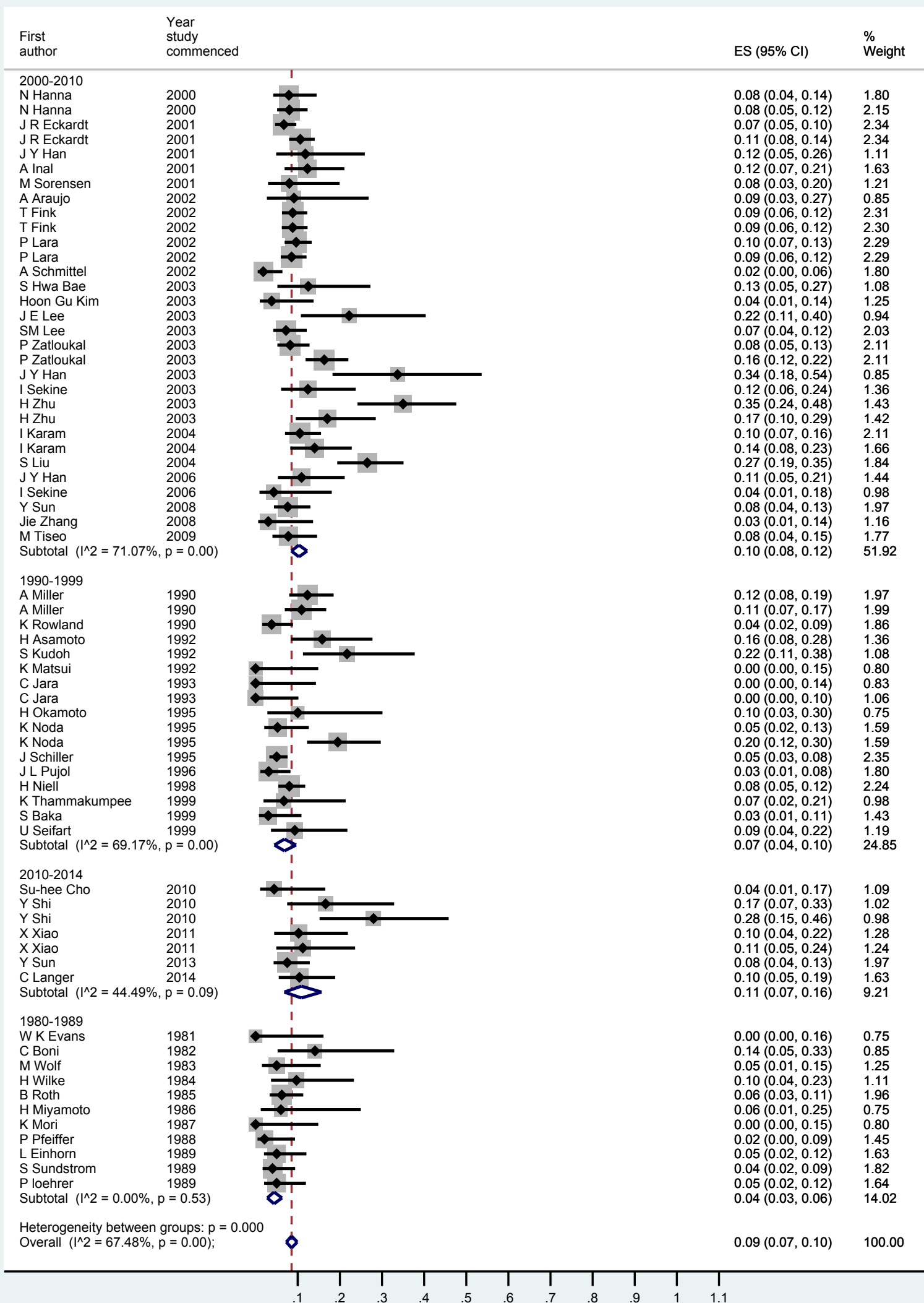


Proportion of 2 year survival in extensive stage by region

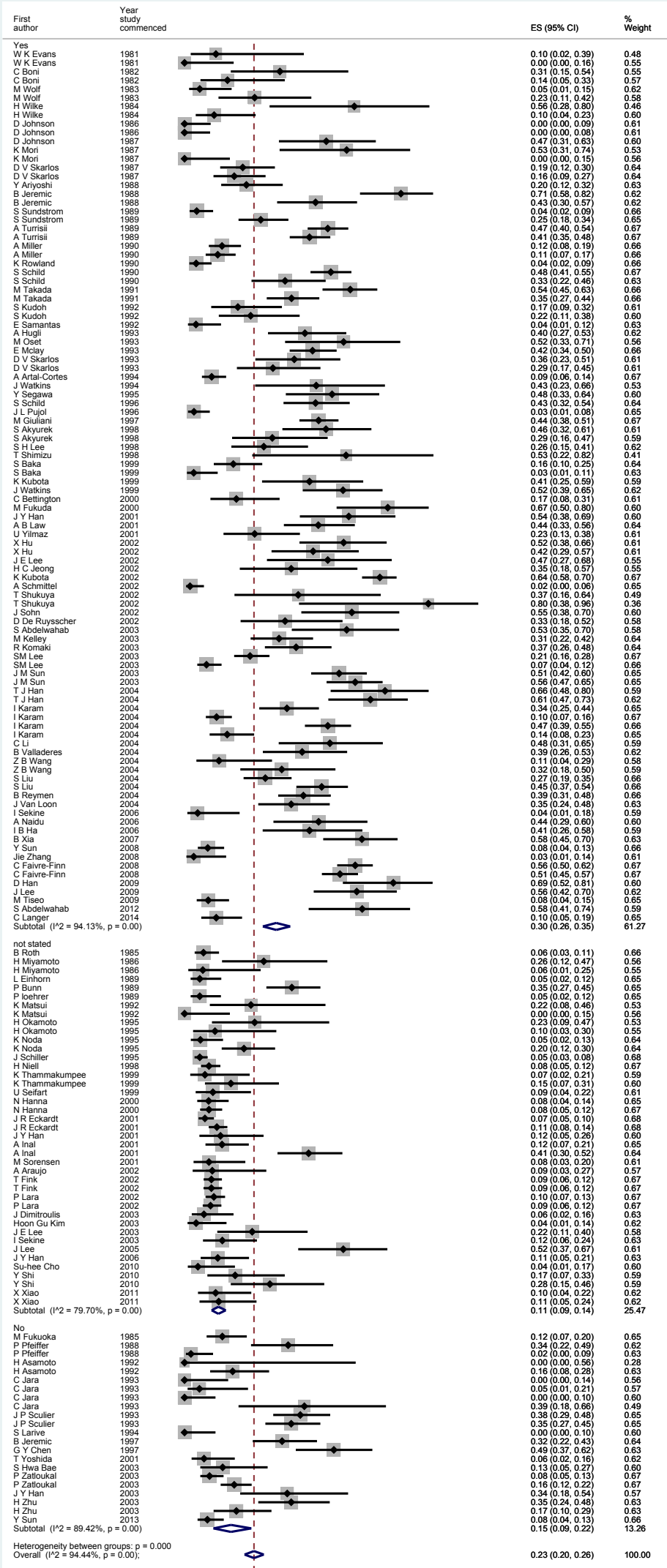


2 year survival after chemotherapy by study year

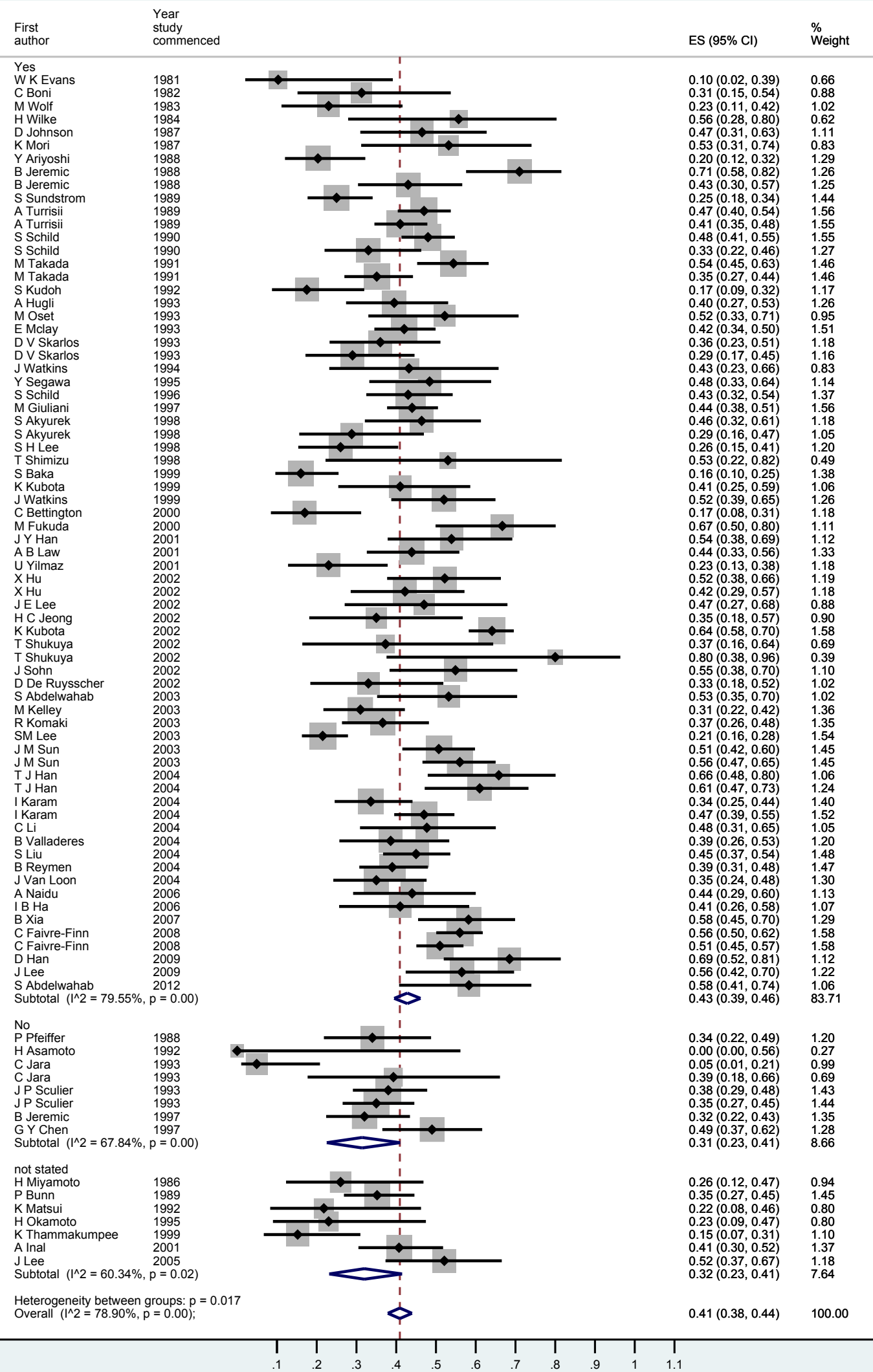




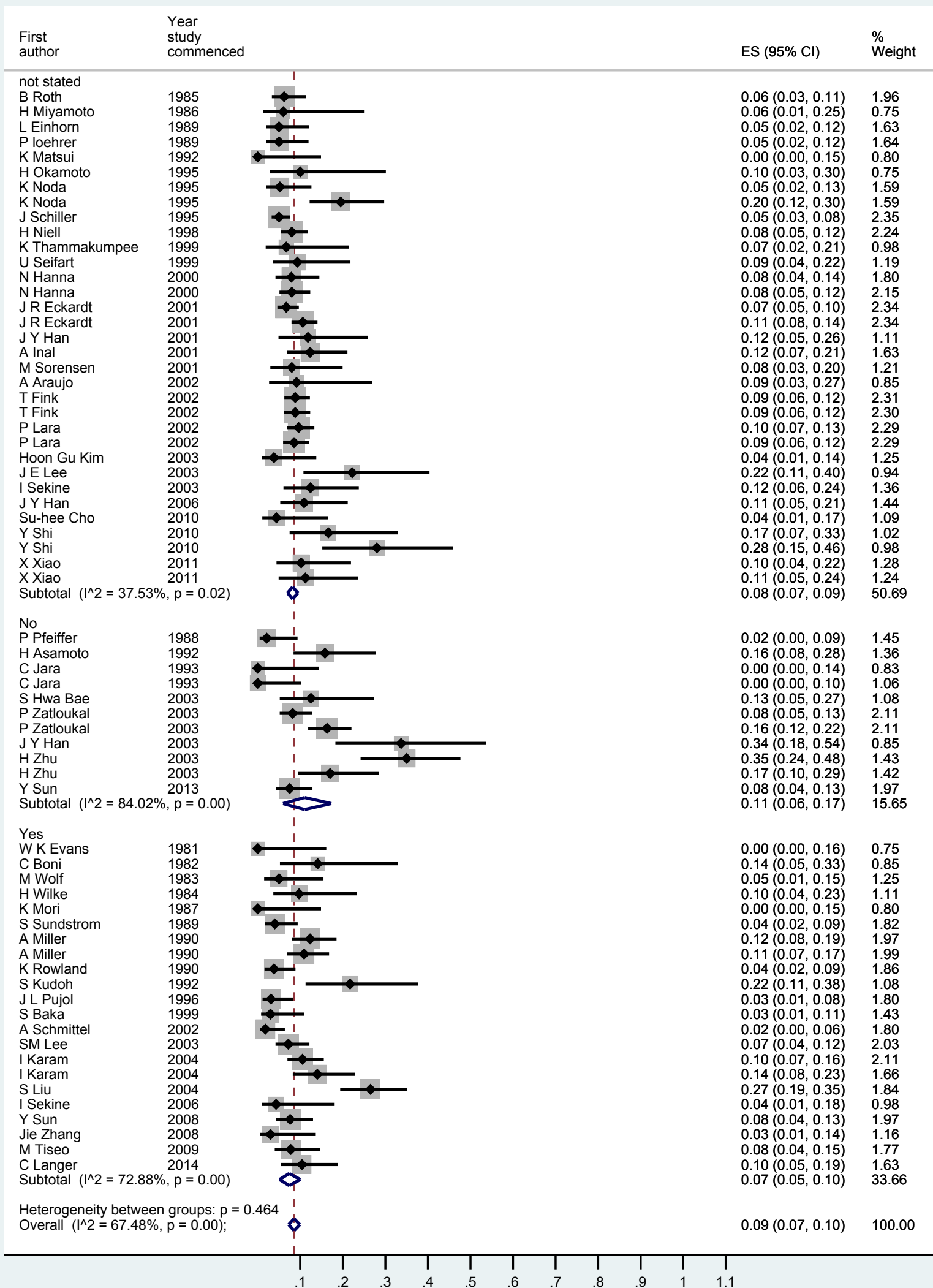
Proportion of 2 year survival in extensive stage by study year



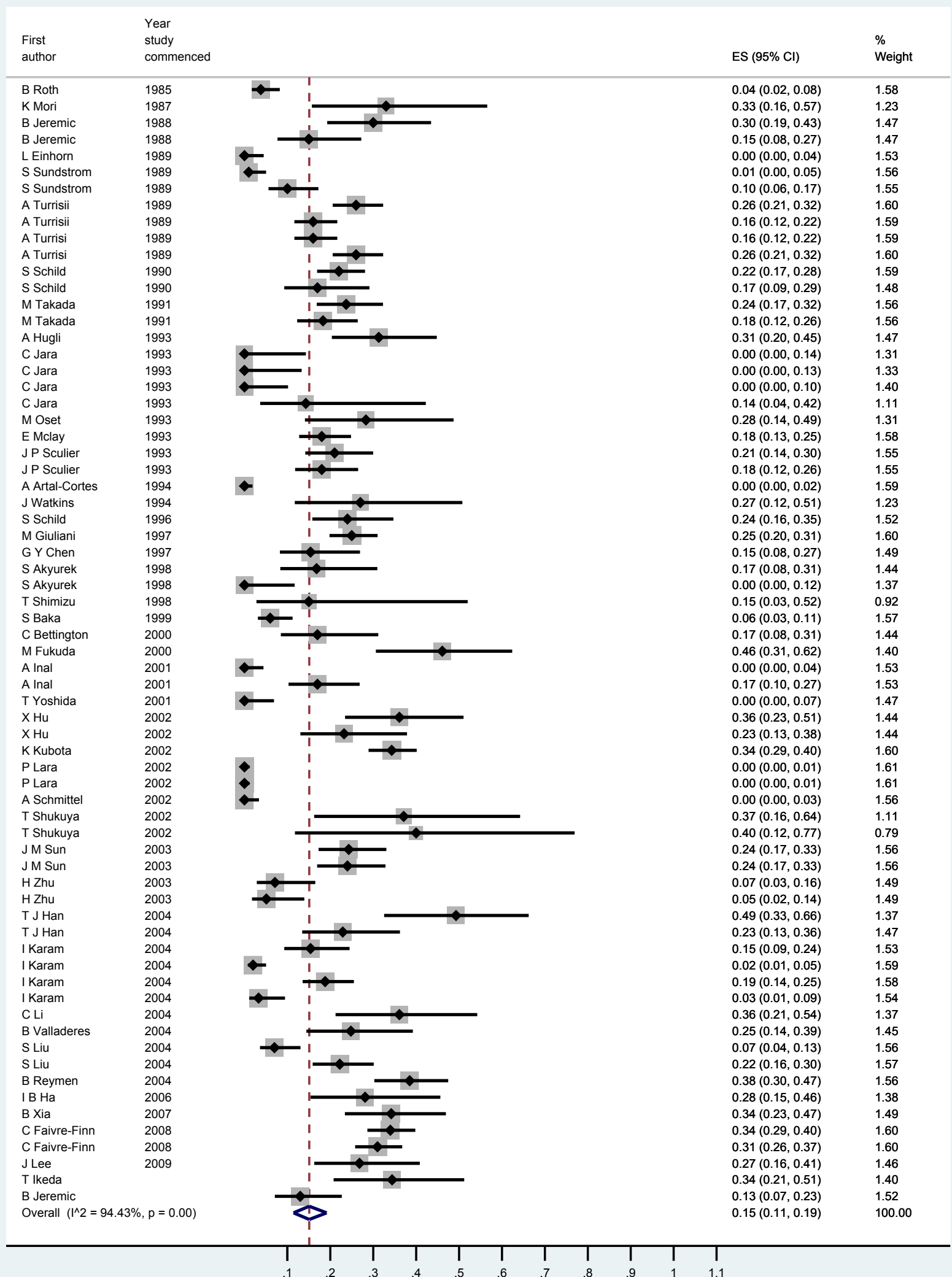
2 year survival after chemotherapy by PCI



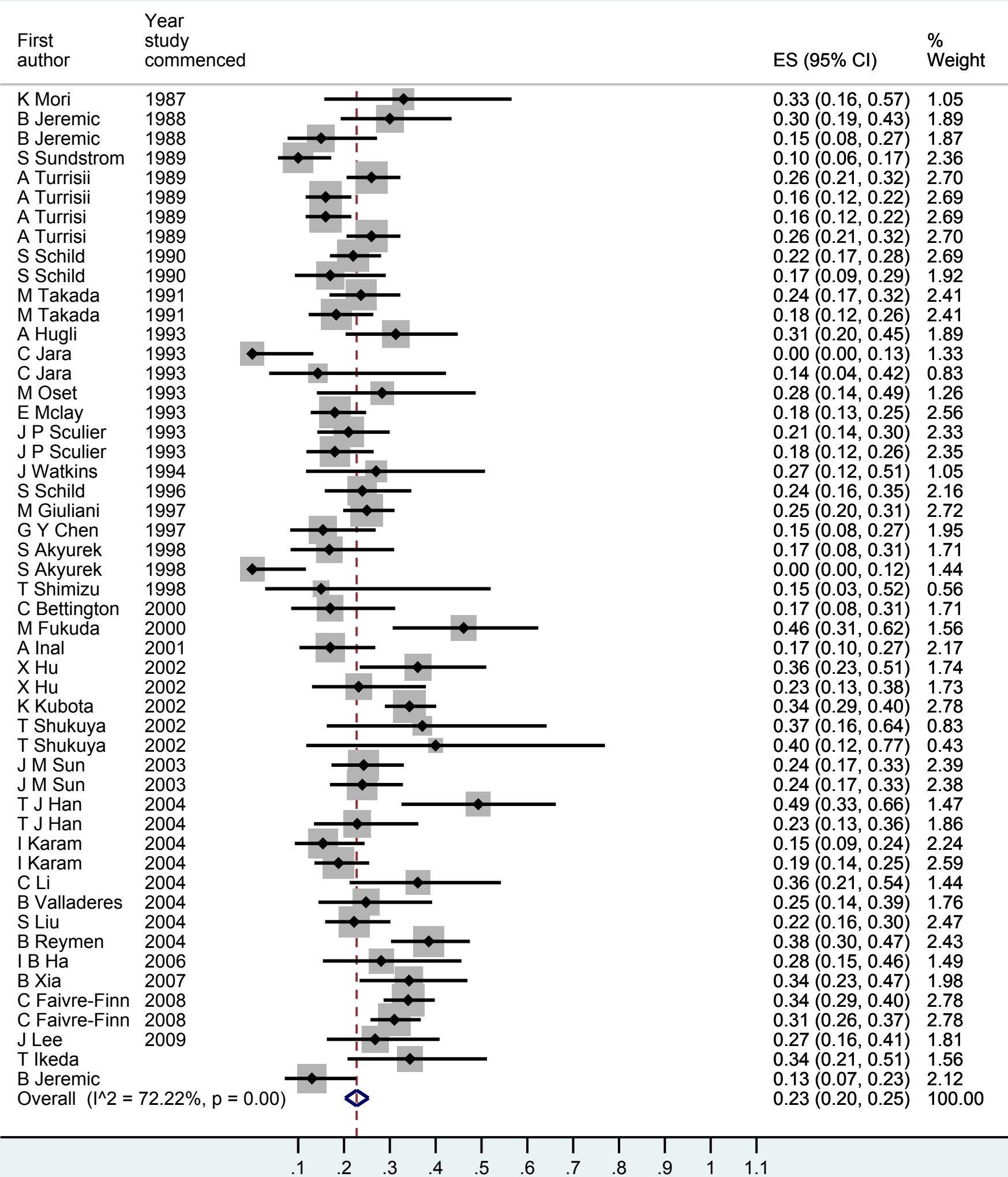
Proportion of 2 year survival in limited stage by PCI



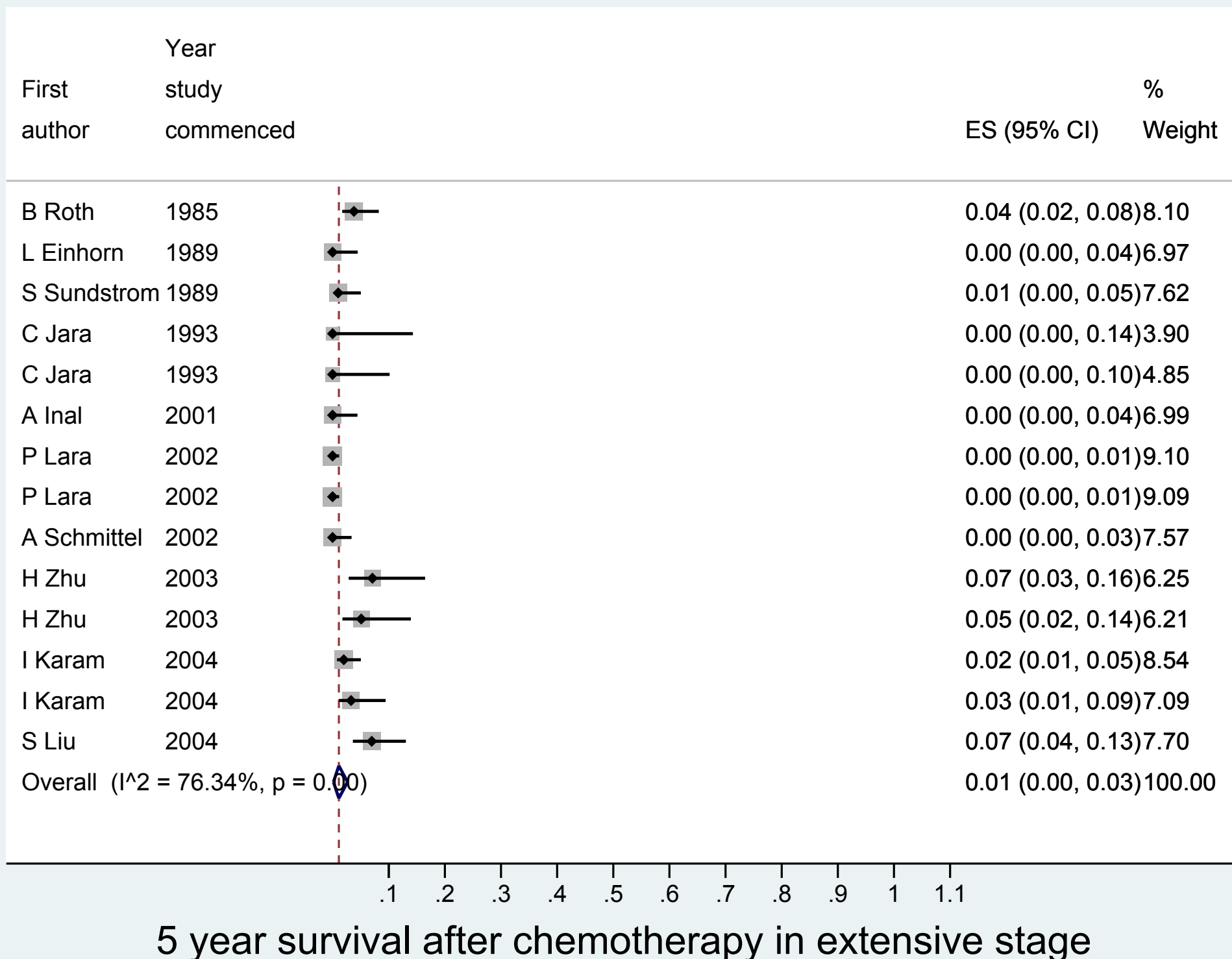
5-year survival

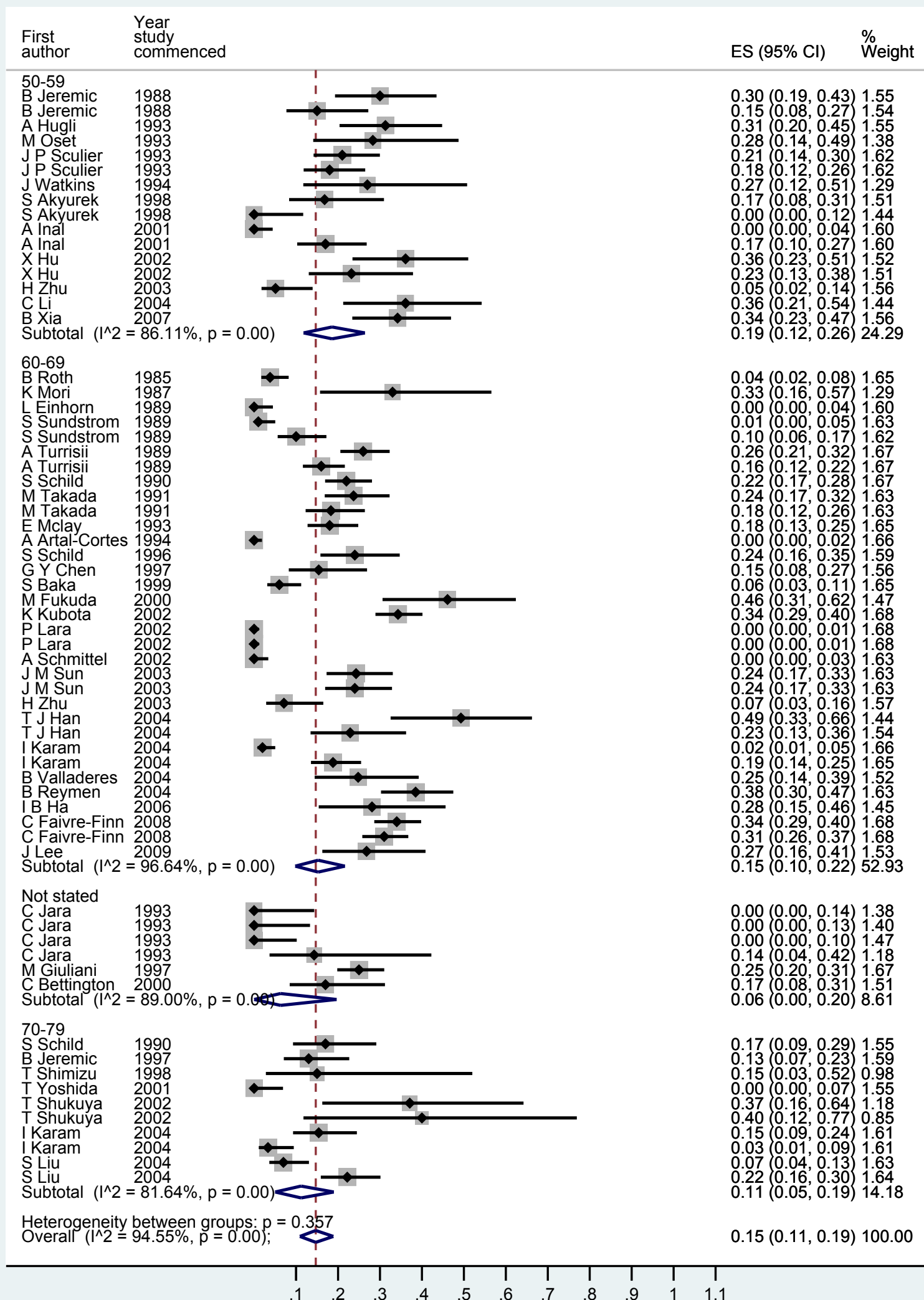


5 year survival after chemotherapy

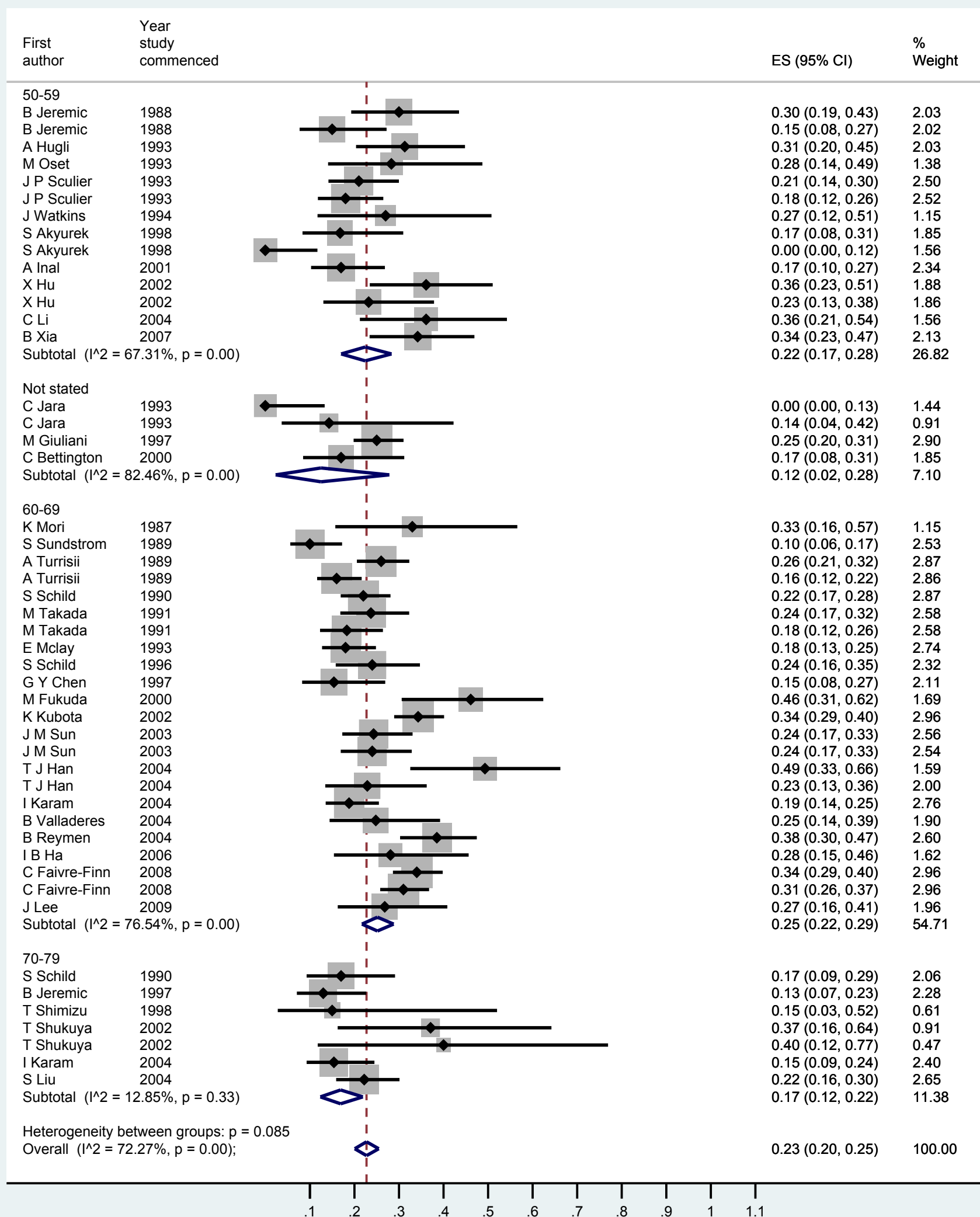


5 year survival after chemotherapy in limited stage

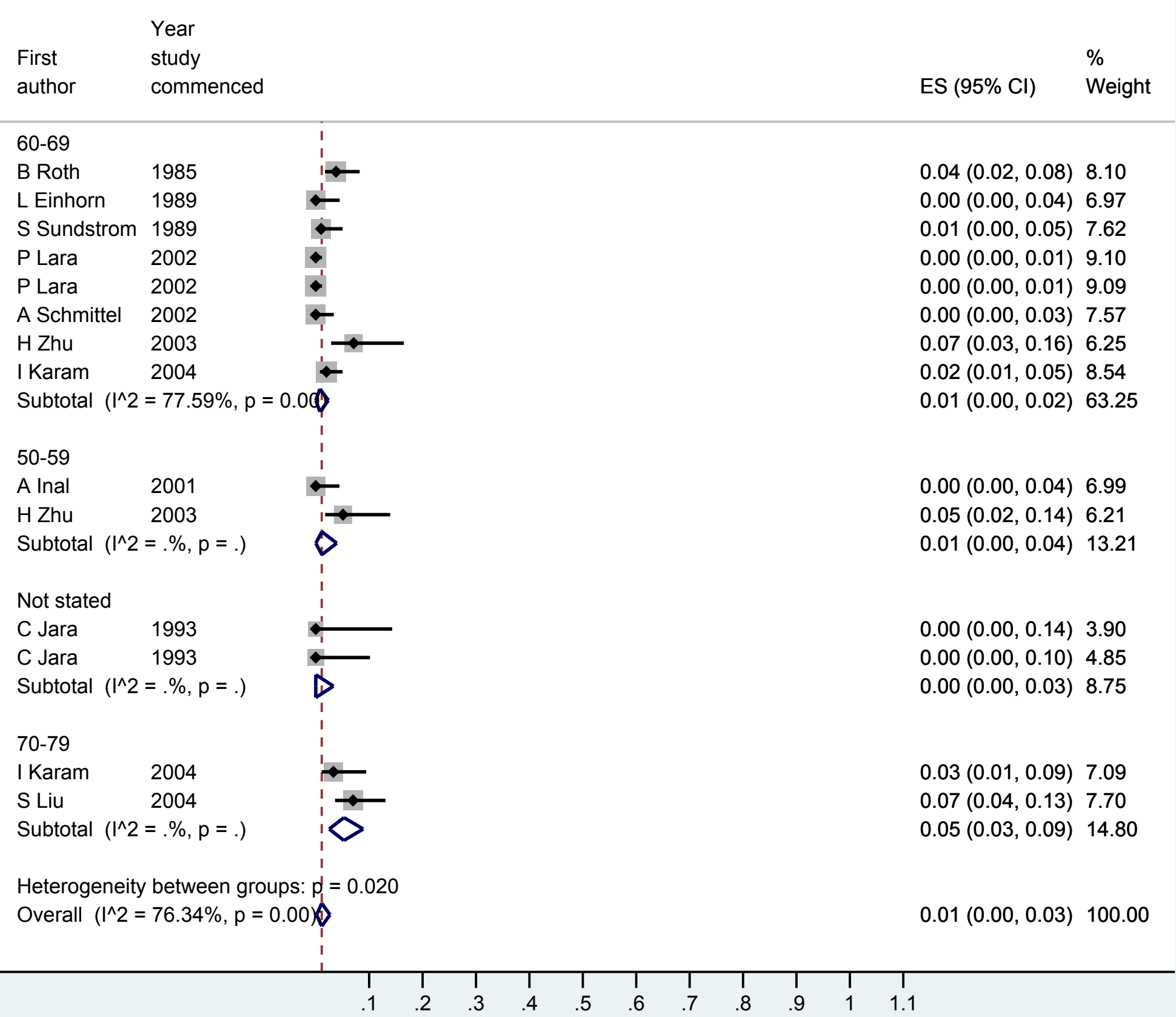




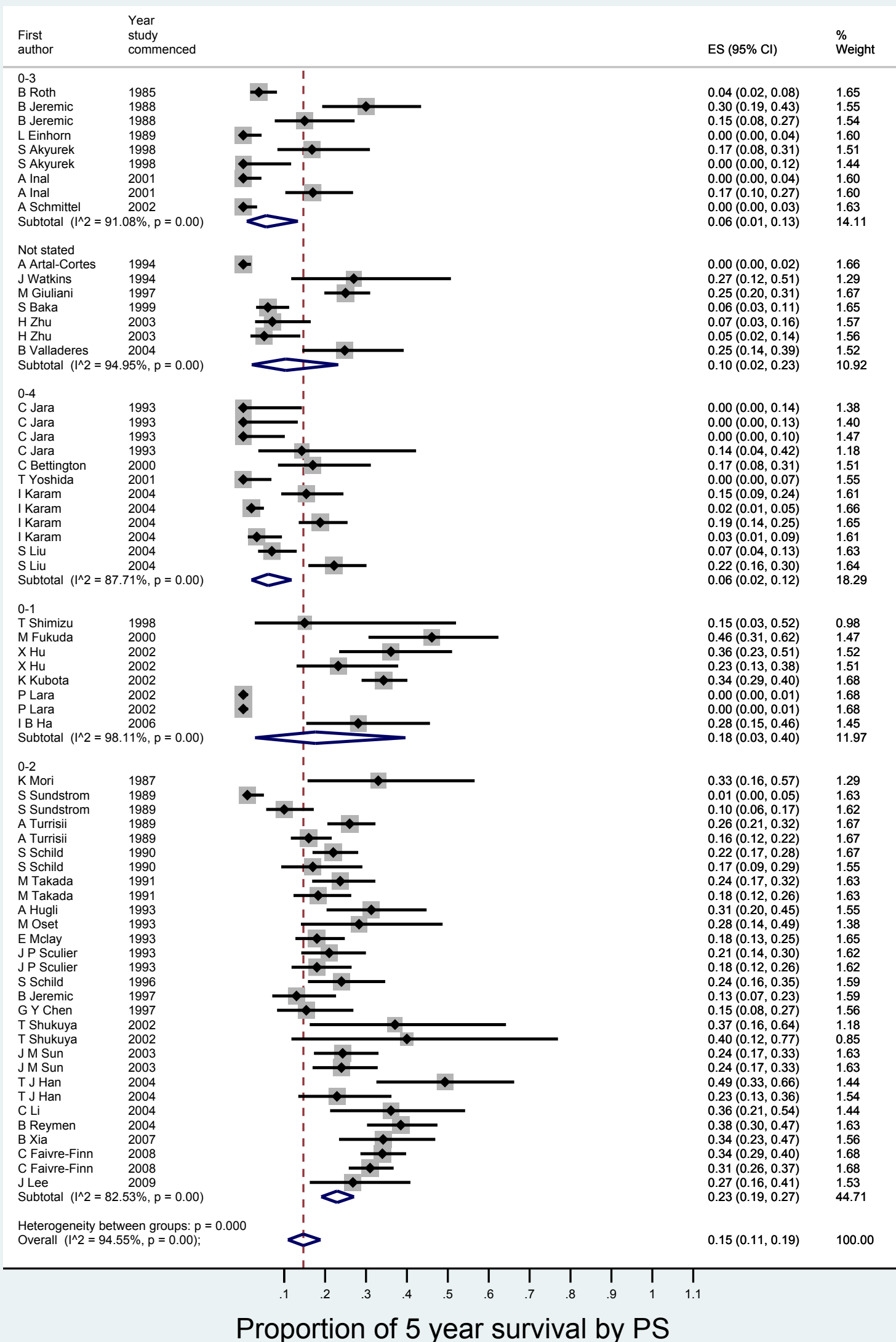
Proportion of 5 year survival by median participant age

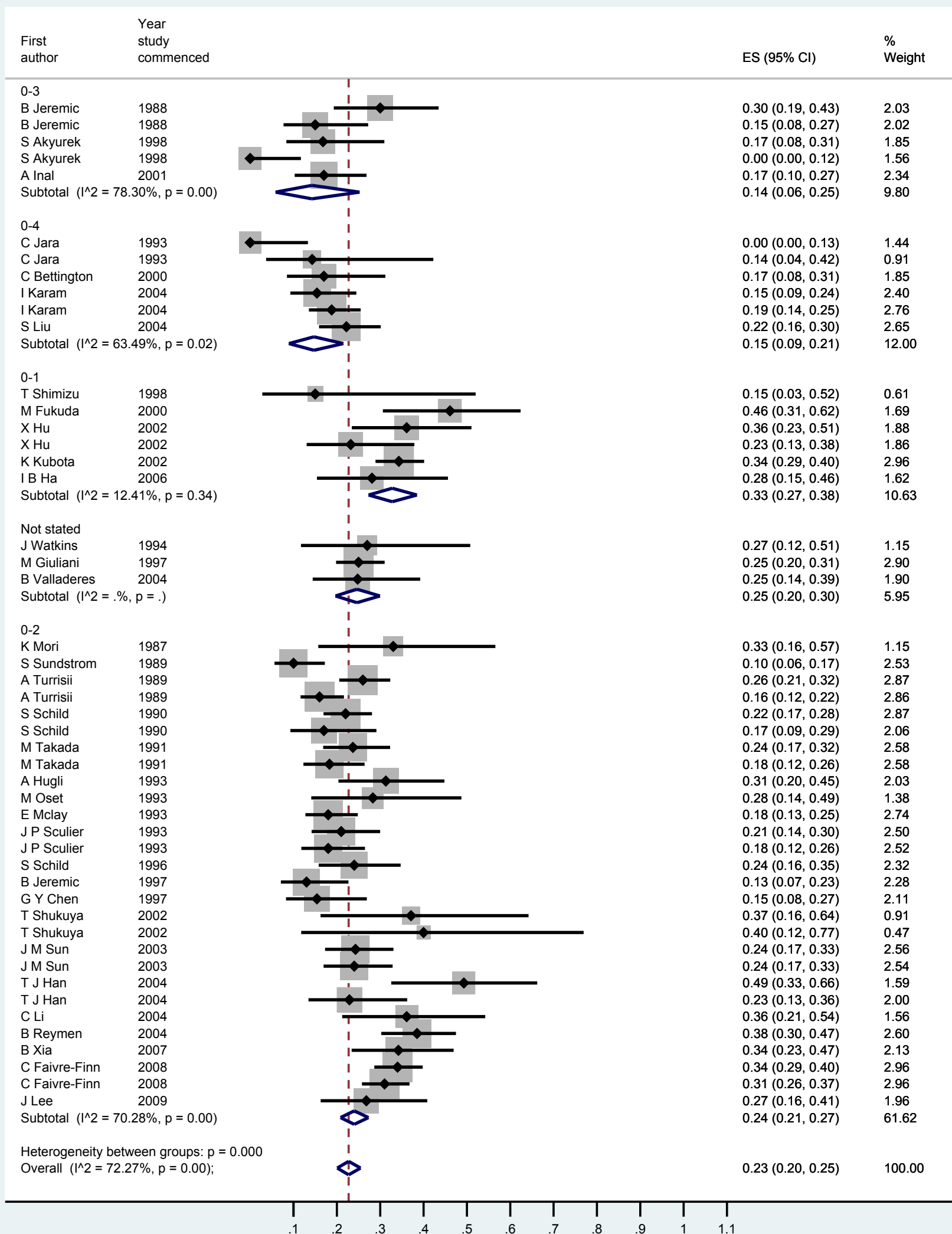


Proportion of 5 year survival in limited stage by median participant age

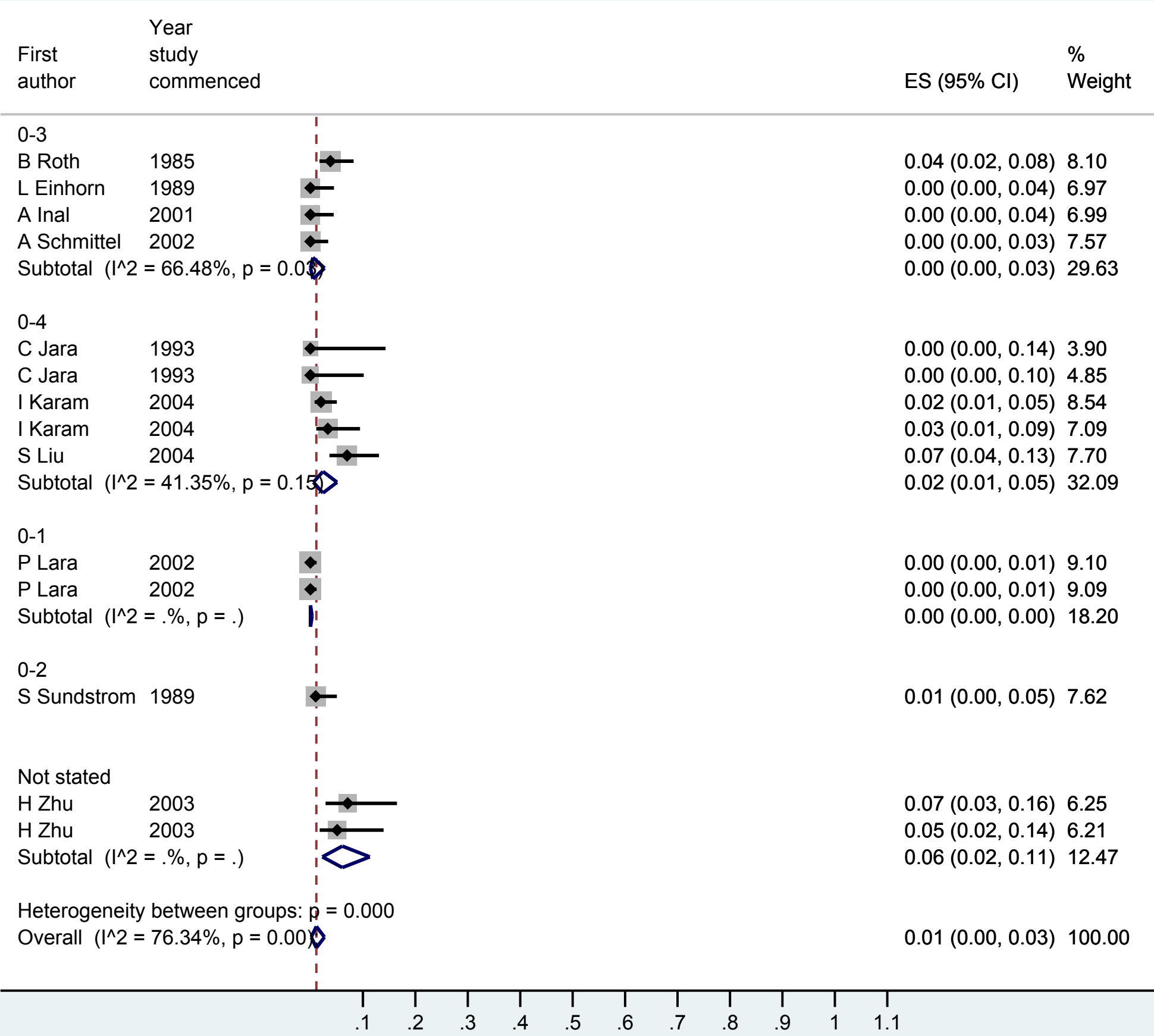


Proportion of 5 year survival in extensive stage by median participant age

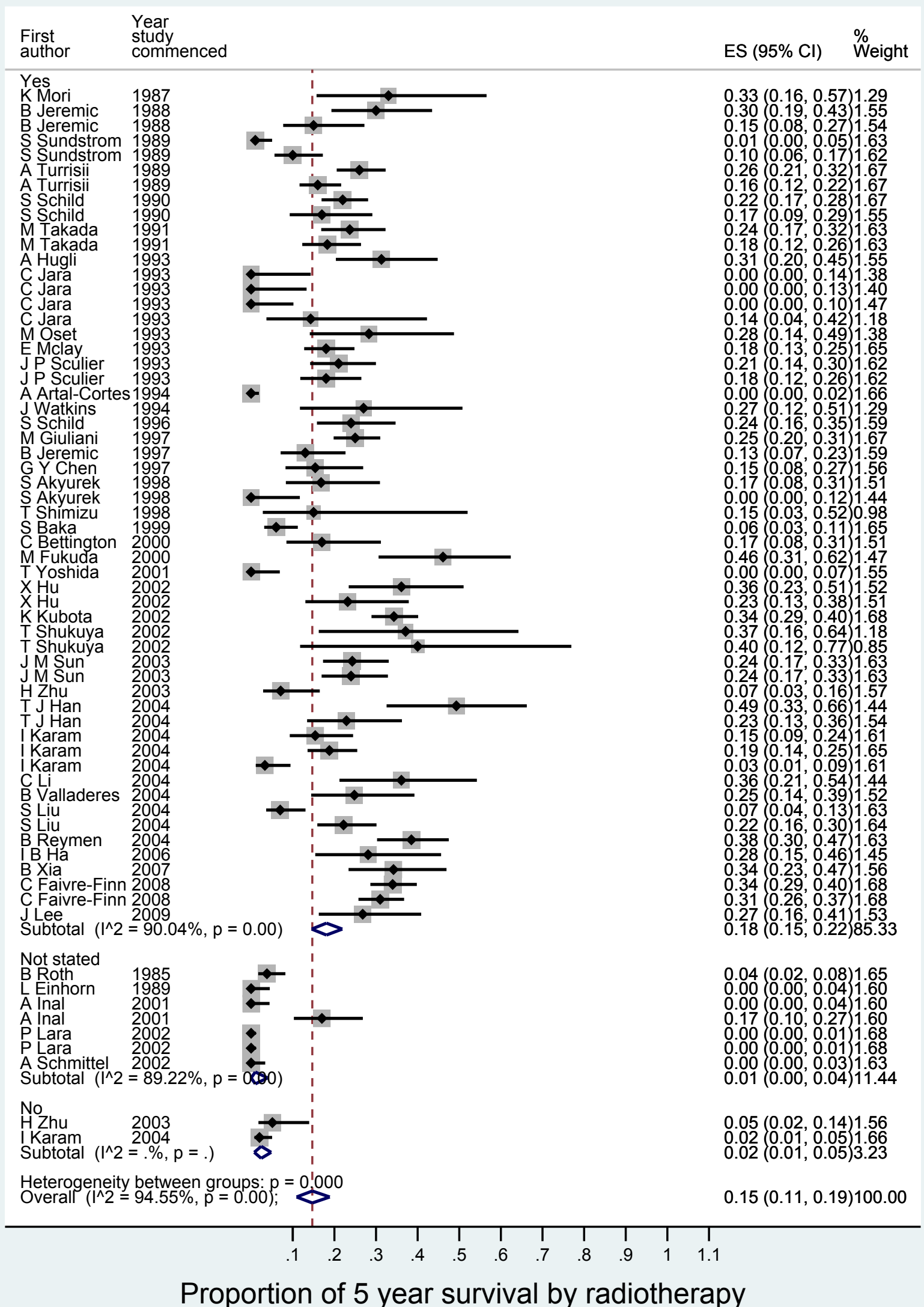


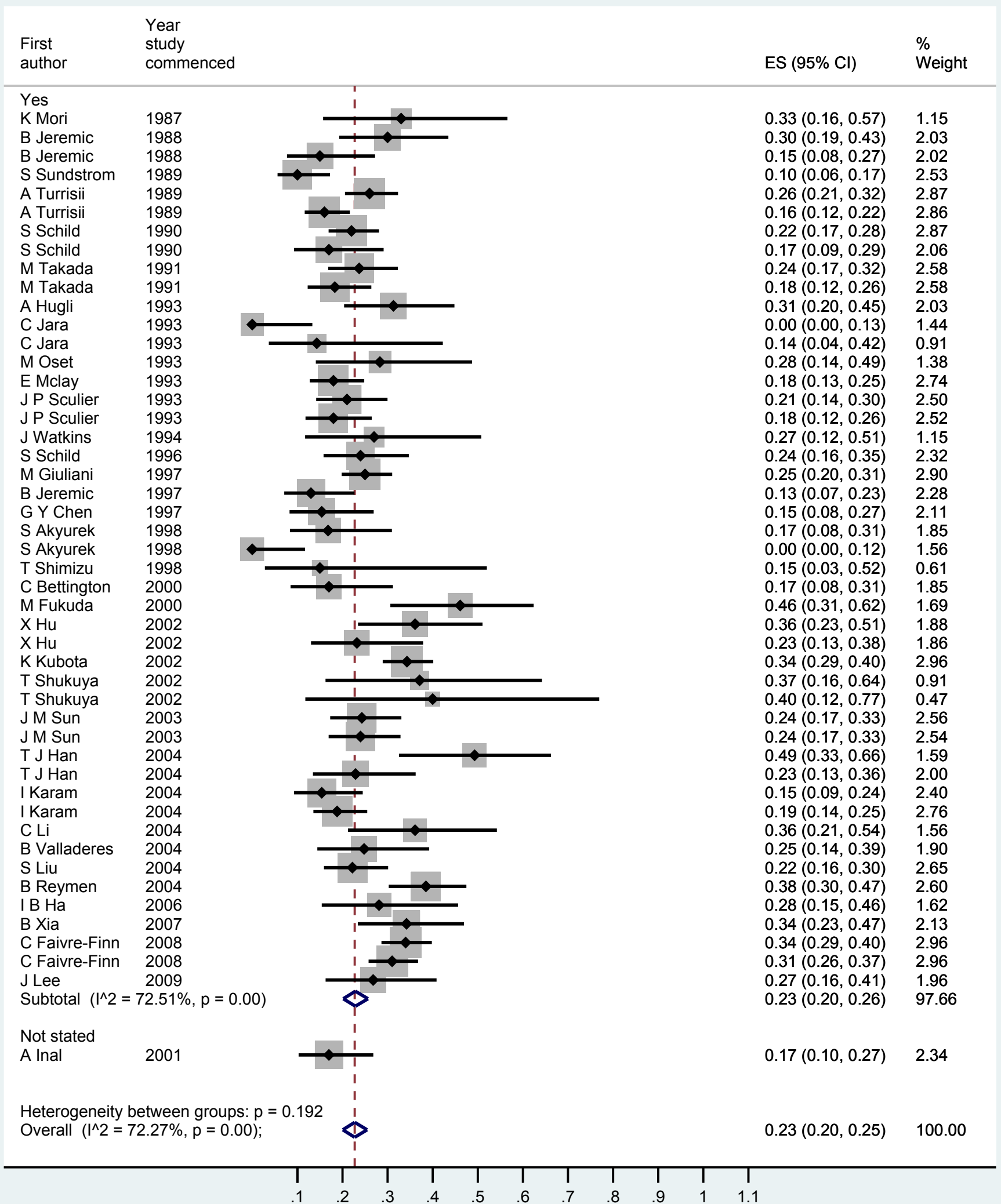


Proportion of 5 year survival in limited stage by PS

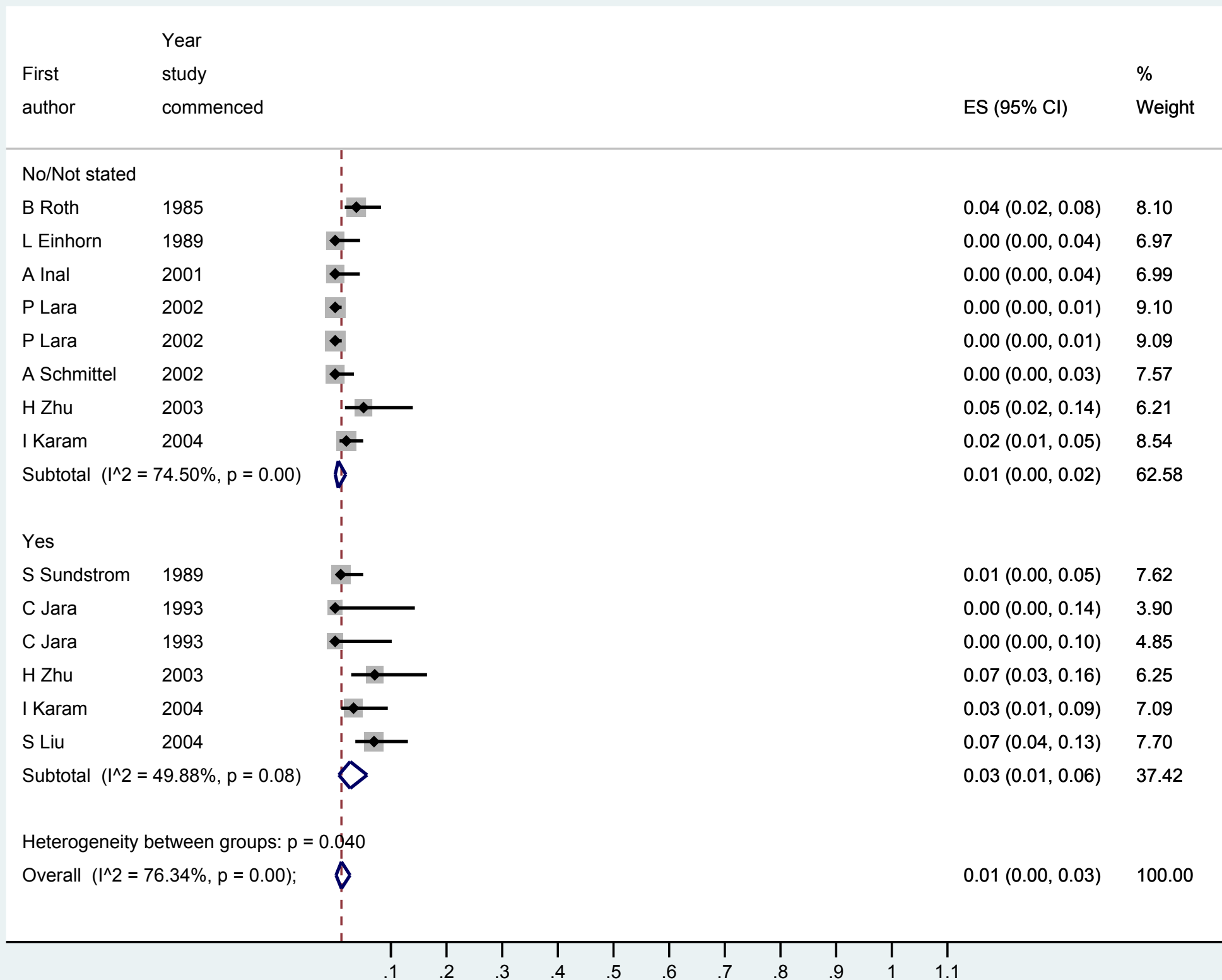


Proportion of 5 year survival in extensive stage by PS

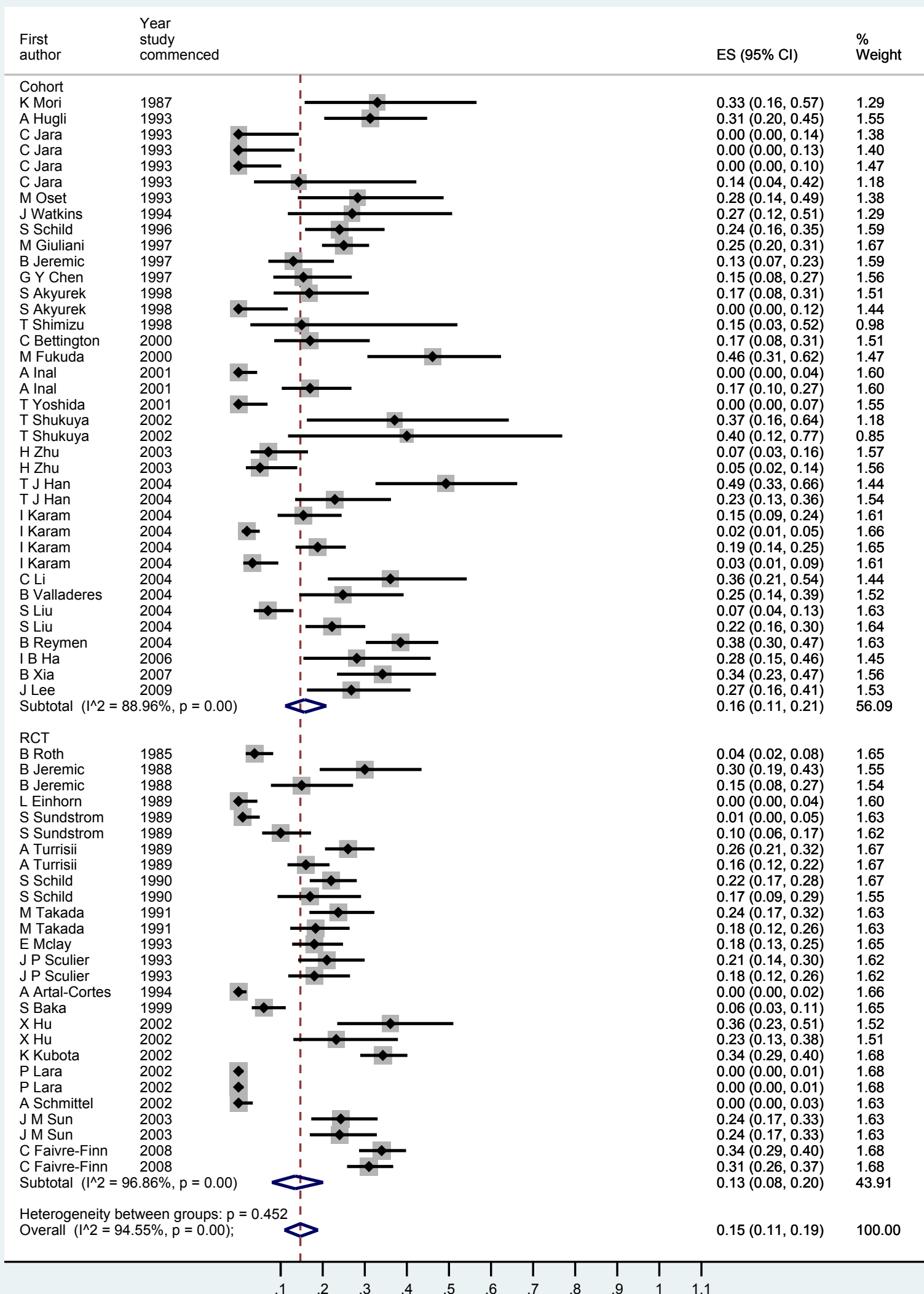




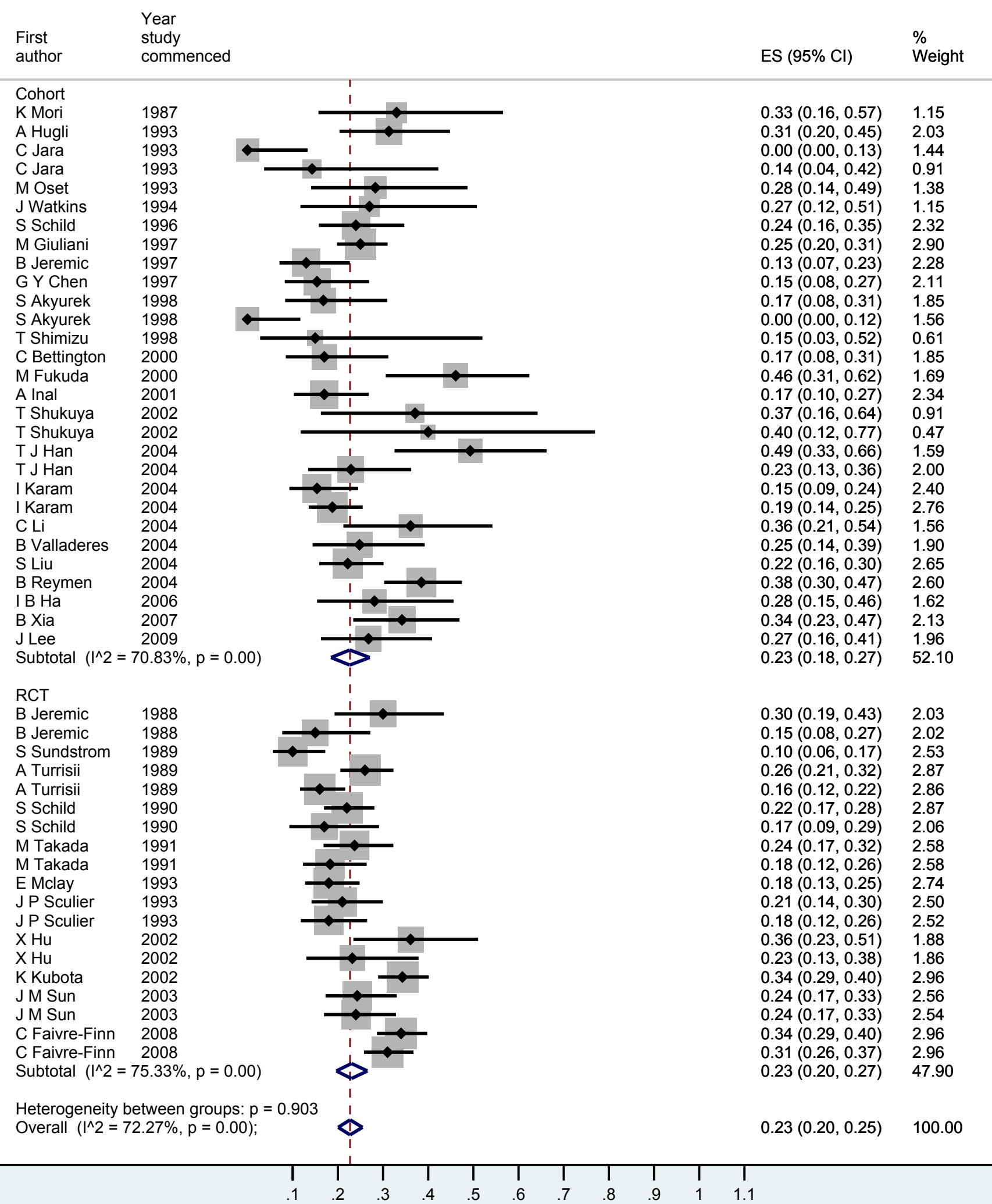
Proportion of 5 year survival in limited stage by radiotherapy



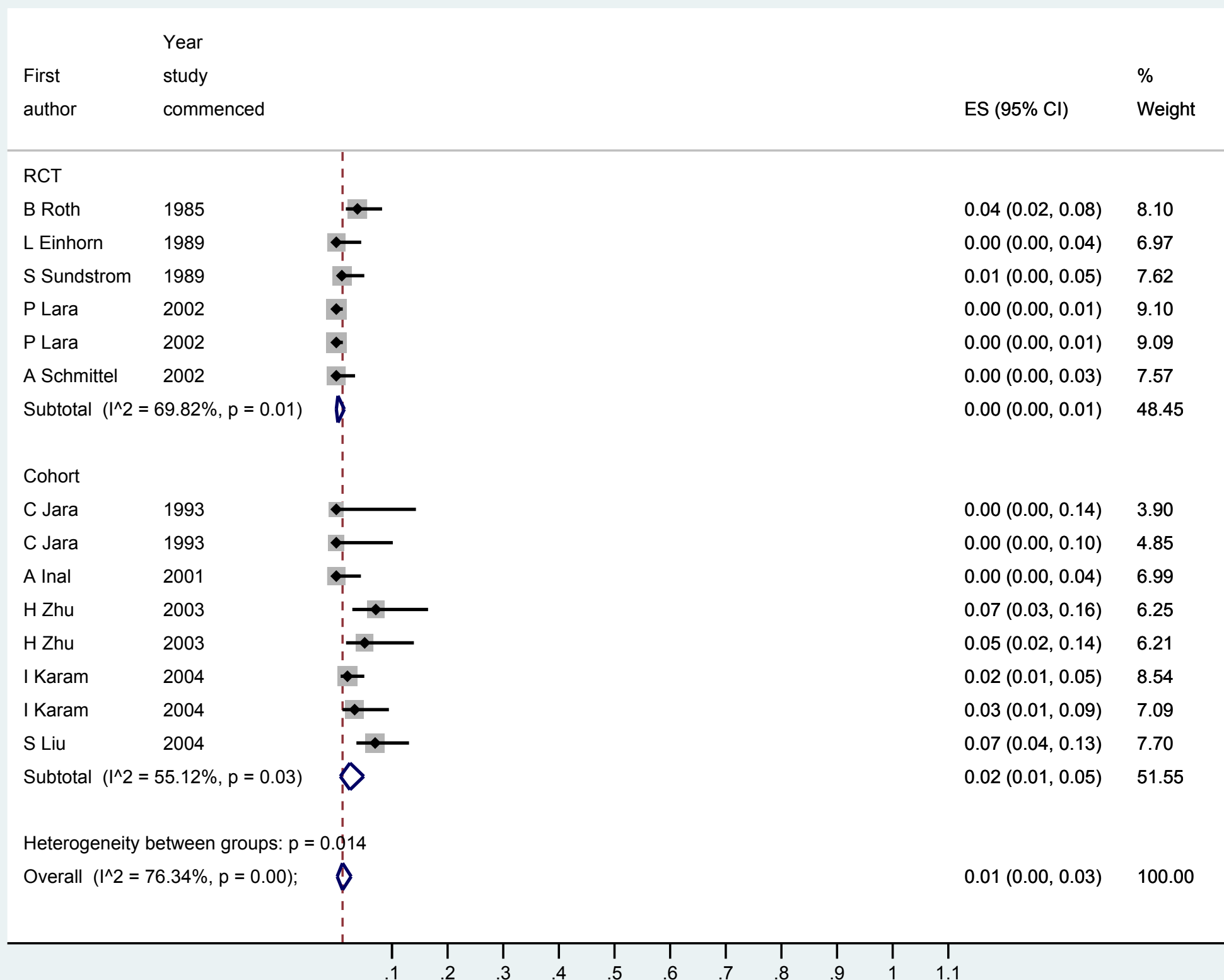
Proportion of 5 year survival in extensive stage by radiotherapy



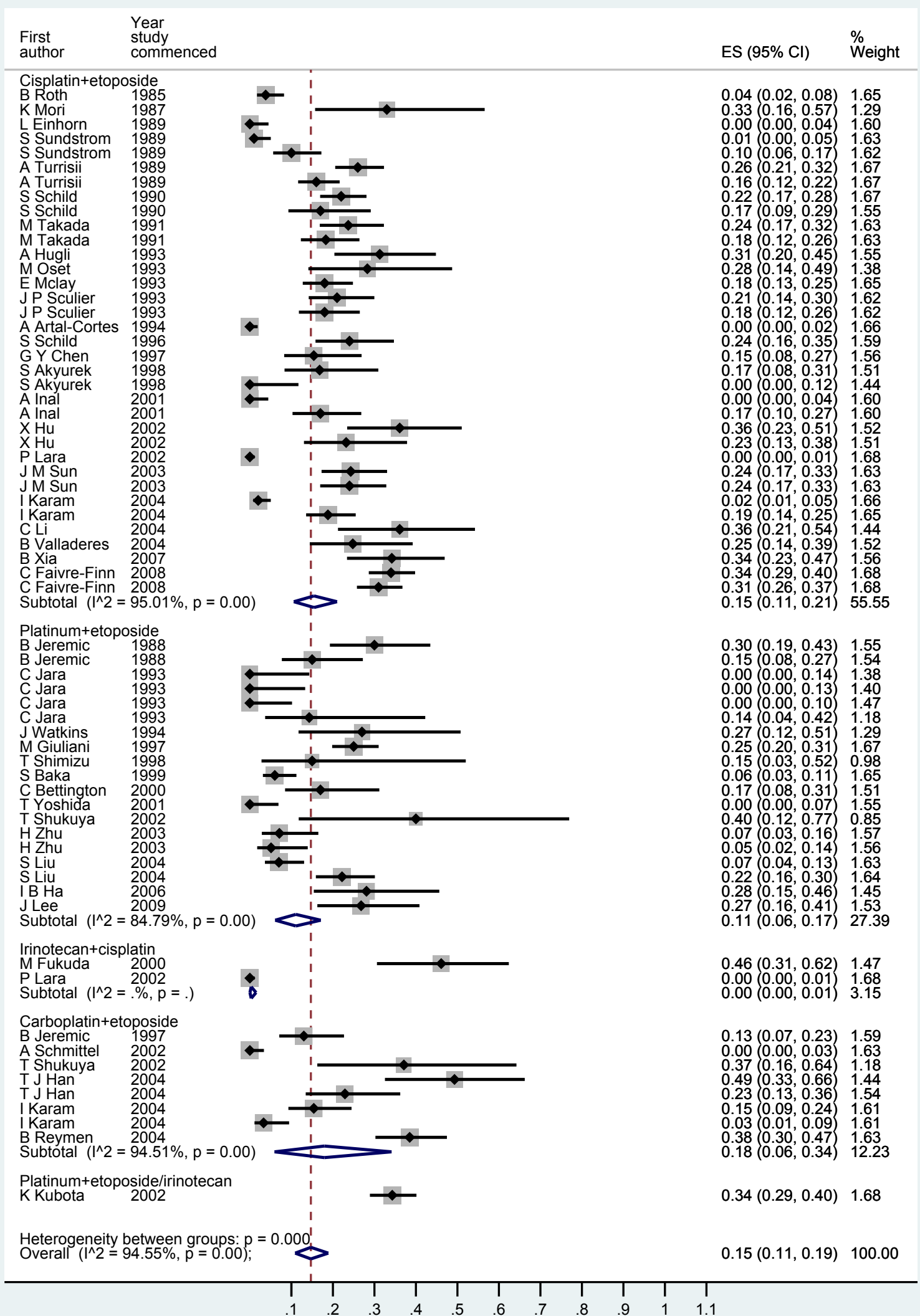
5 year survival after chemotherapy by study design



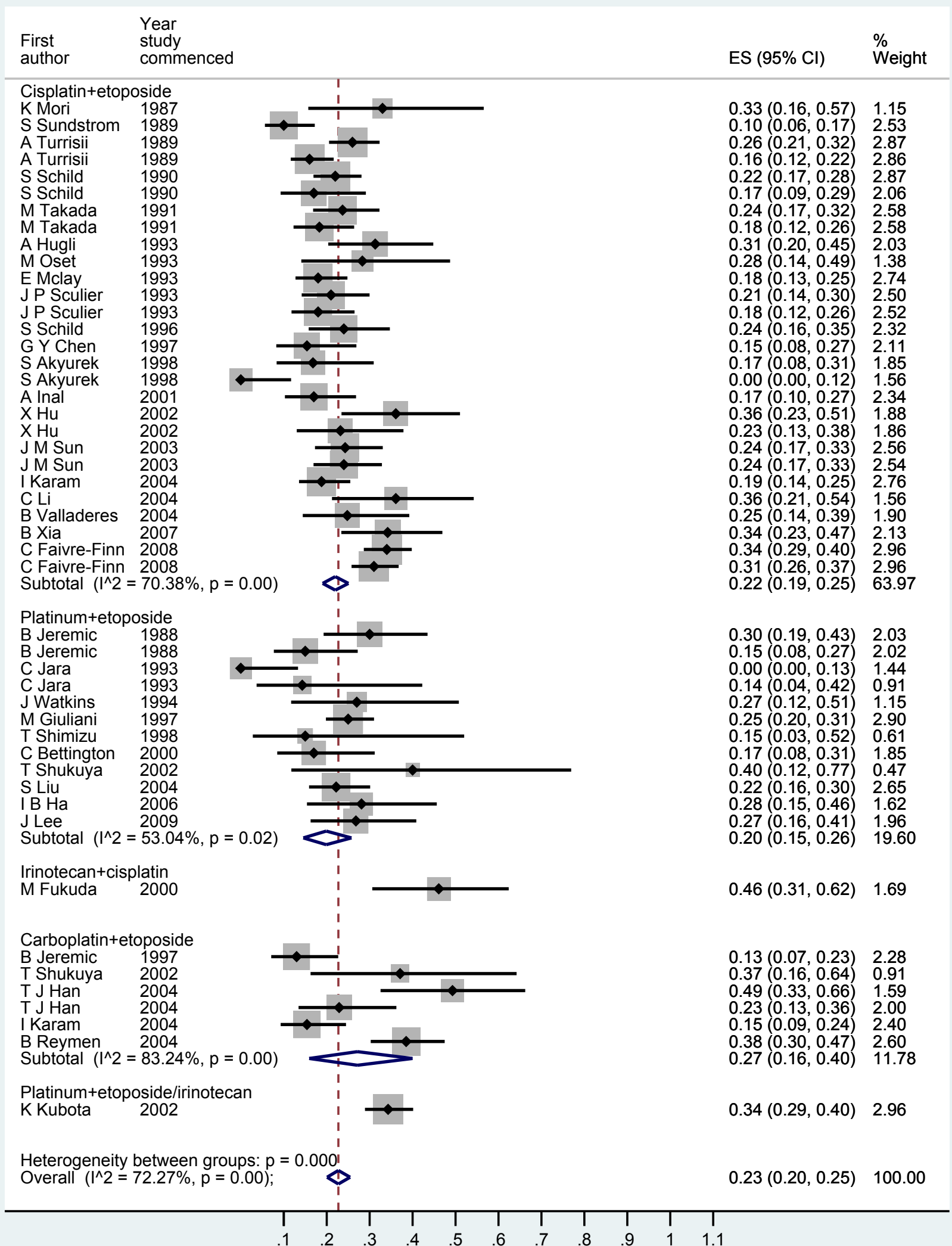
Proportion of 5 year survival in limited stage by study design



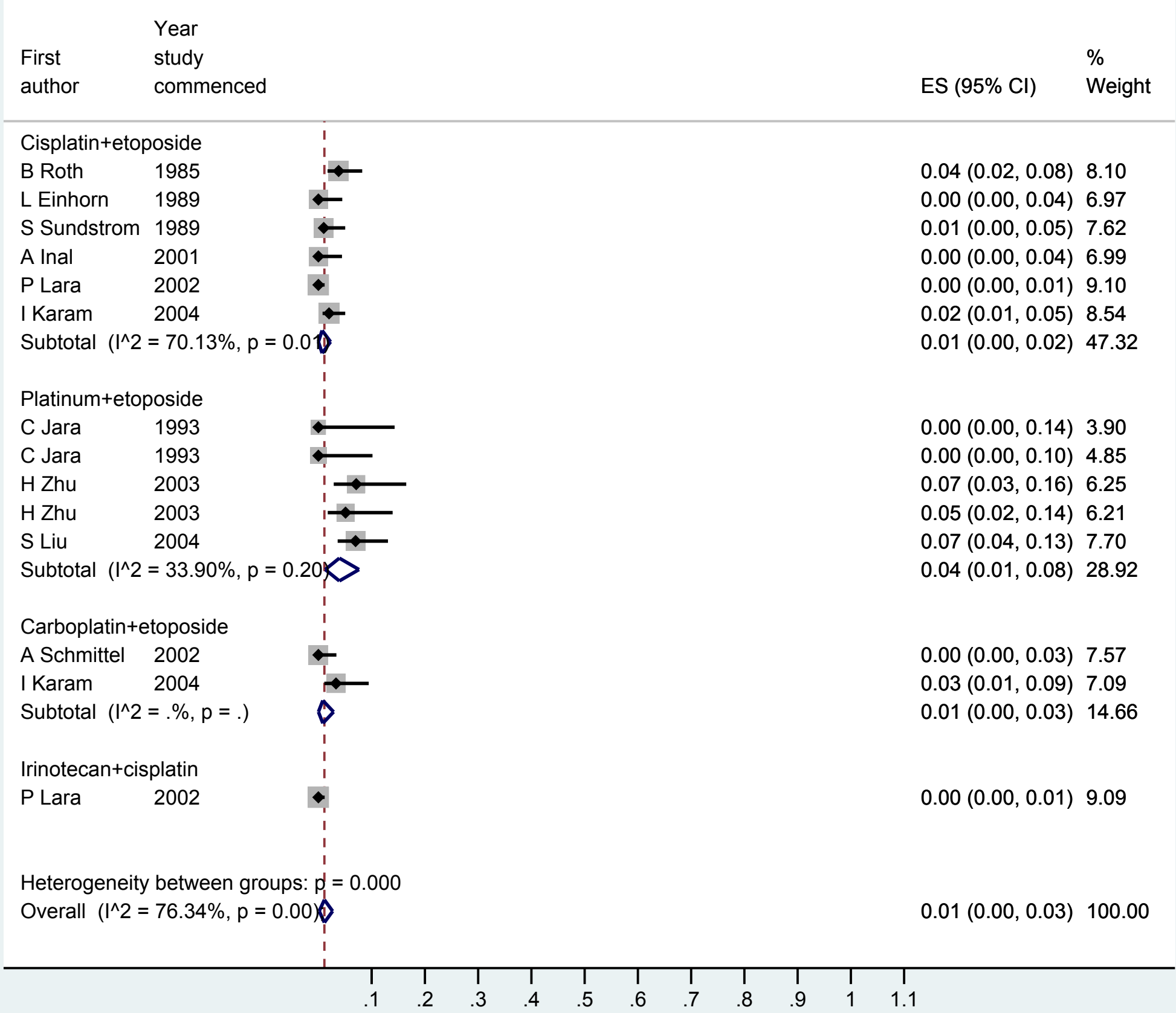
Proportion of 5 year survival in extensive stage by study design



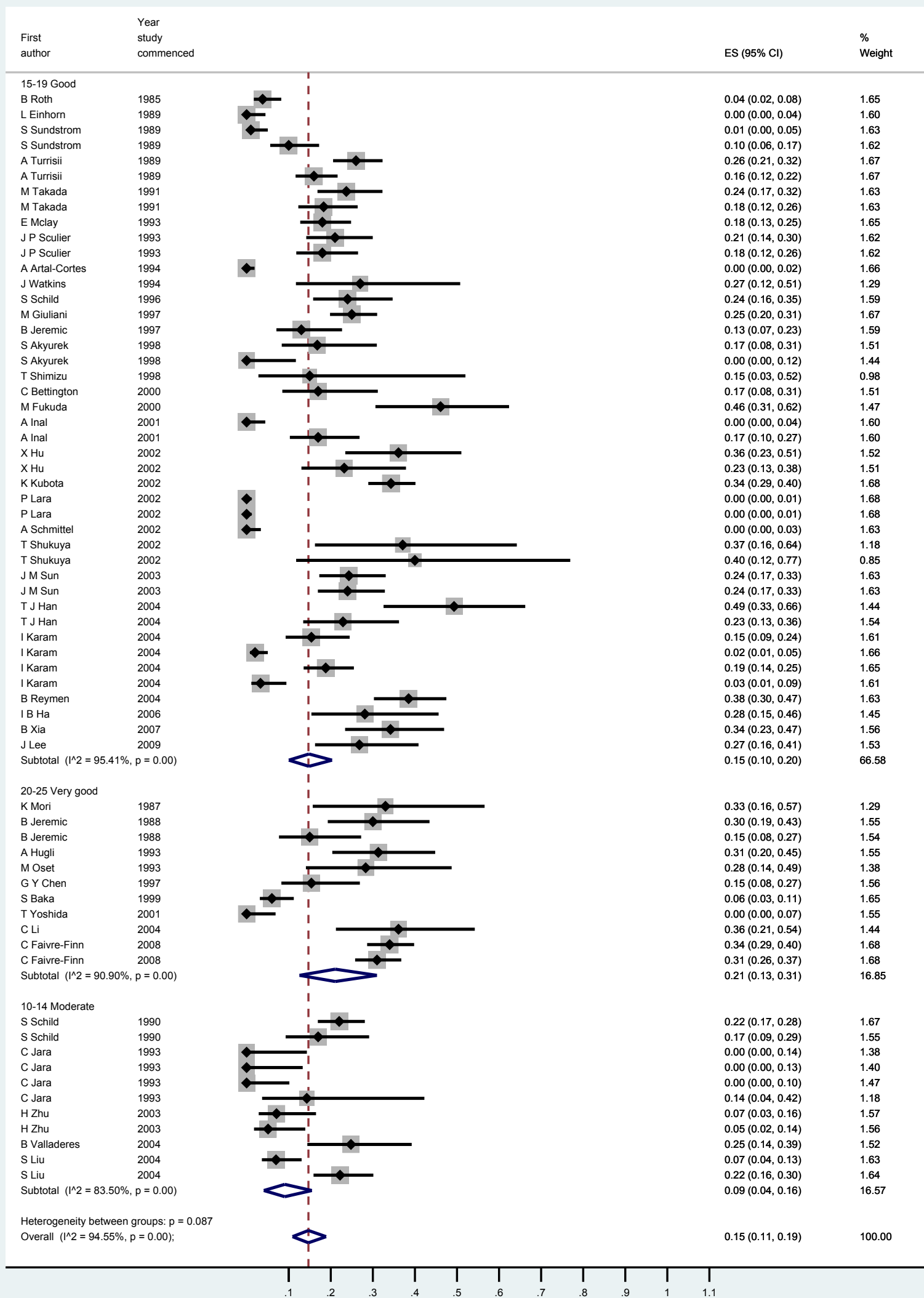
5 year survival after chemotherapy by drug

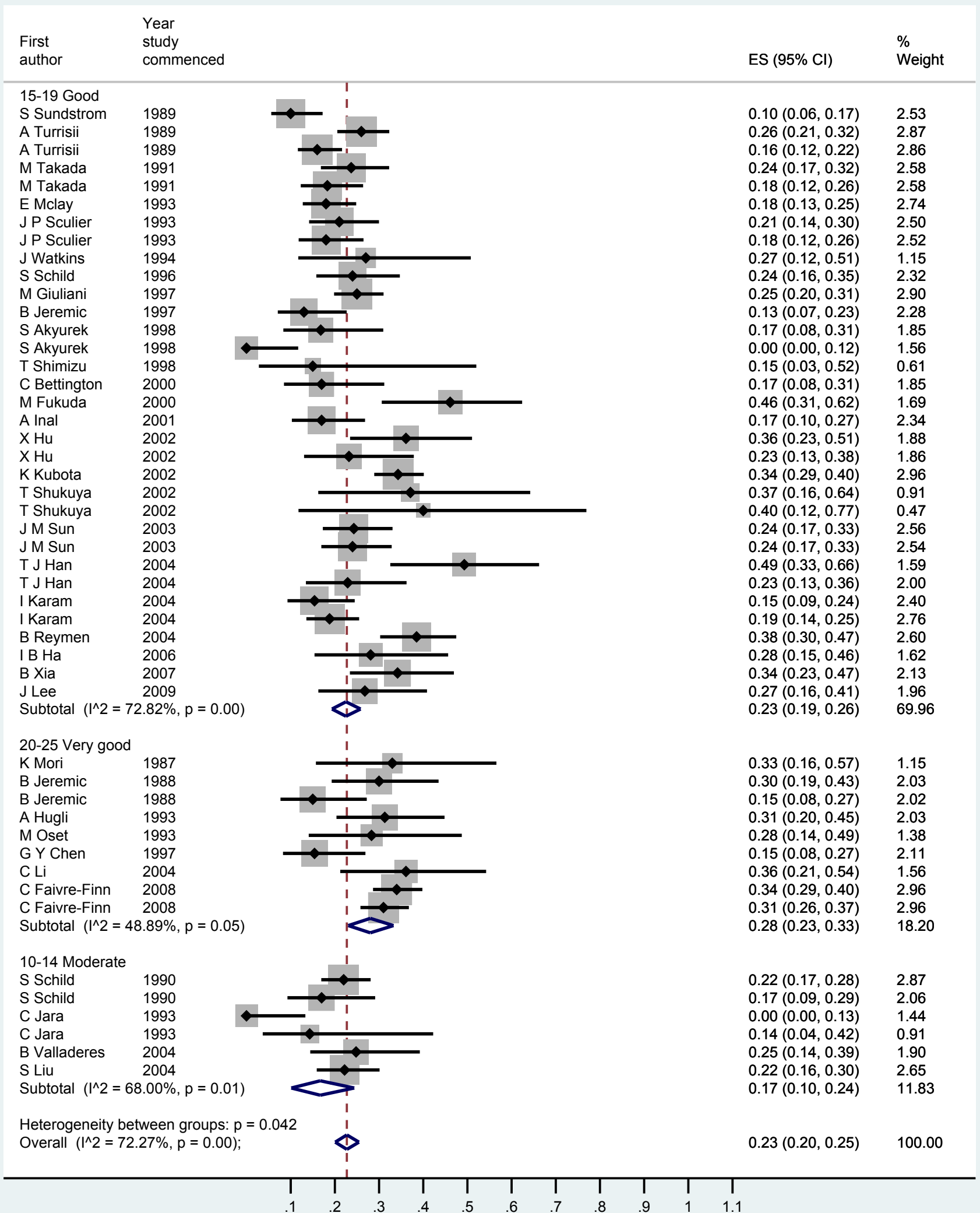


Proportion of 5 year survival in limited stage by drug

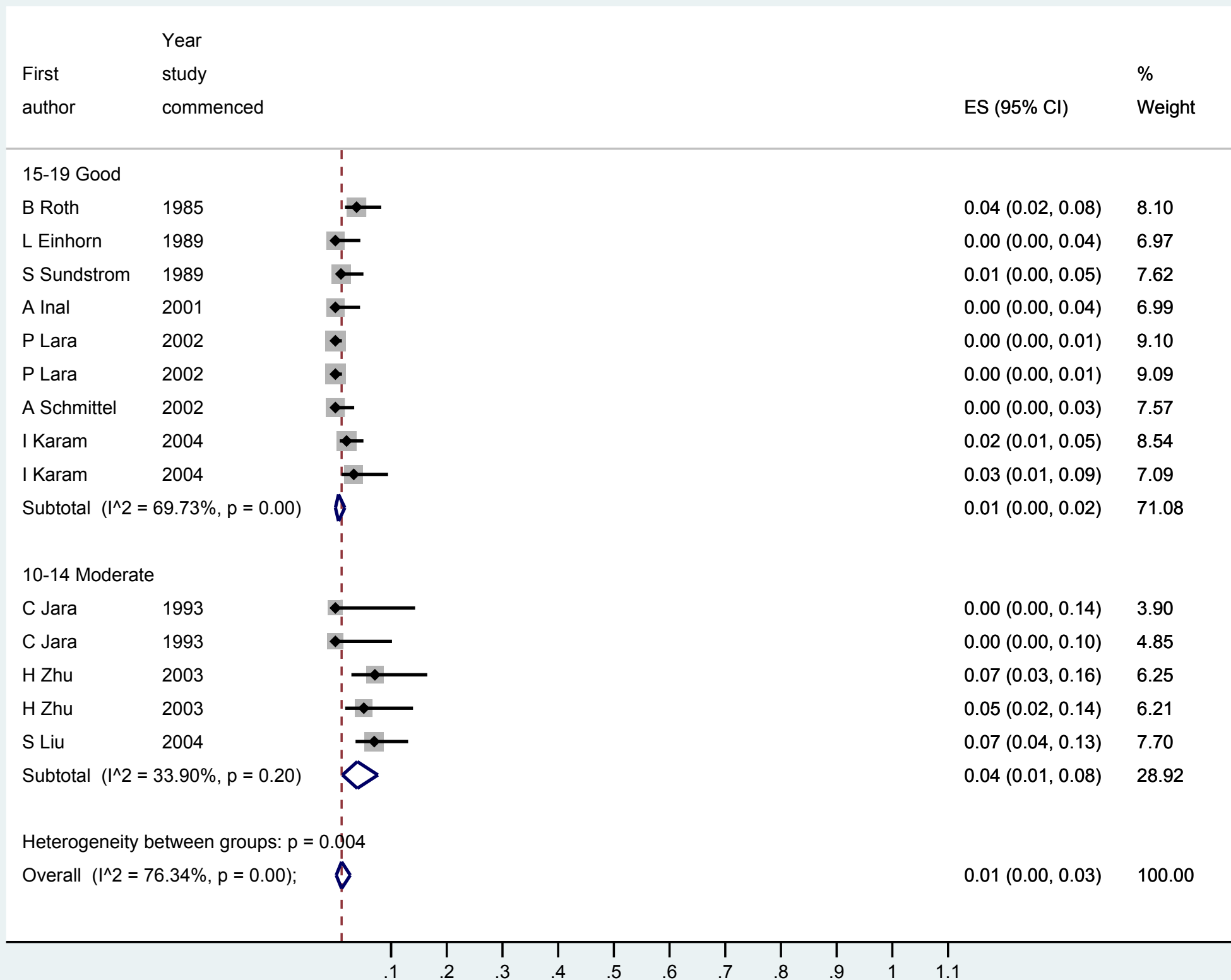


Proportion of 5 year survival in extensive stage by drug

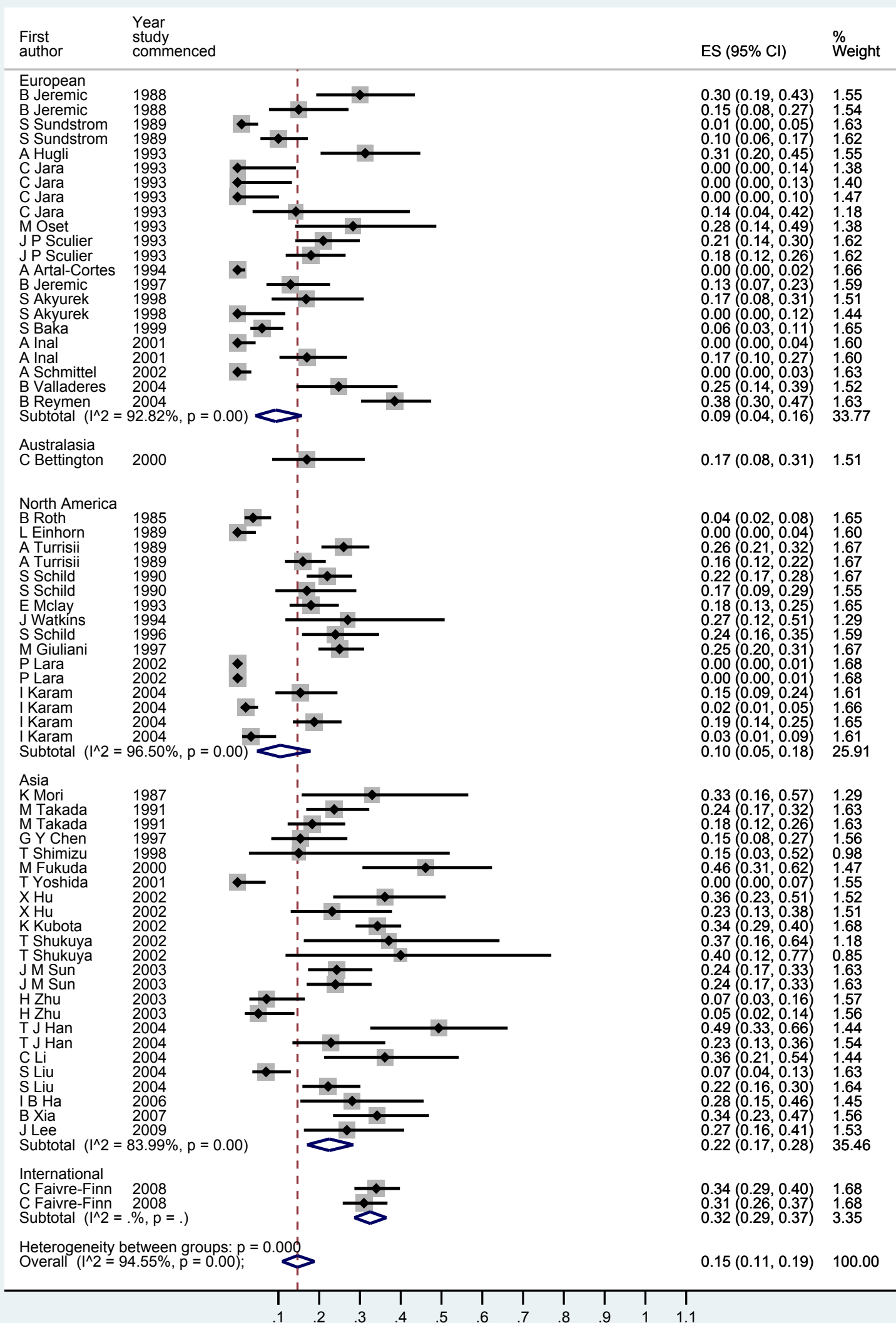


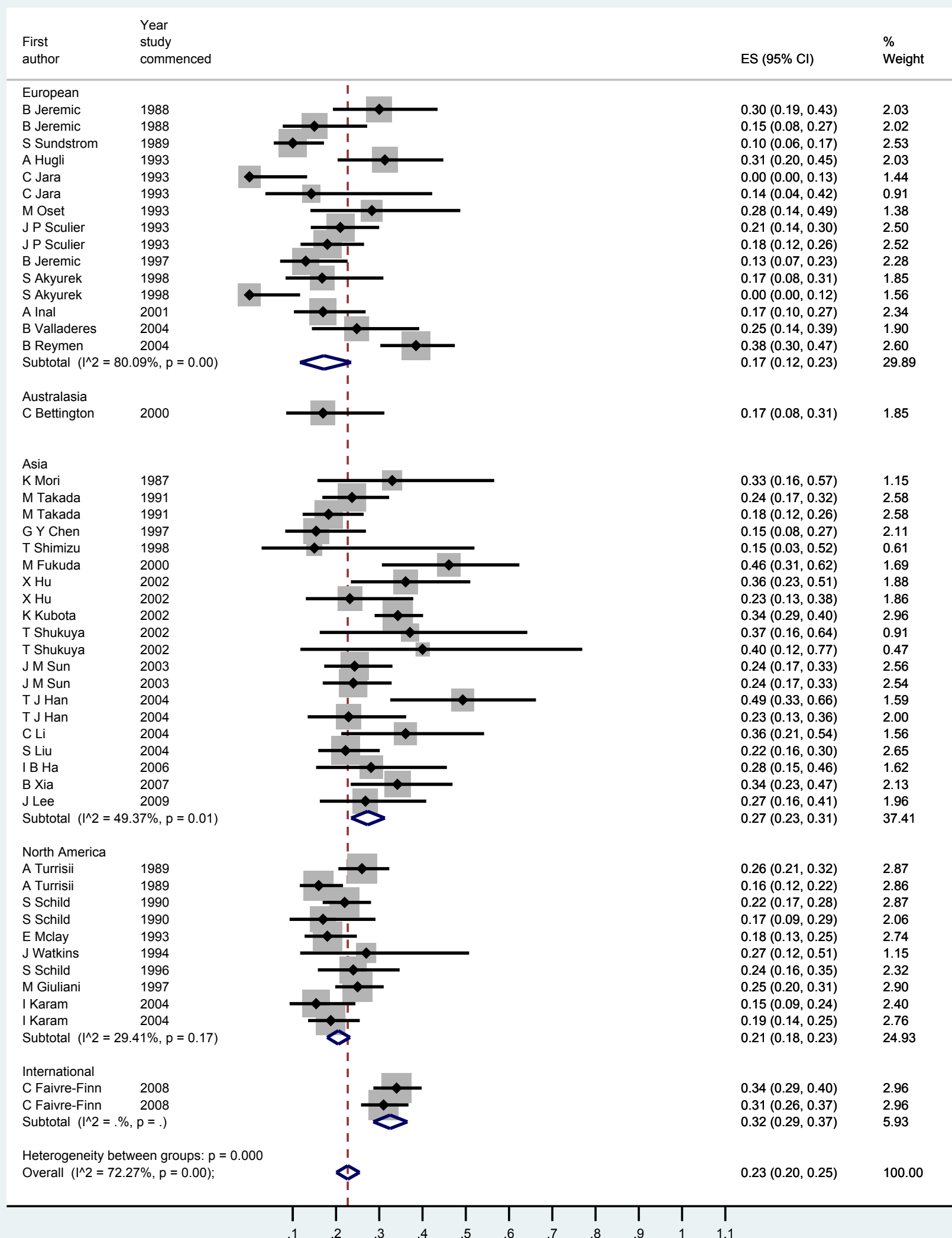


Proportion of 5 year survival in limited stage by quality score

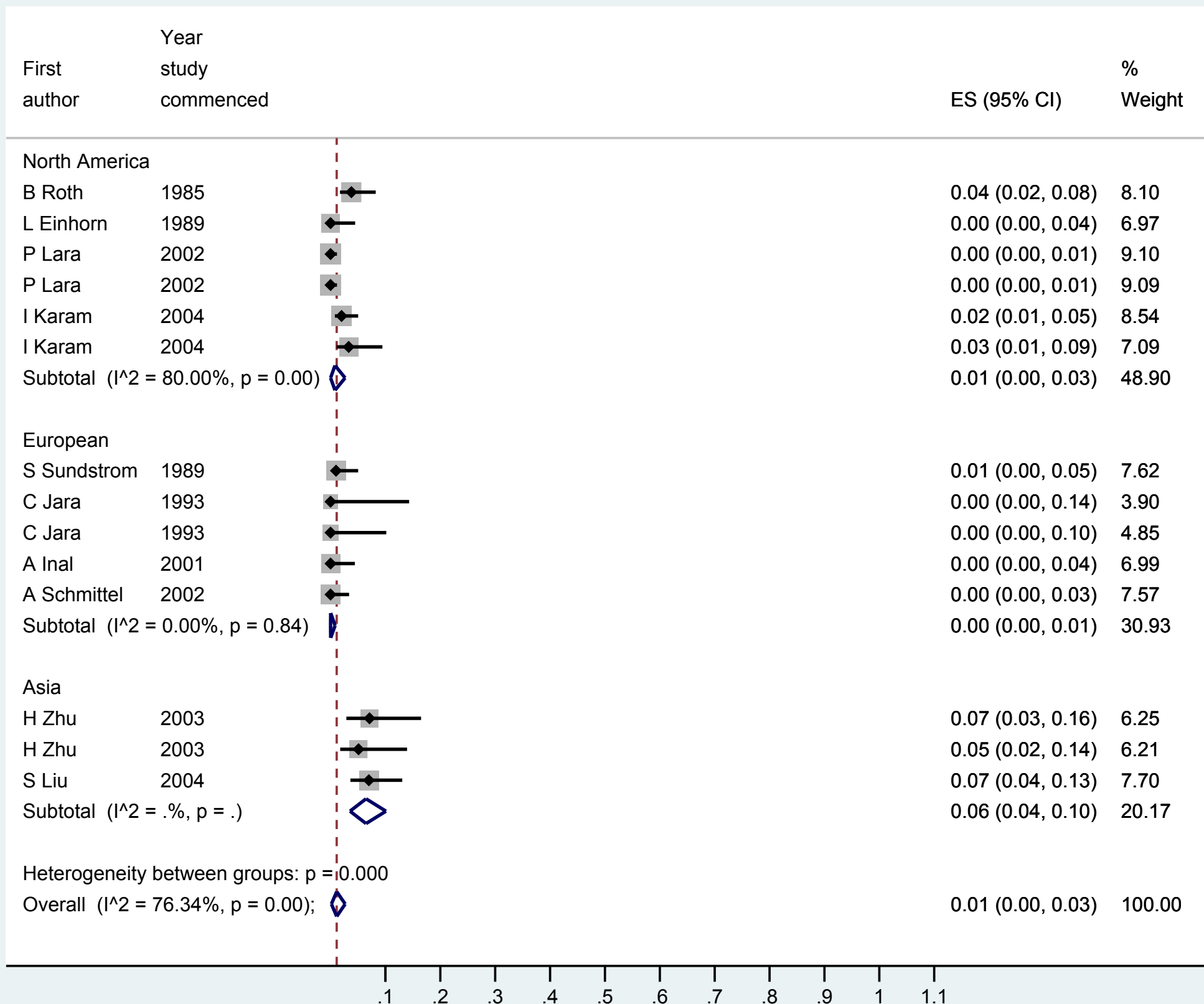


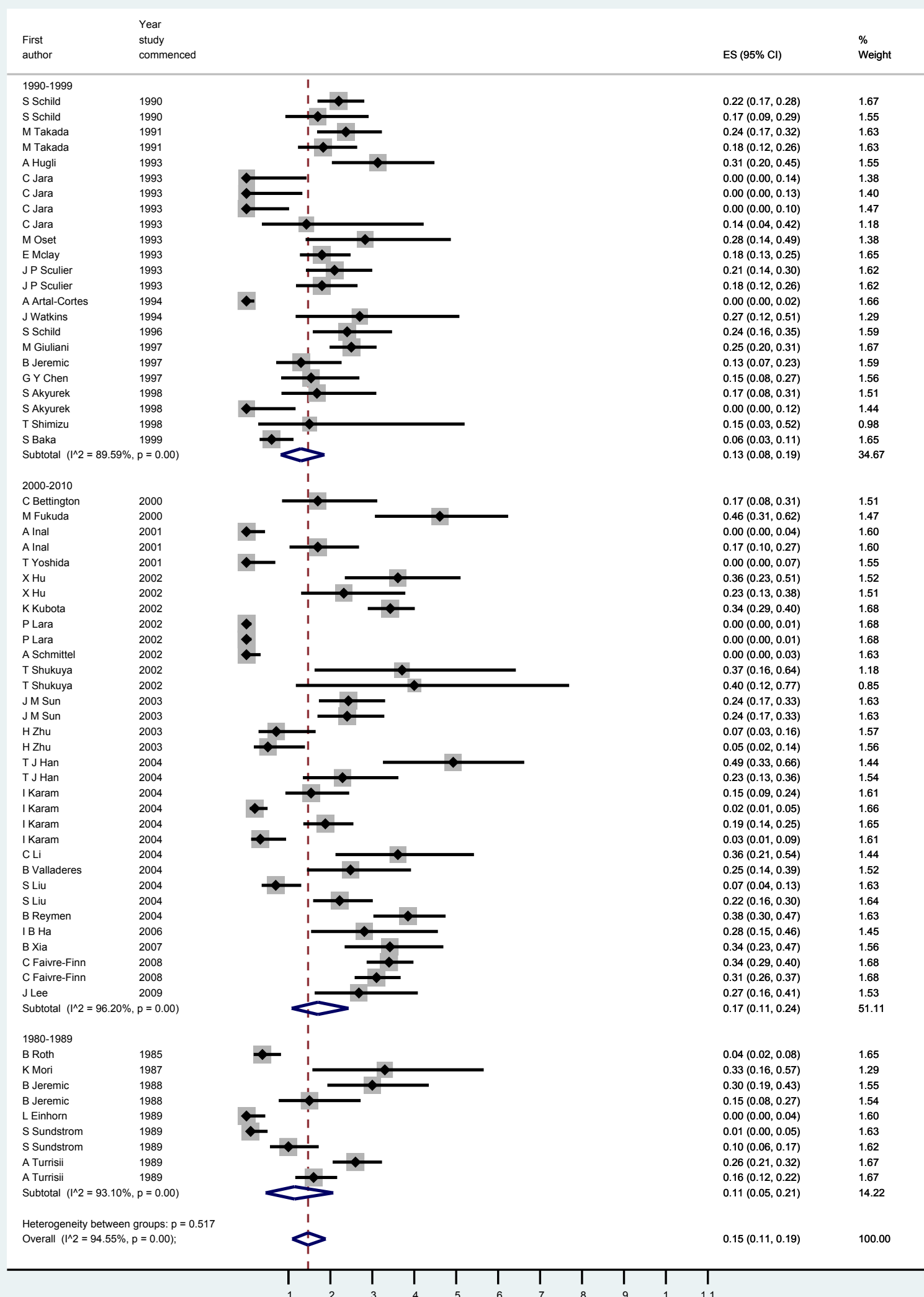
Proportion of 5 year survival in extensive stage by quality score



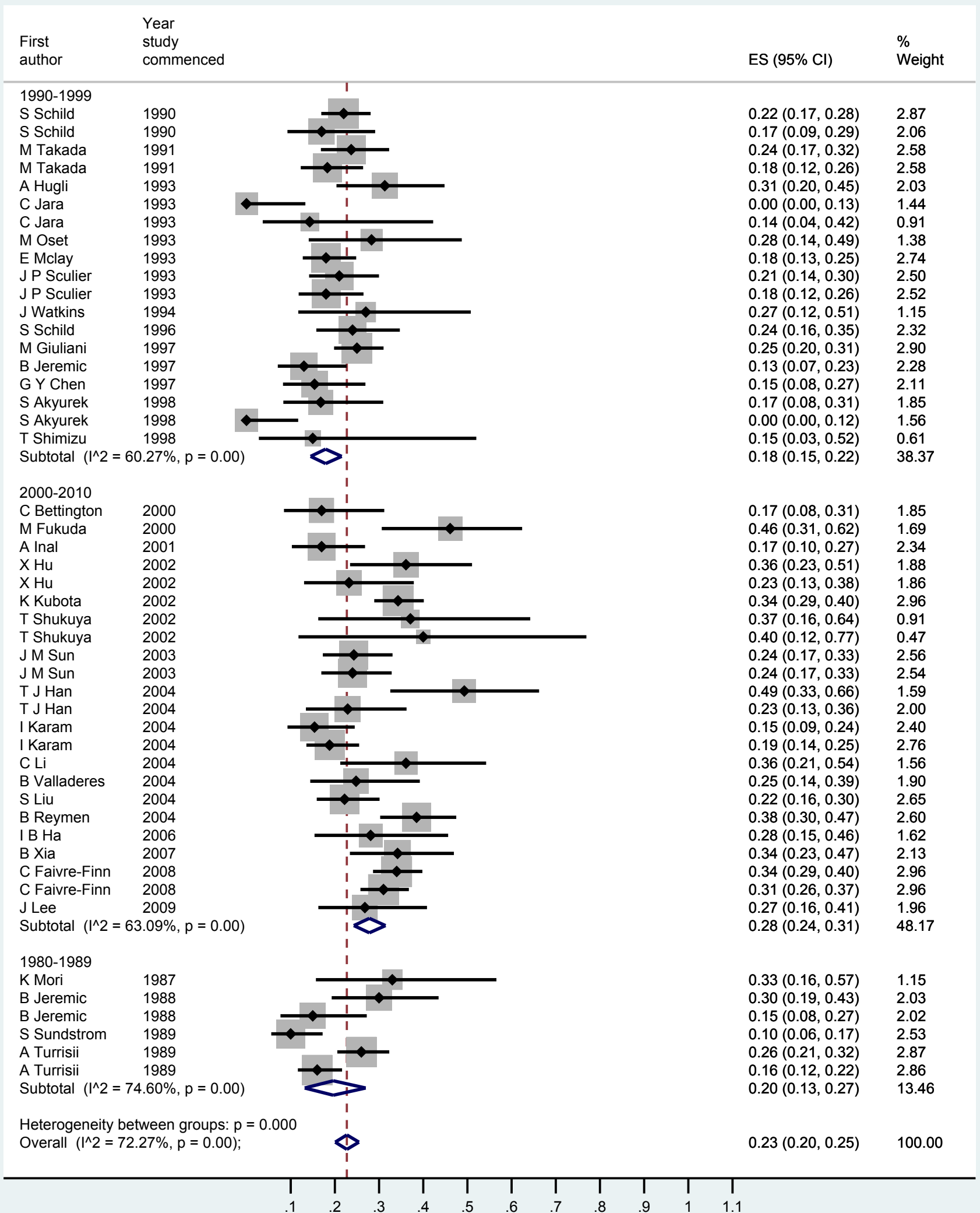


Proportion of 5 year survival in limited stage by region

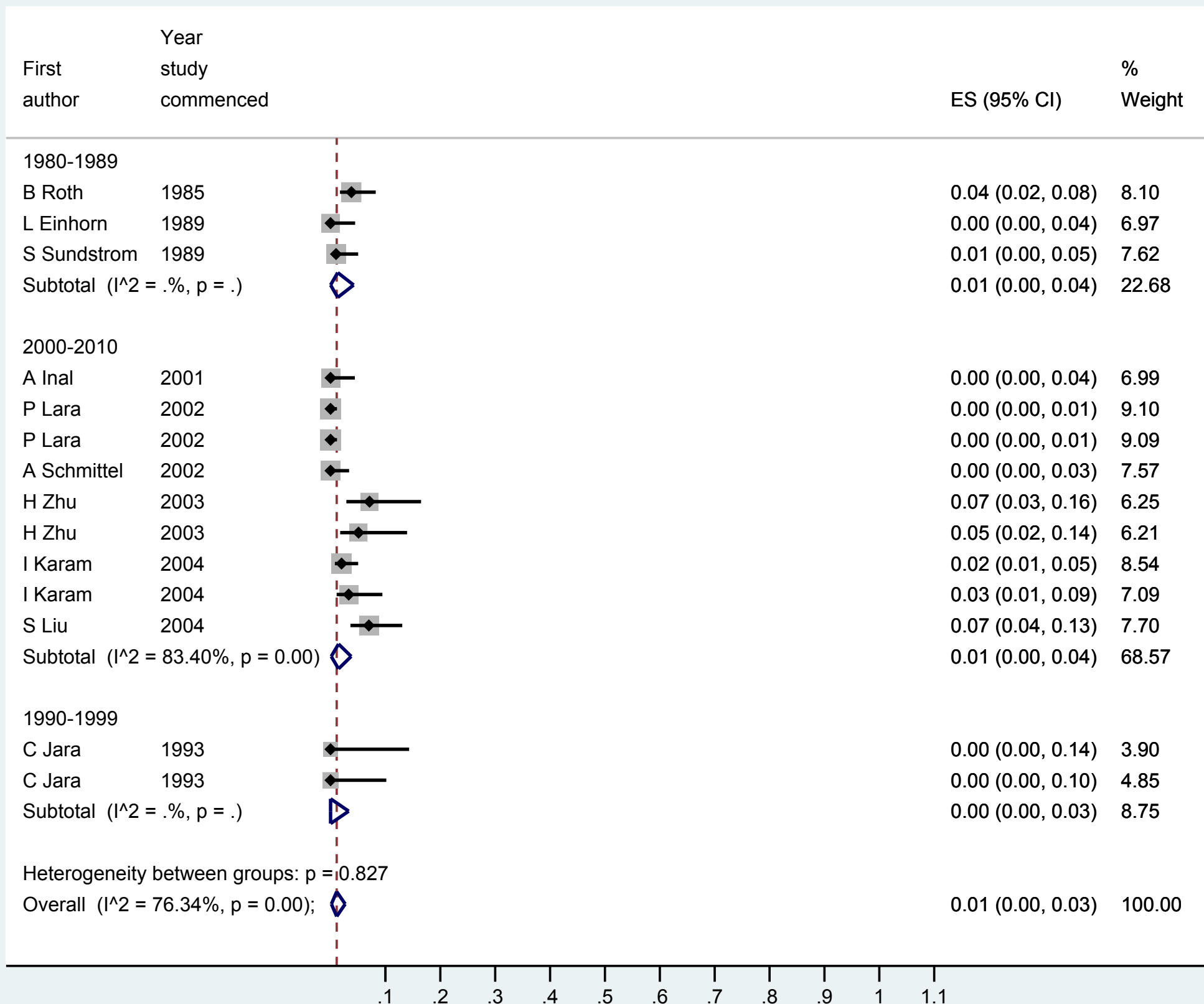




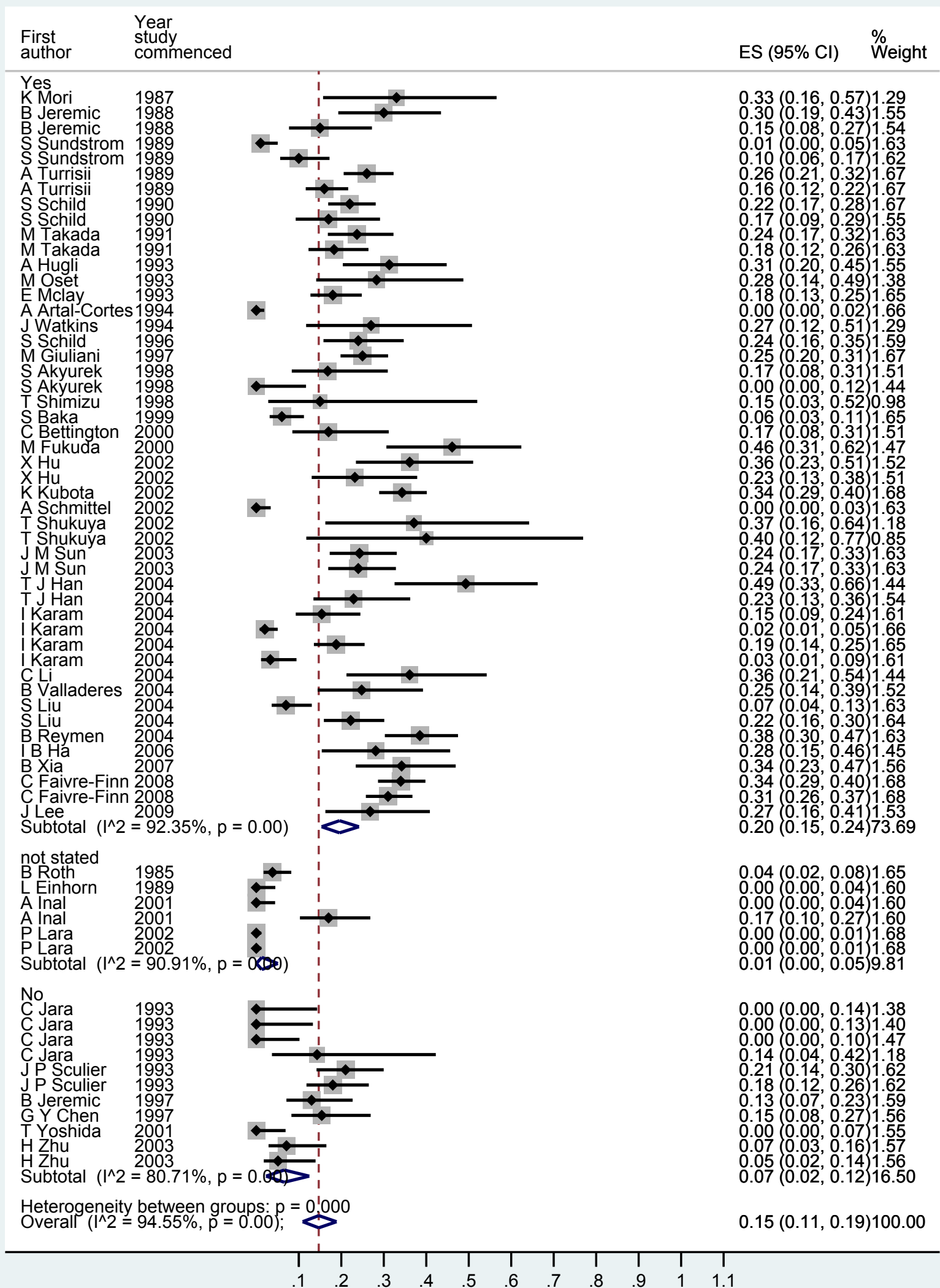
5 year survival after chemotherapy by study year



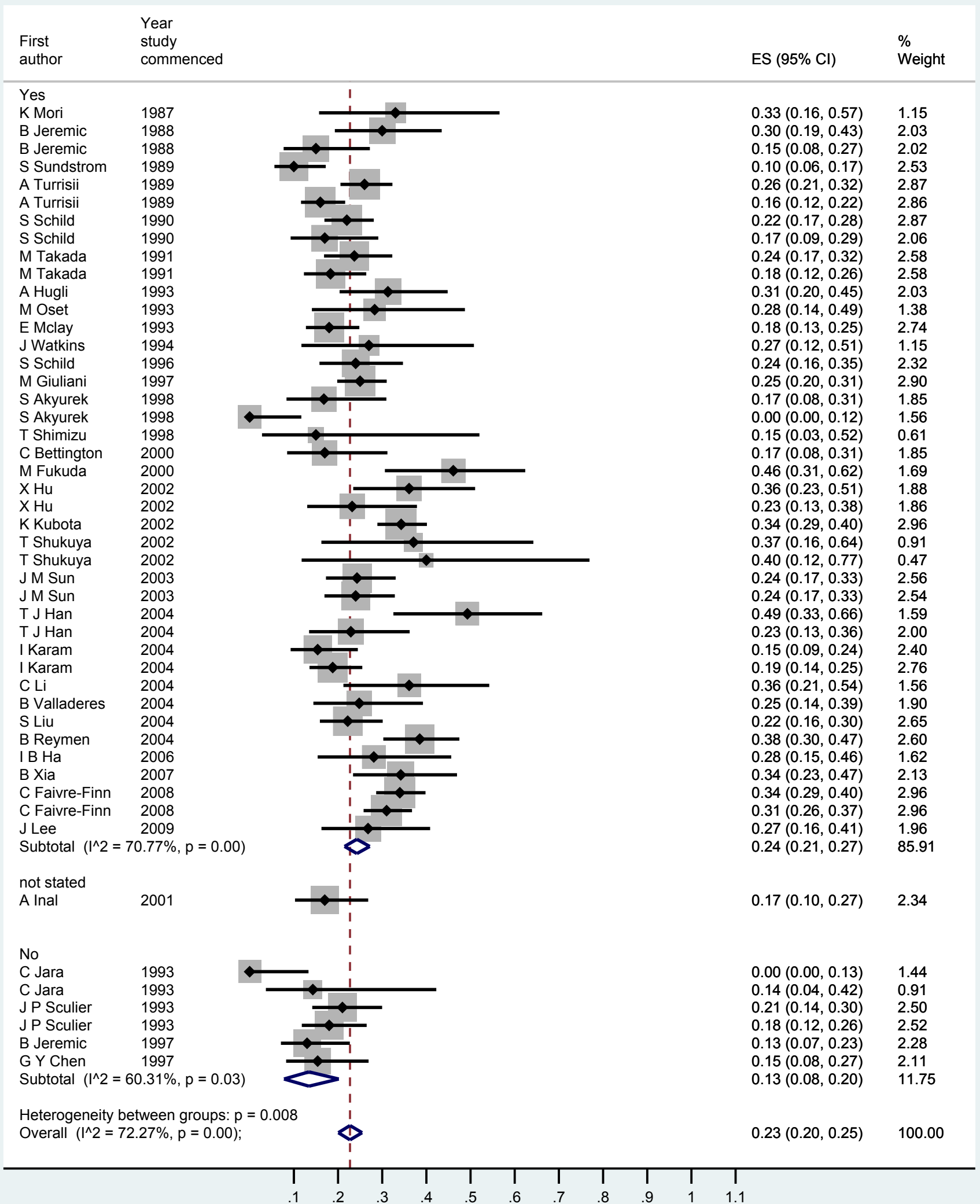
Proportion of 5 year survival in limited stage by study year



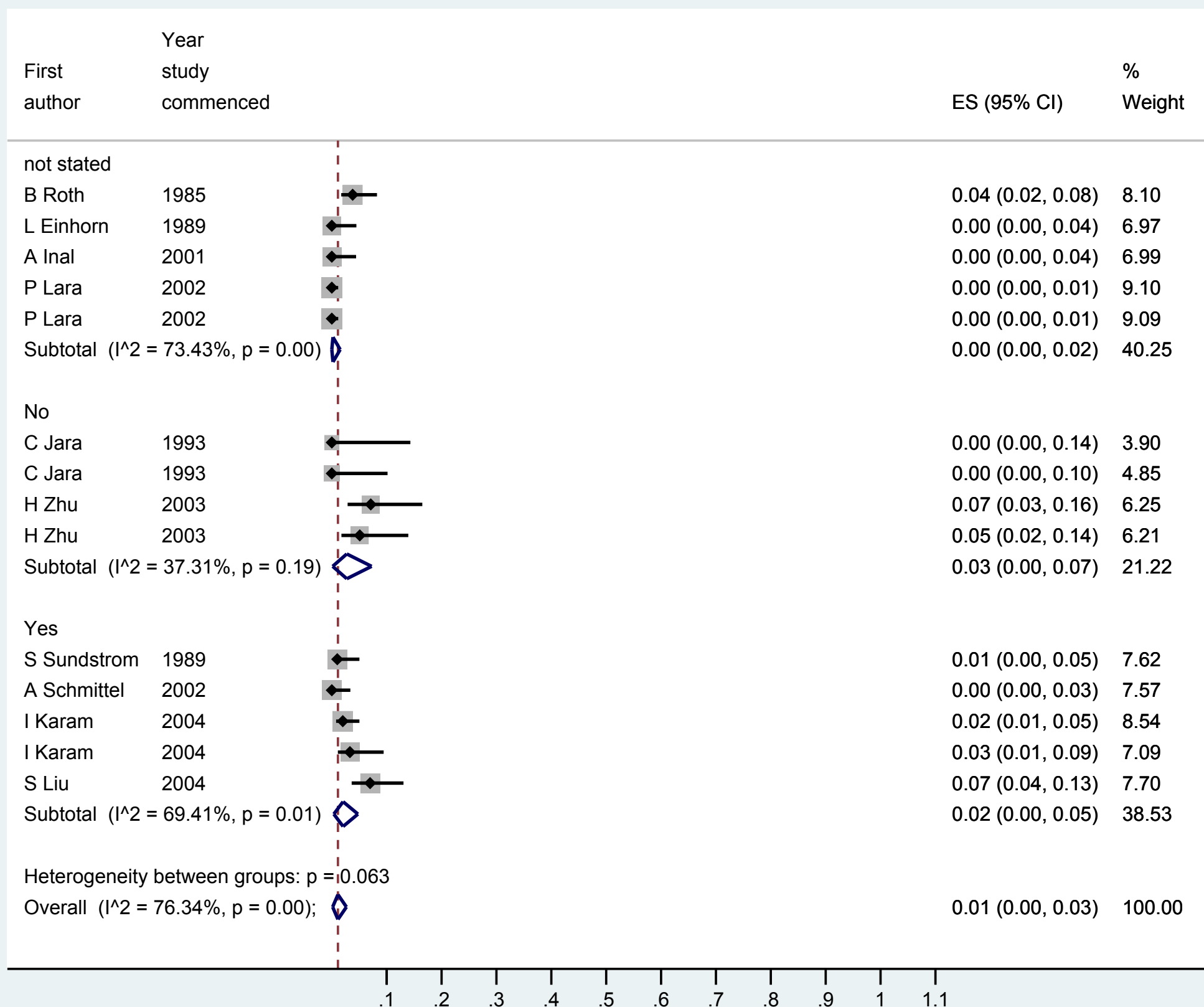
Proportion of 5 year survival in extensive stage by study year



5 year survival after chemotherapy by PCI

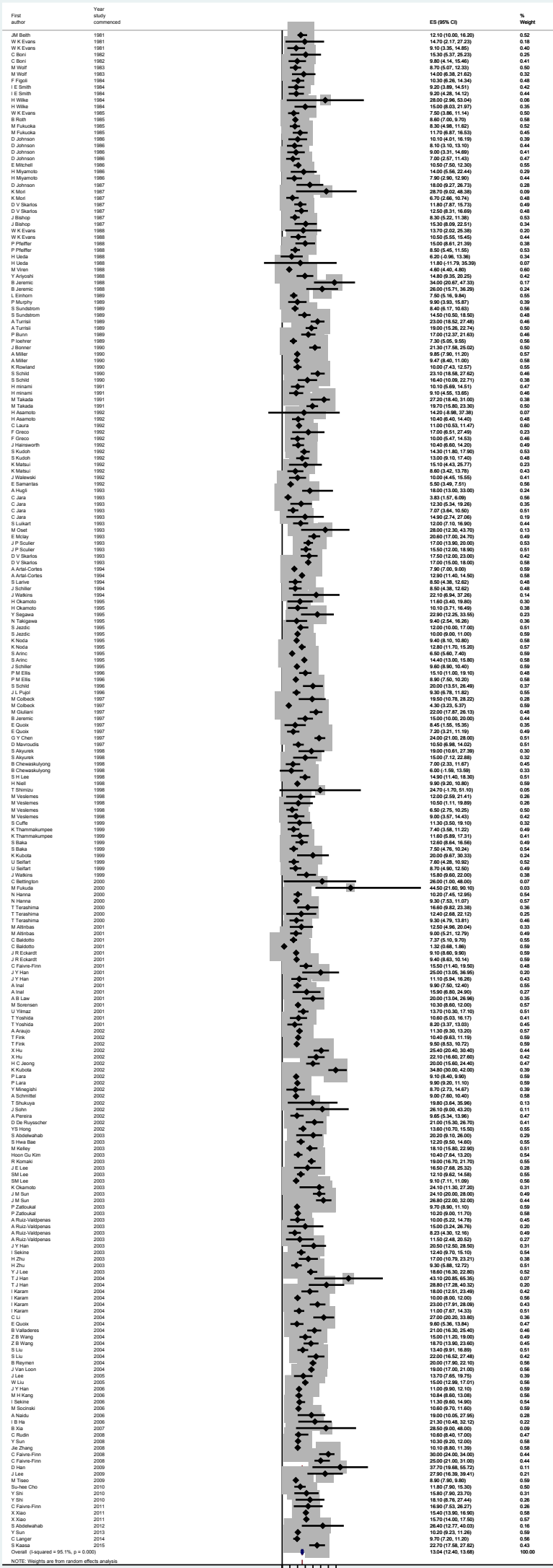


Proportion of 5 year survival in limited stage by PCI

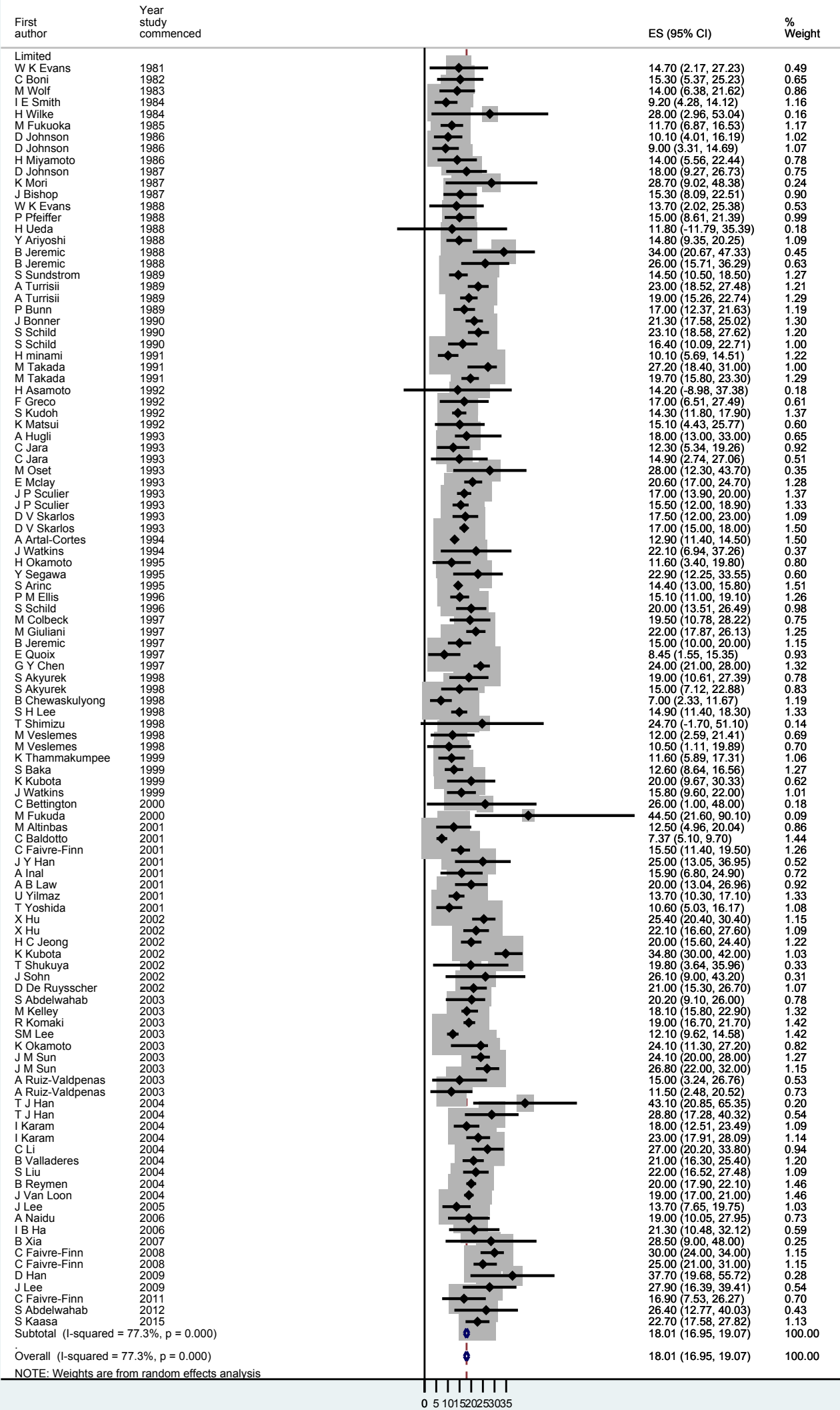


Proportion of 5 year survival in extensive stage by PCI

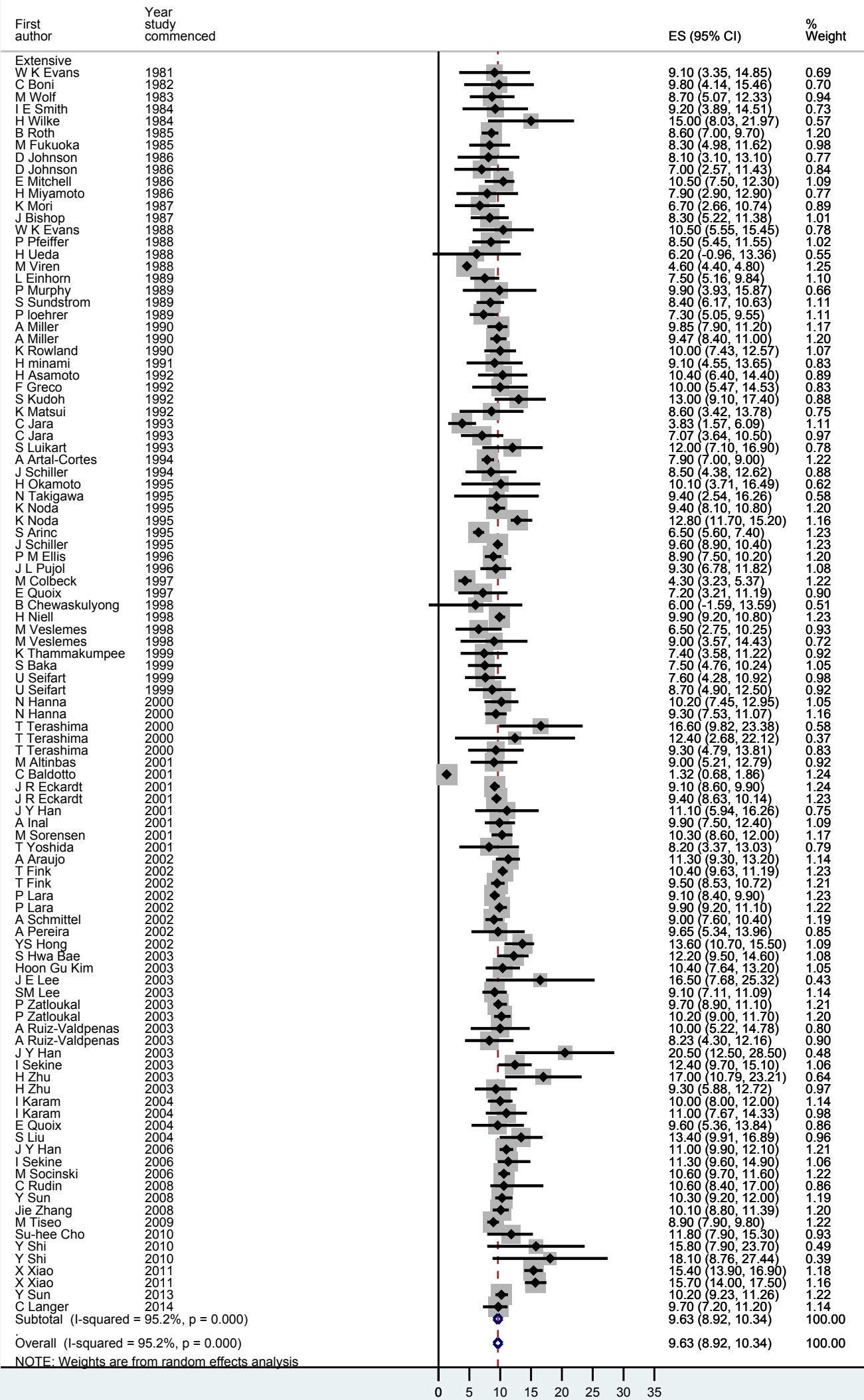
Median survival



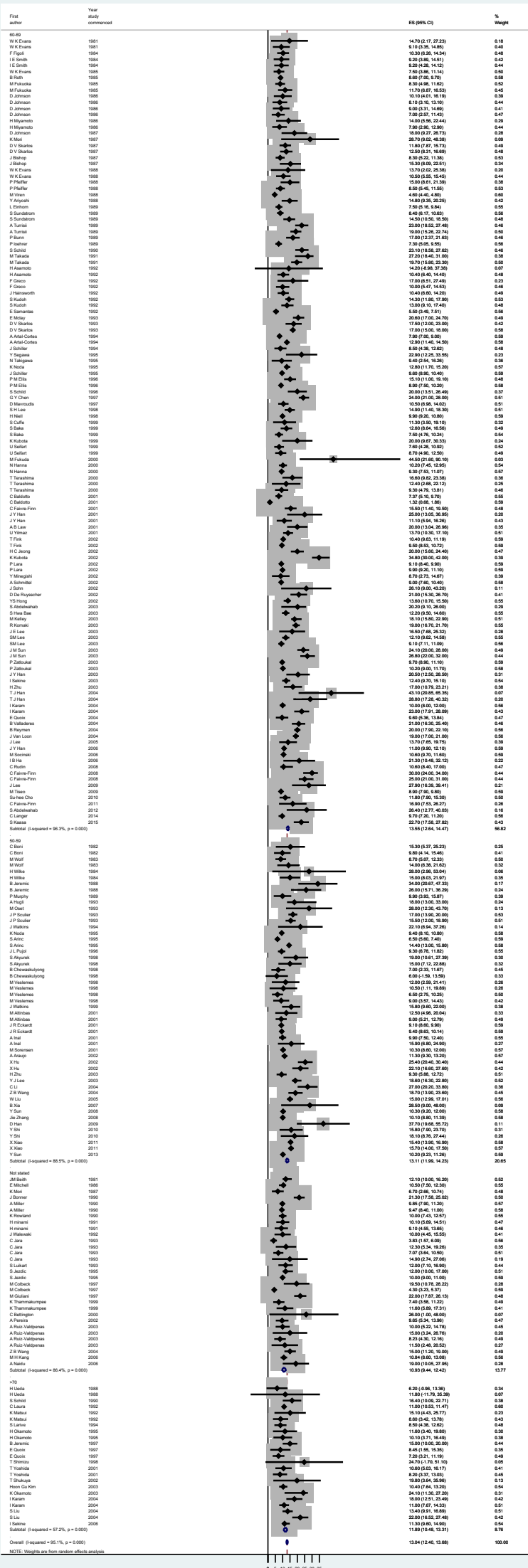
Survival in months all stages

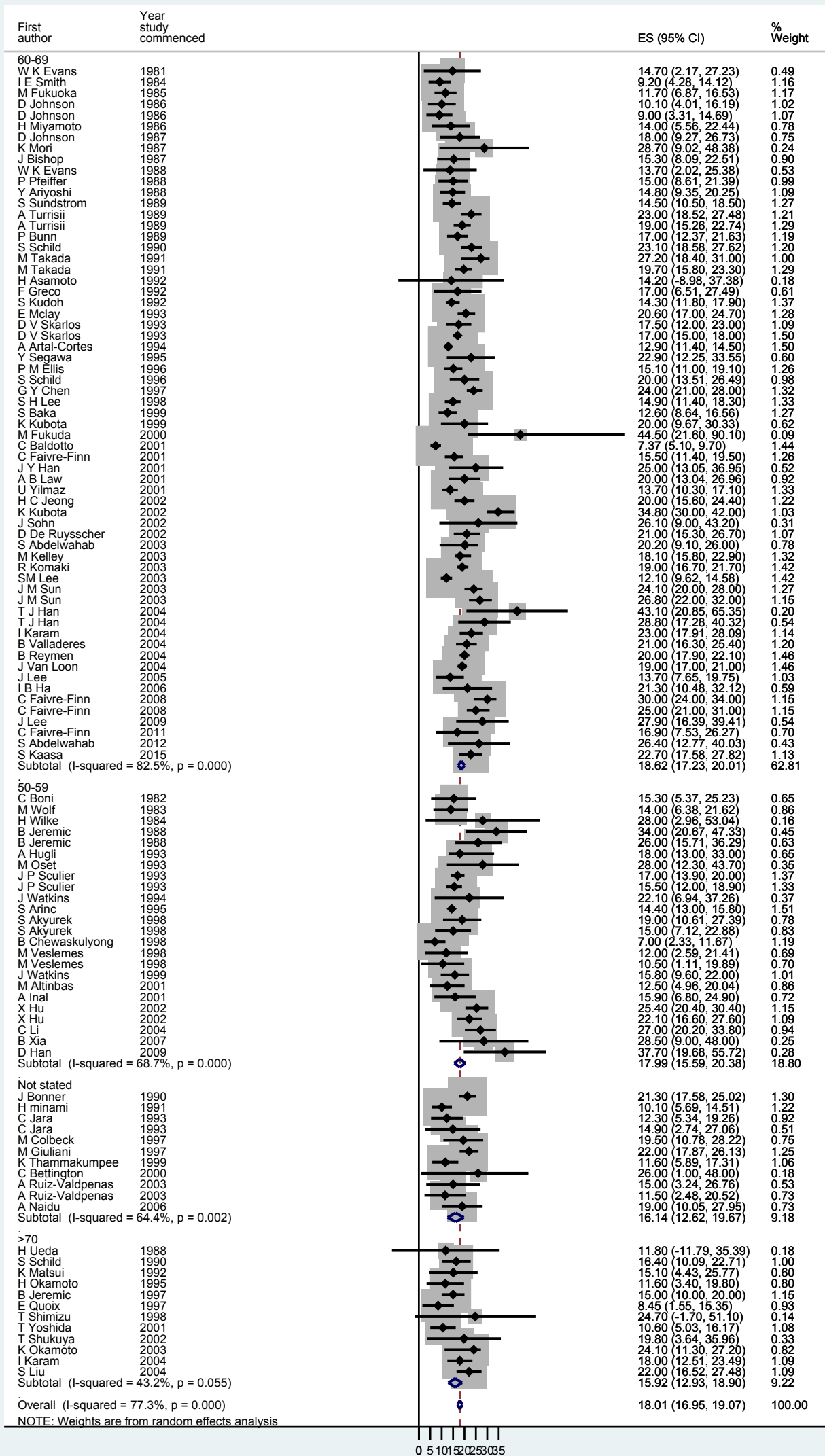


Survival in months limited stage

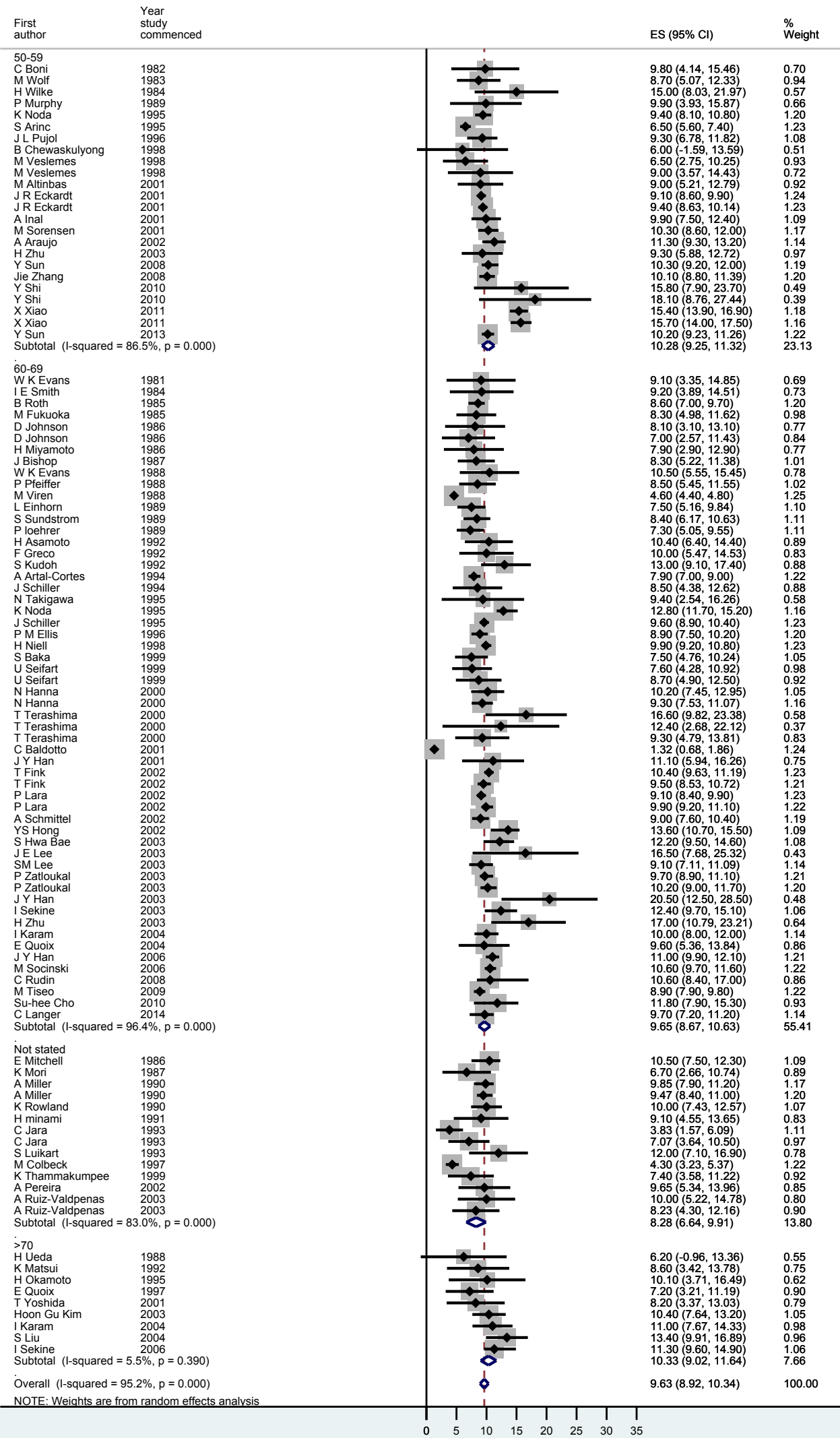


Survival in months extensive stage

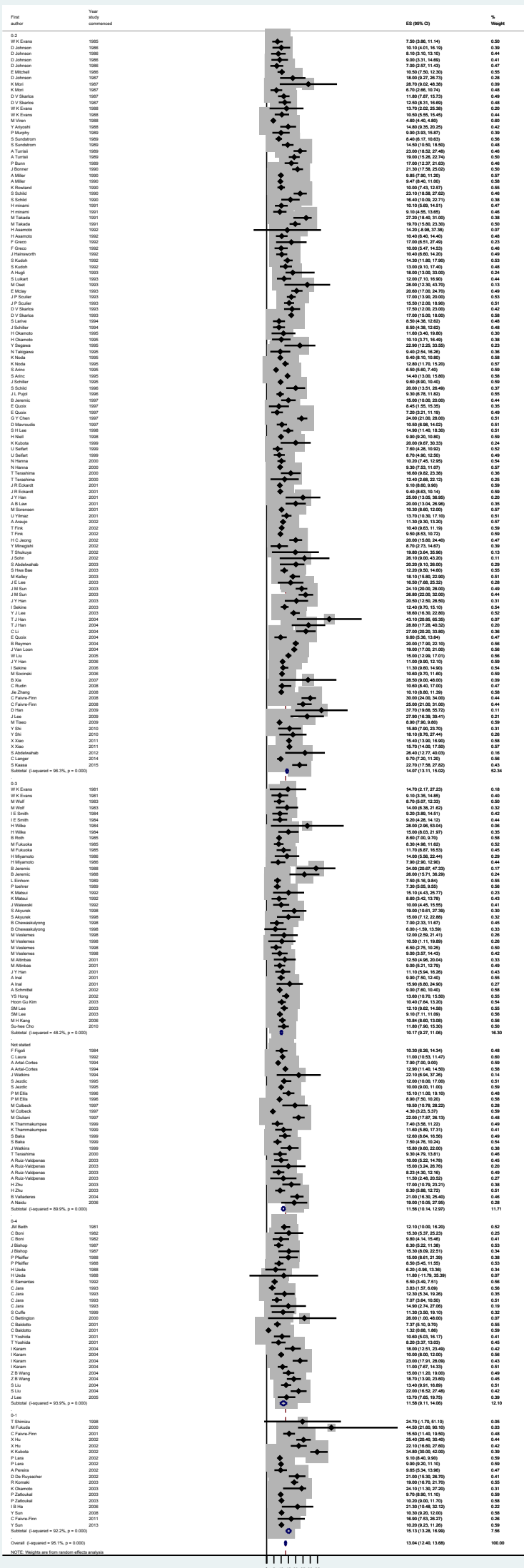


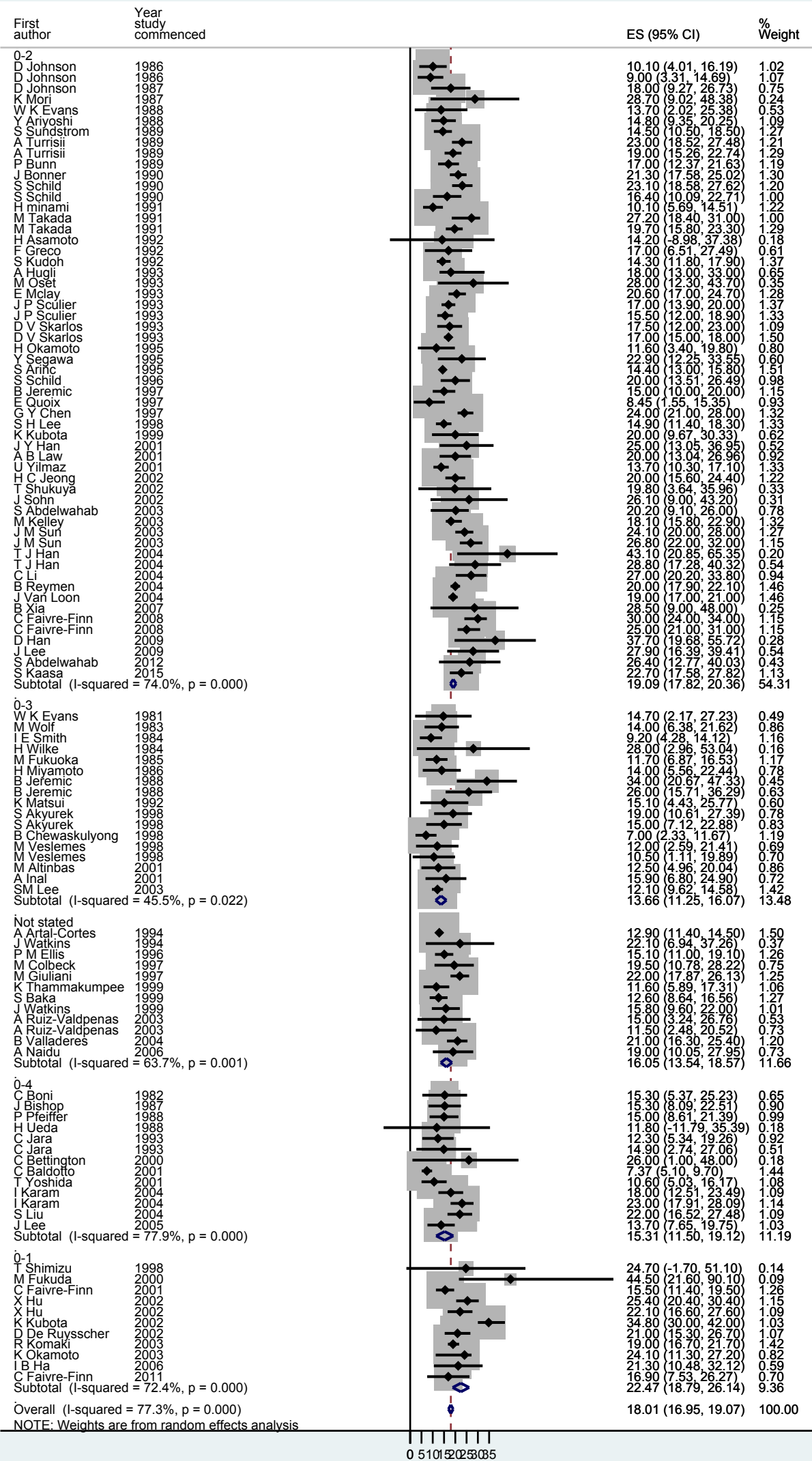


Survival in months for limited stage by participant age

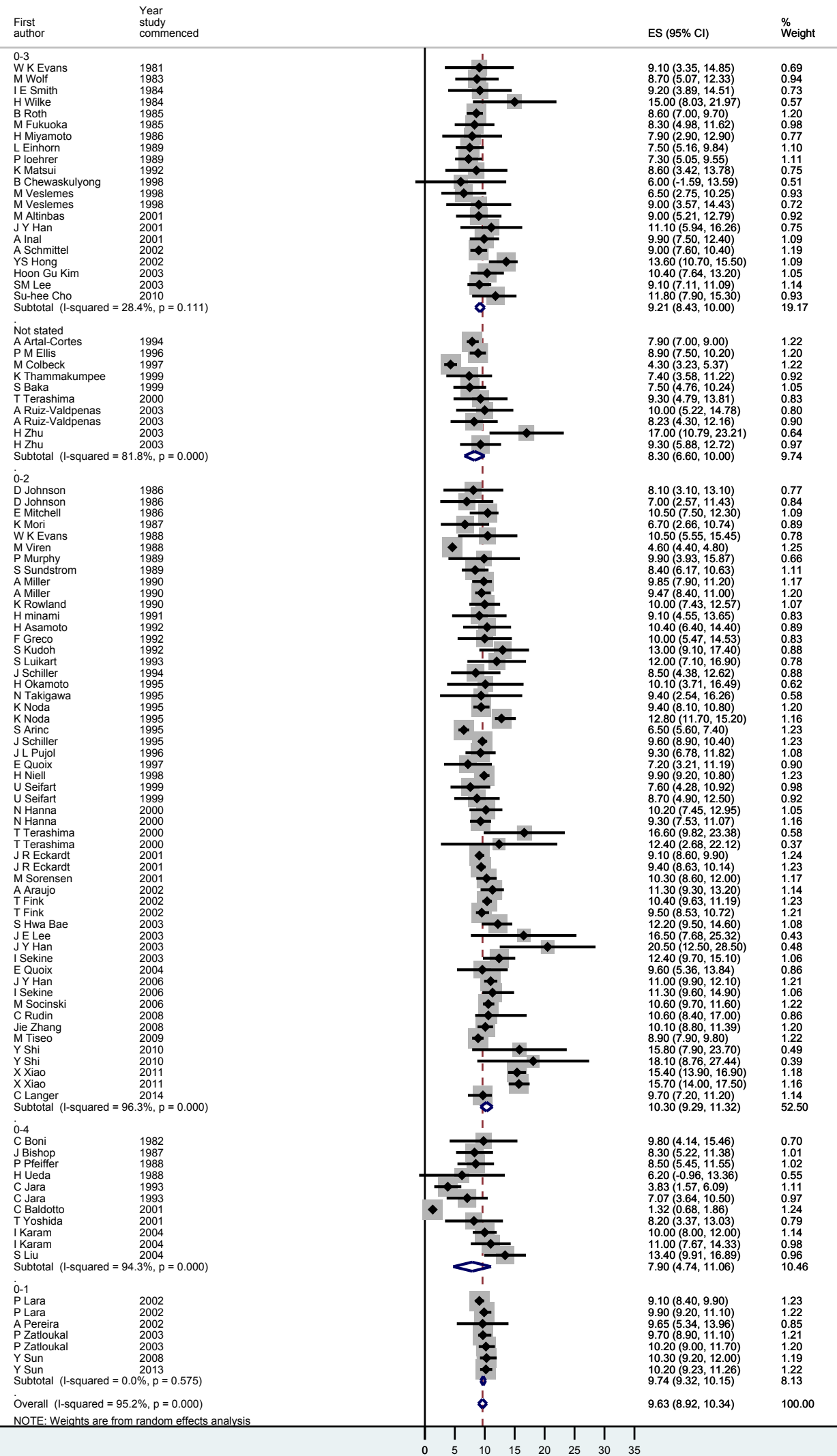


Survival in months for extensive stage by participant age

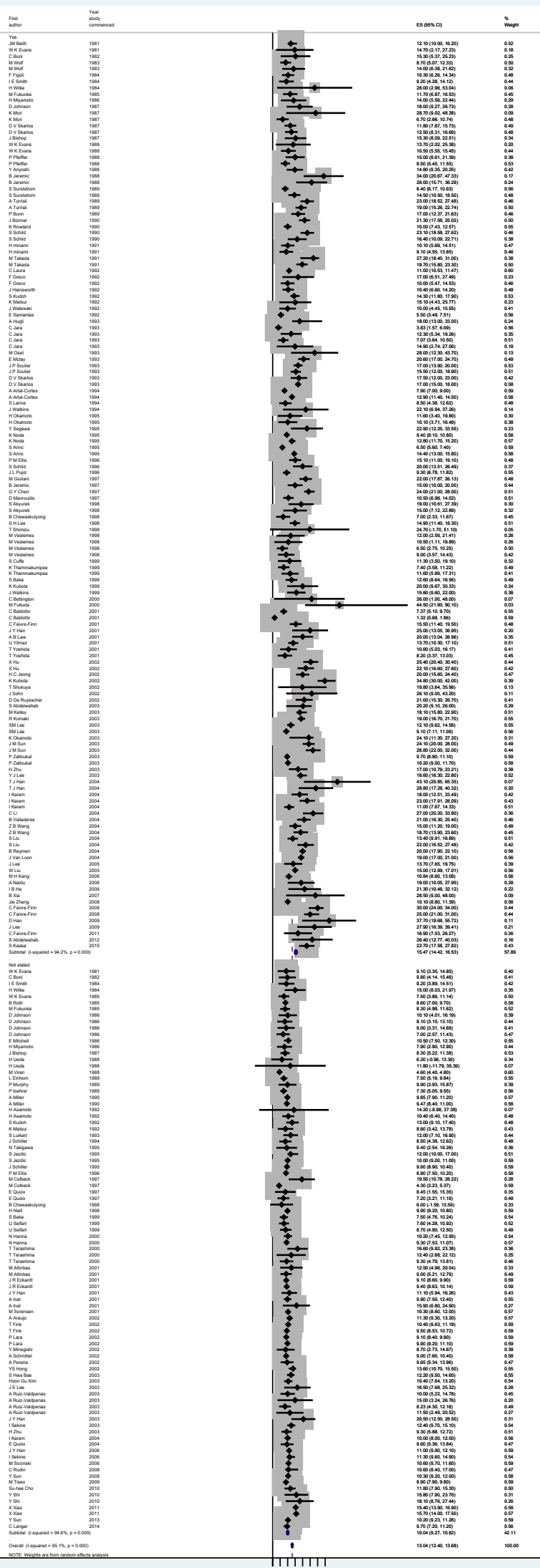


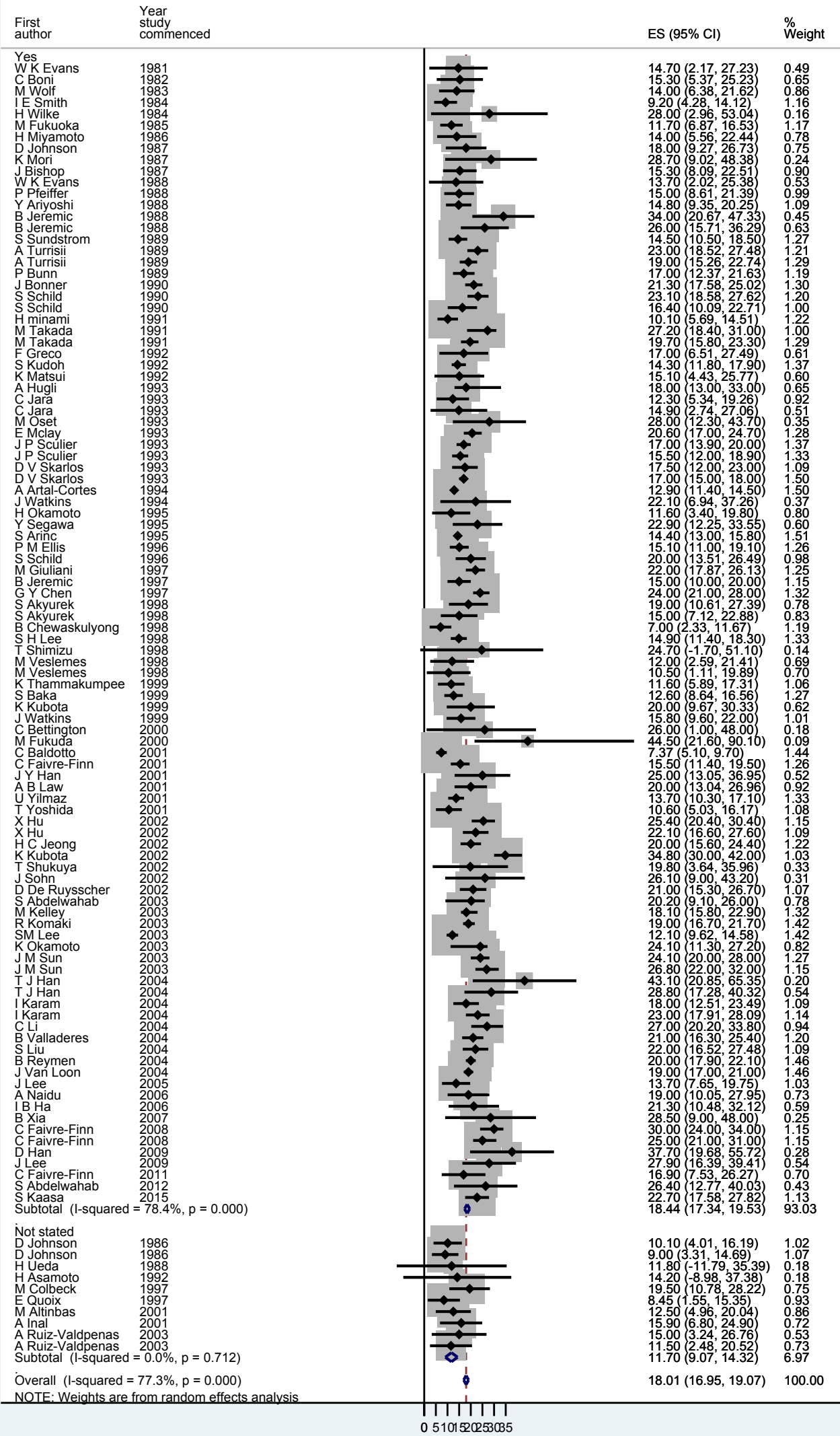


Survival in months for limited stage by PS

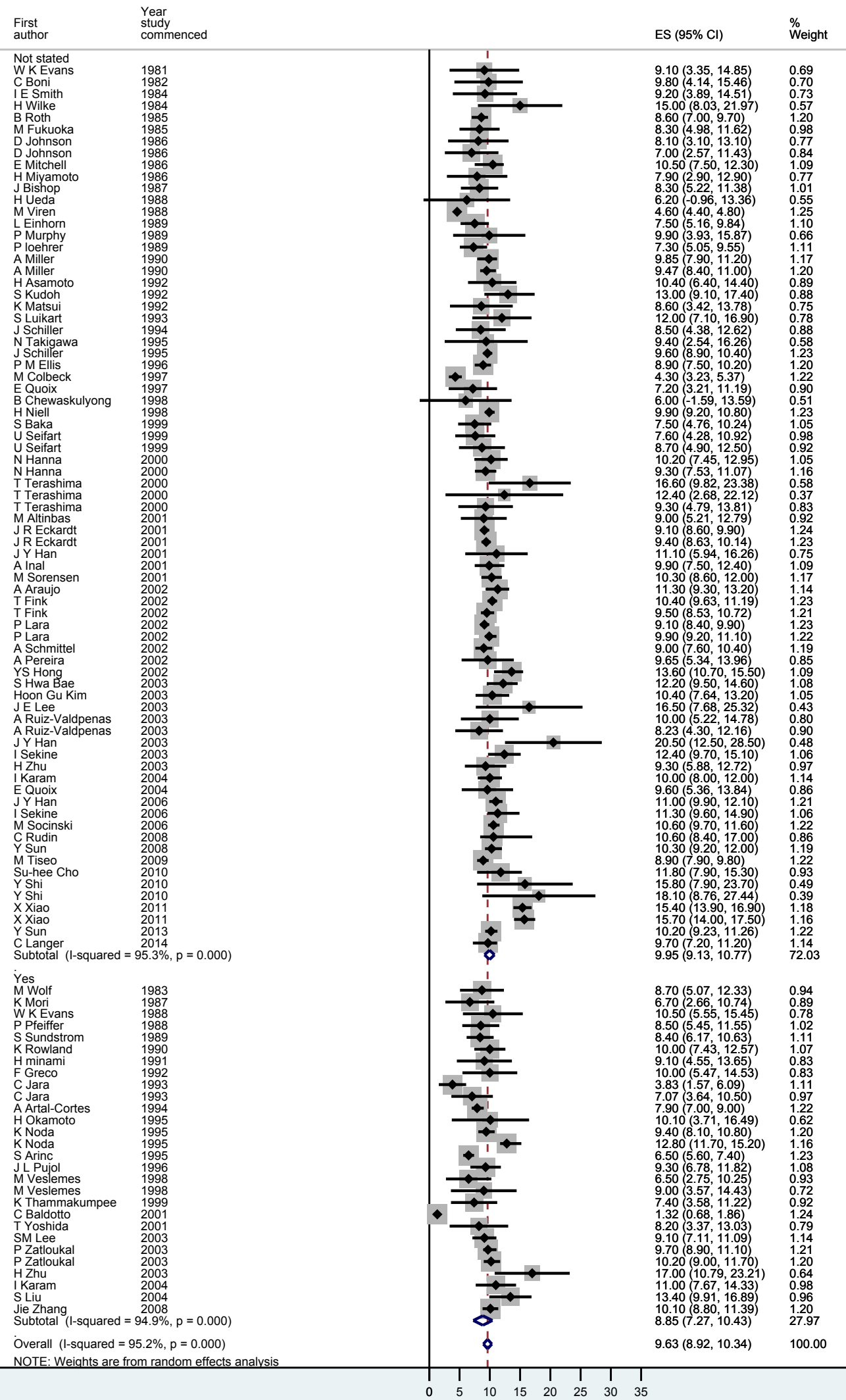


Survival in months for extensive stage by PS

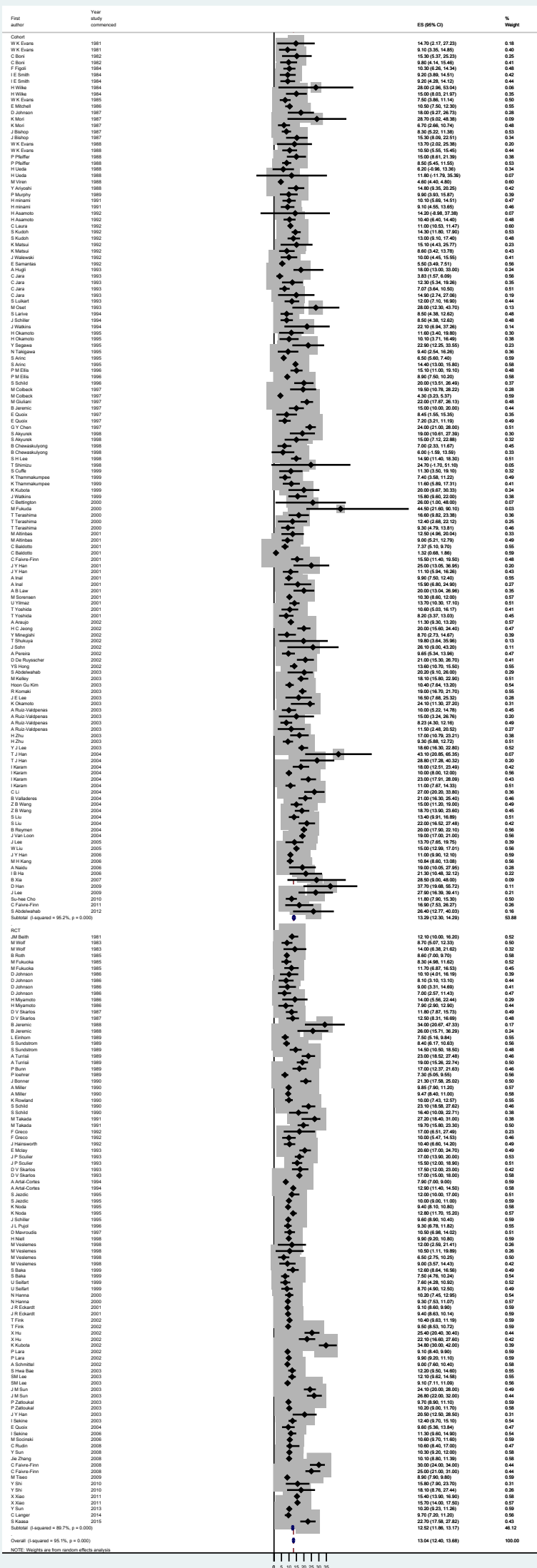


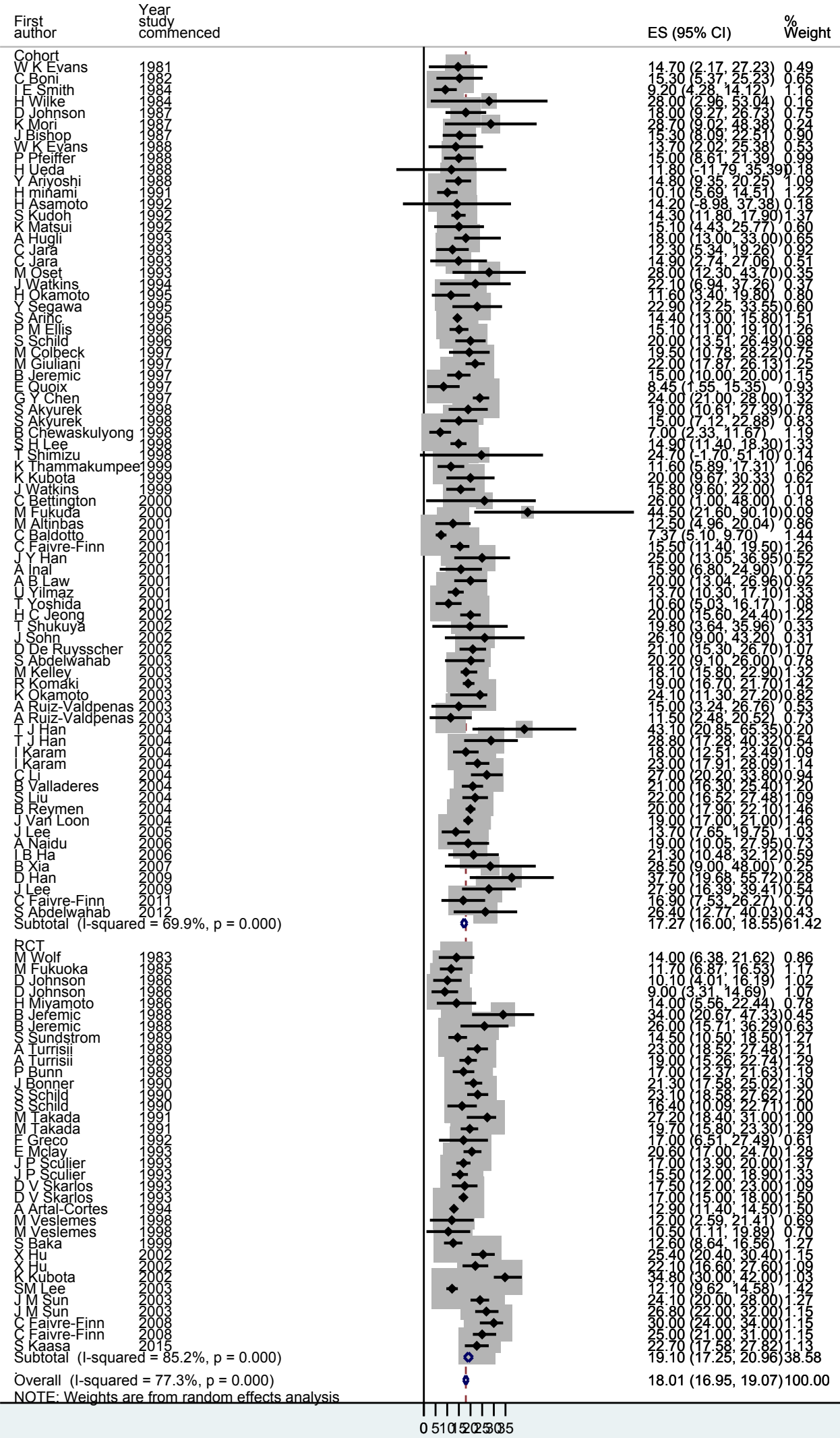


Survival in months for limited stage by radiotherapy

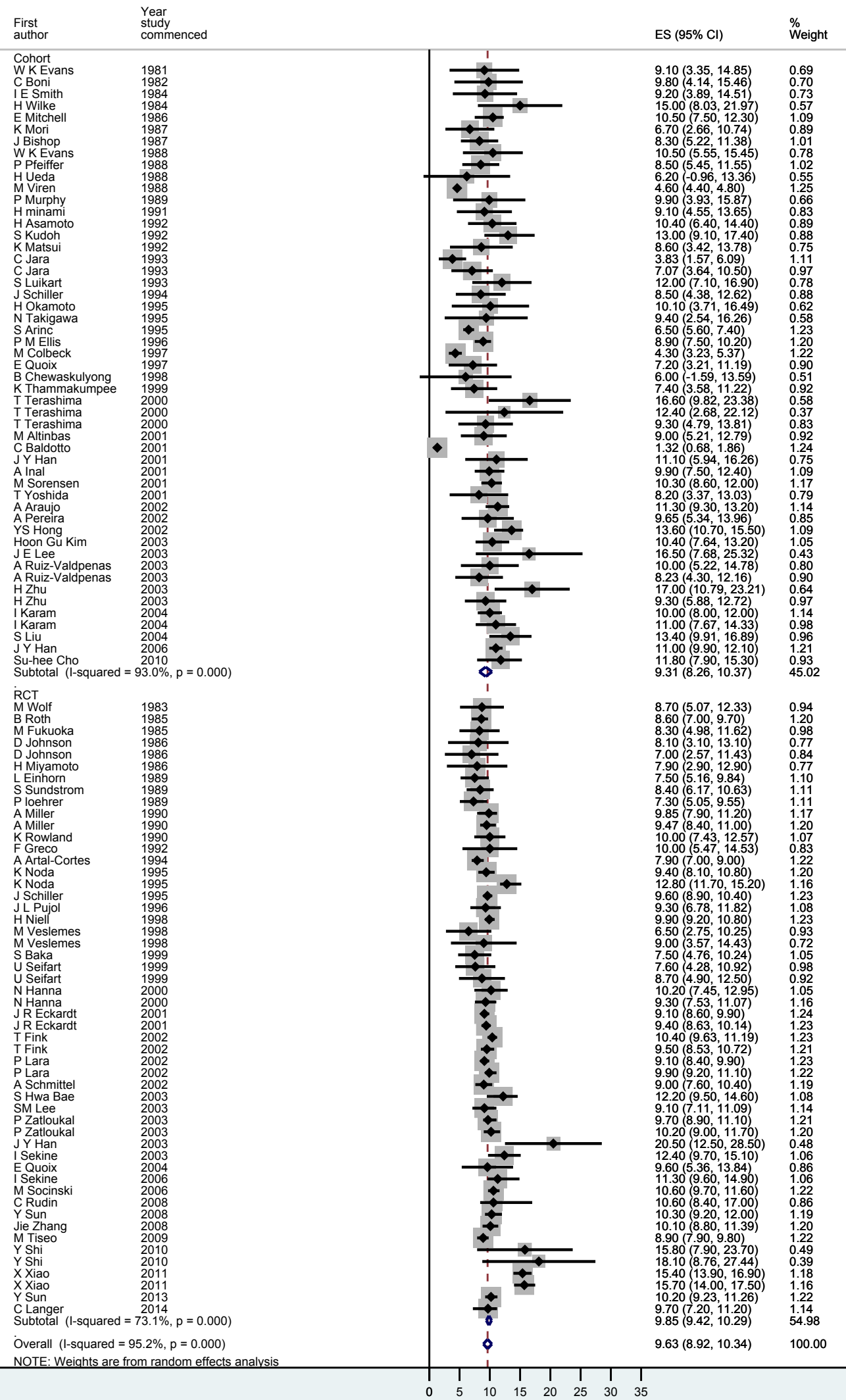


Survival in months for extensive stage by radiotherapy

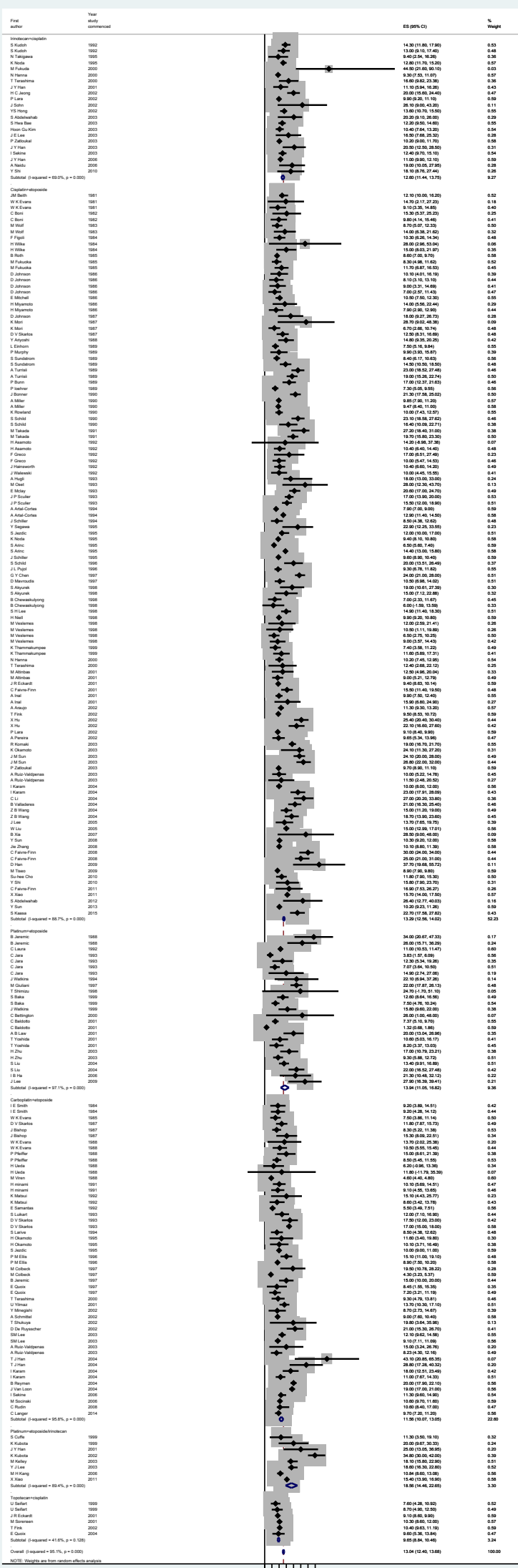


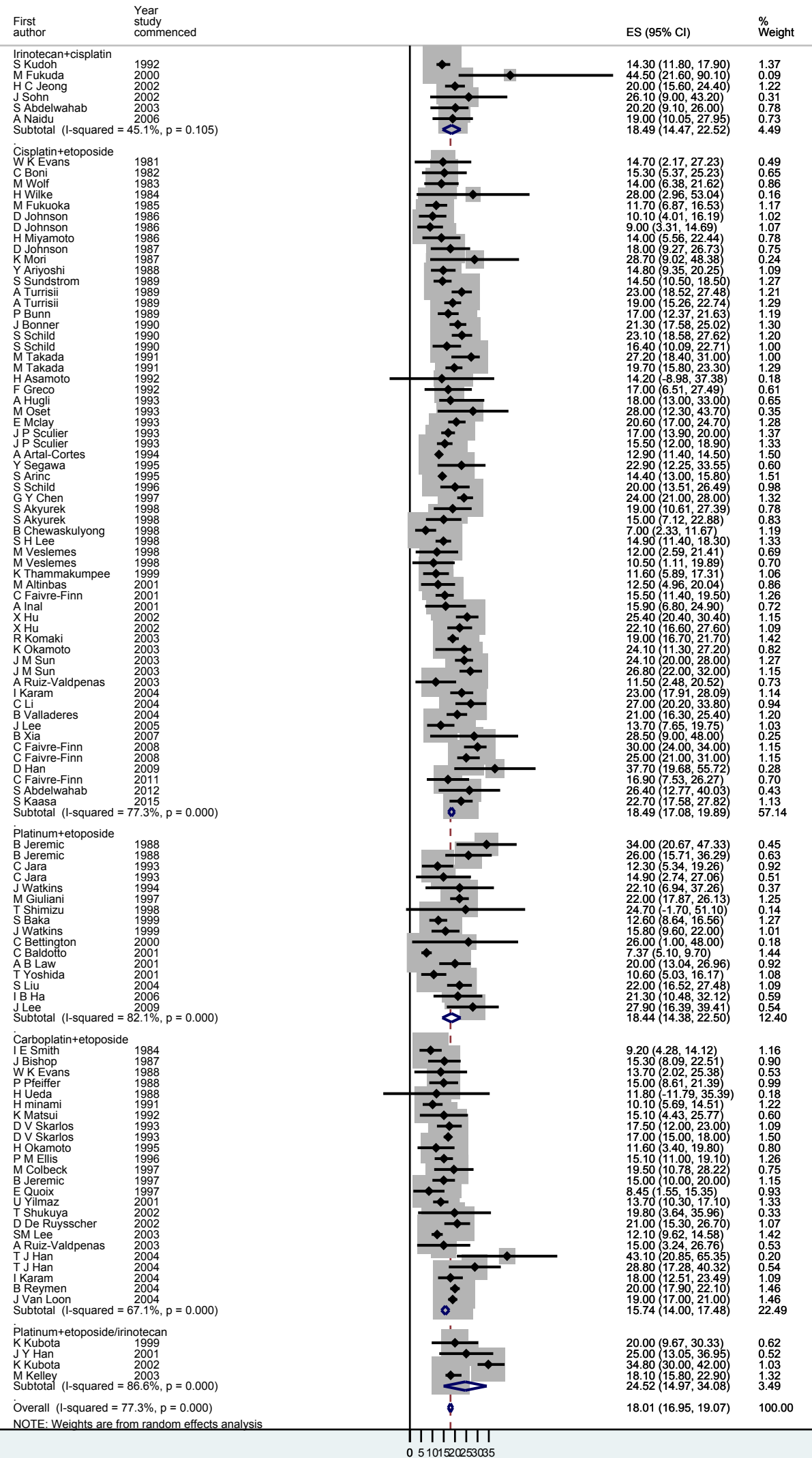


Survival in months for limited stage by study design

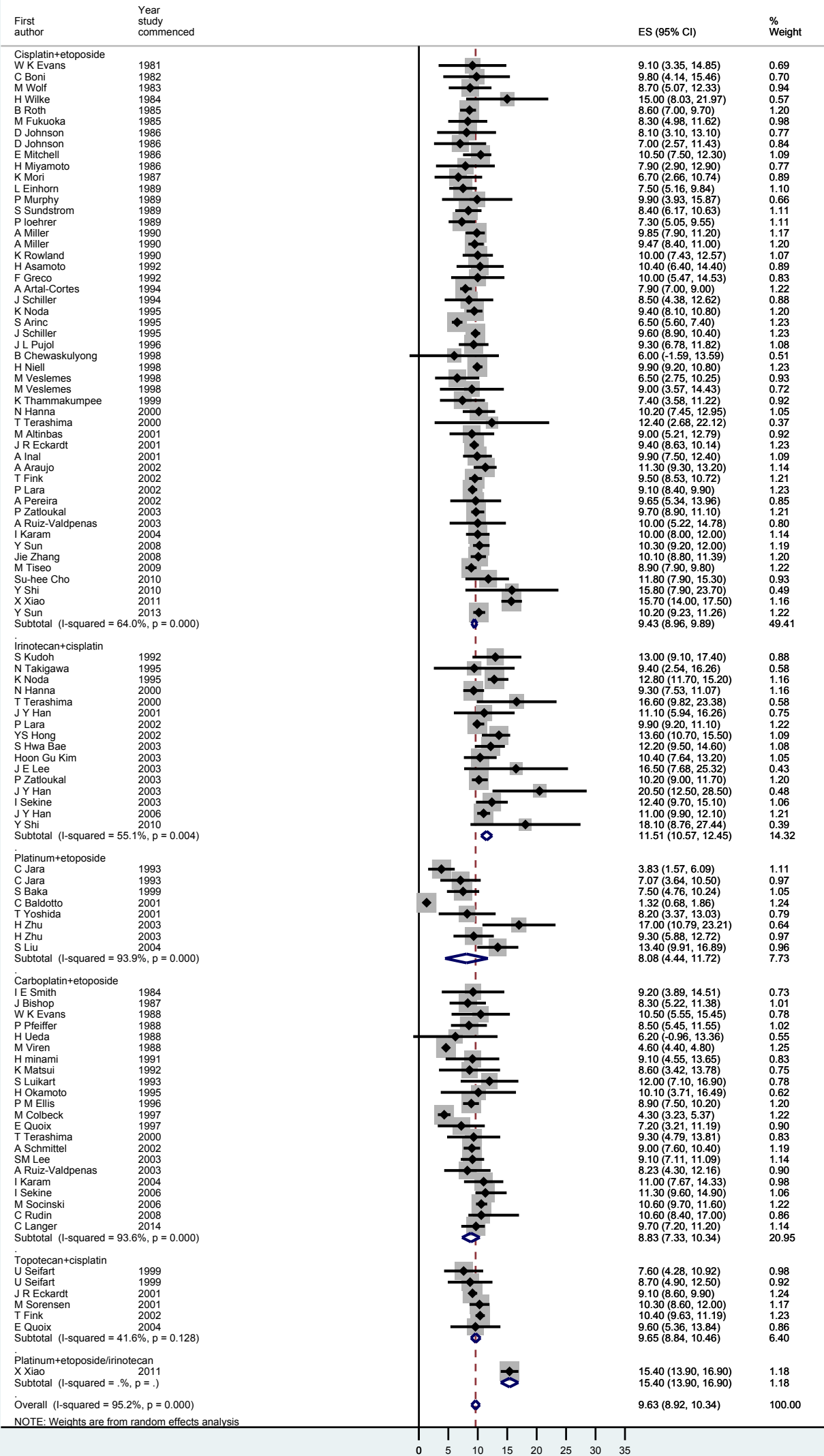


Survival in months for extensive stage by study design

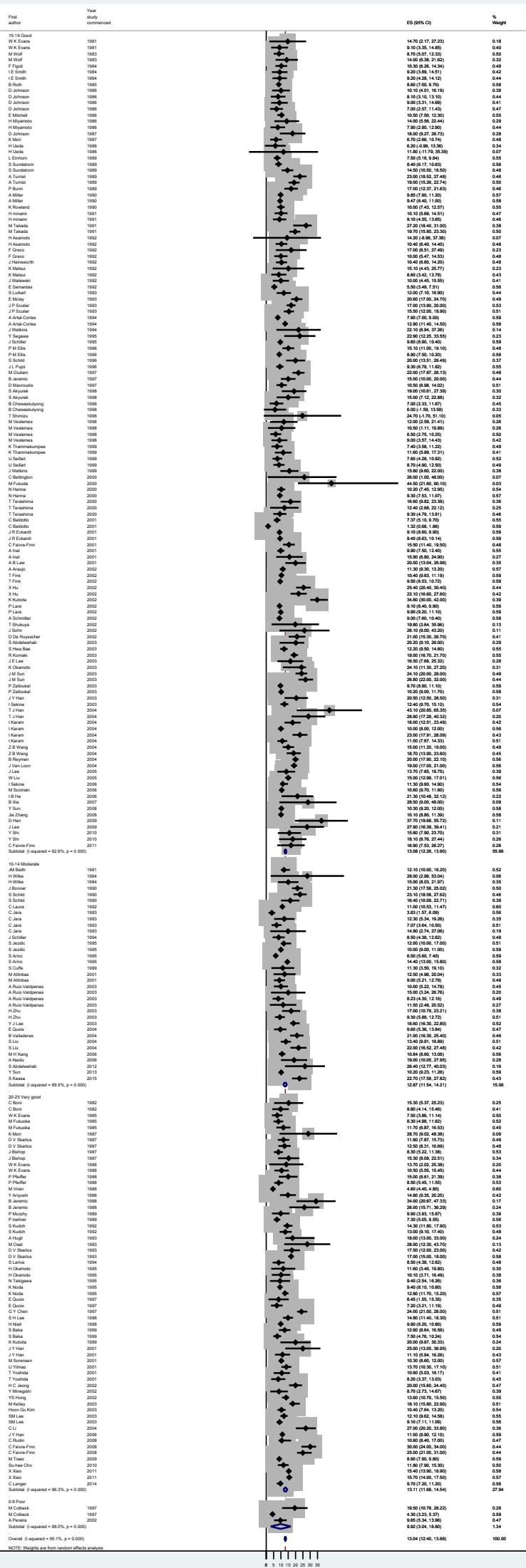


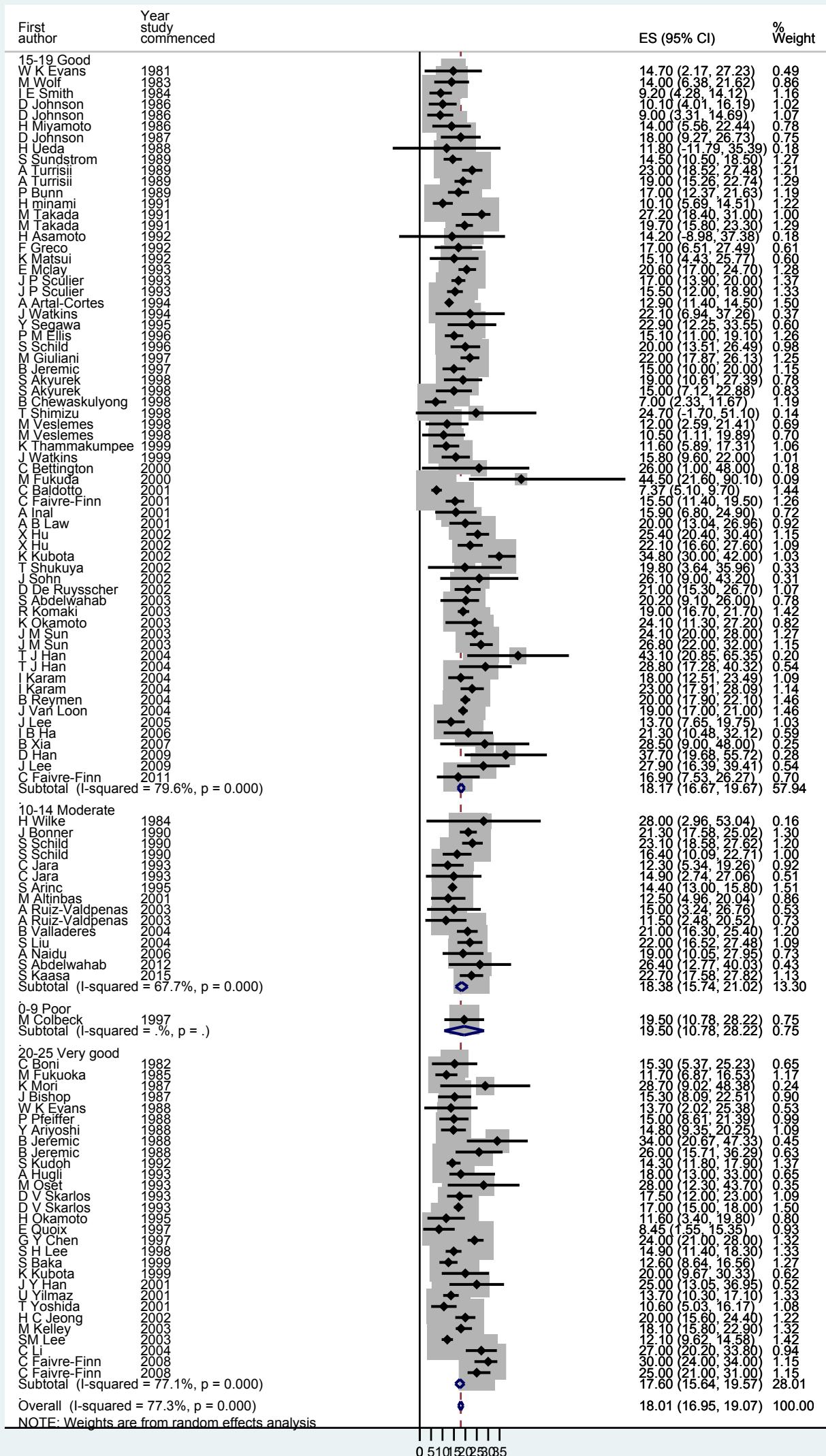


Survival in months for limited stage by chemotherapy

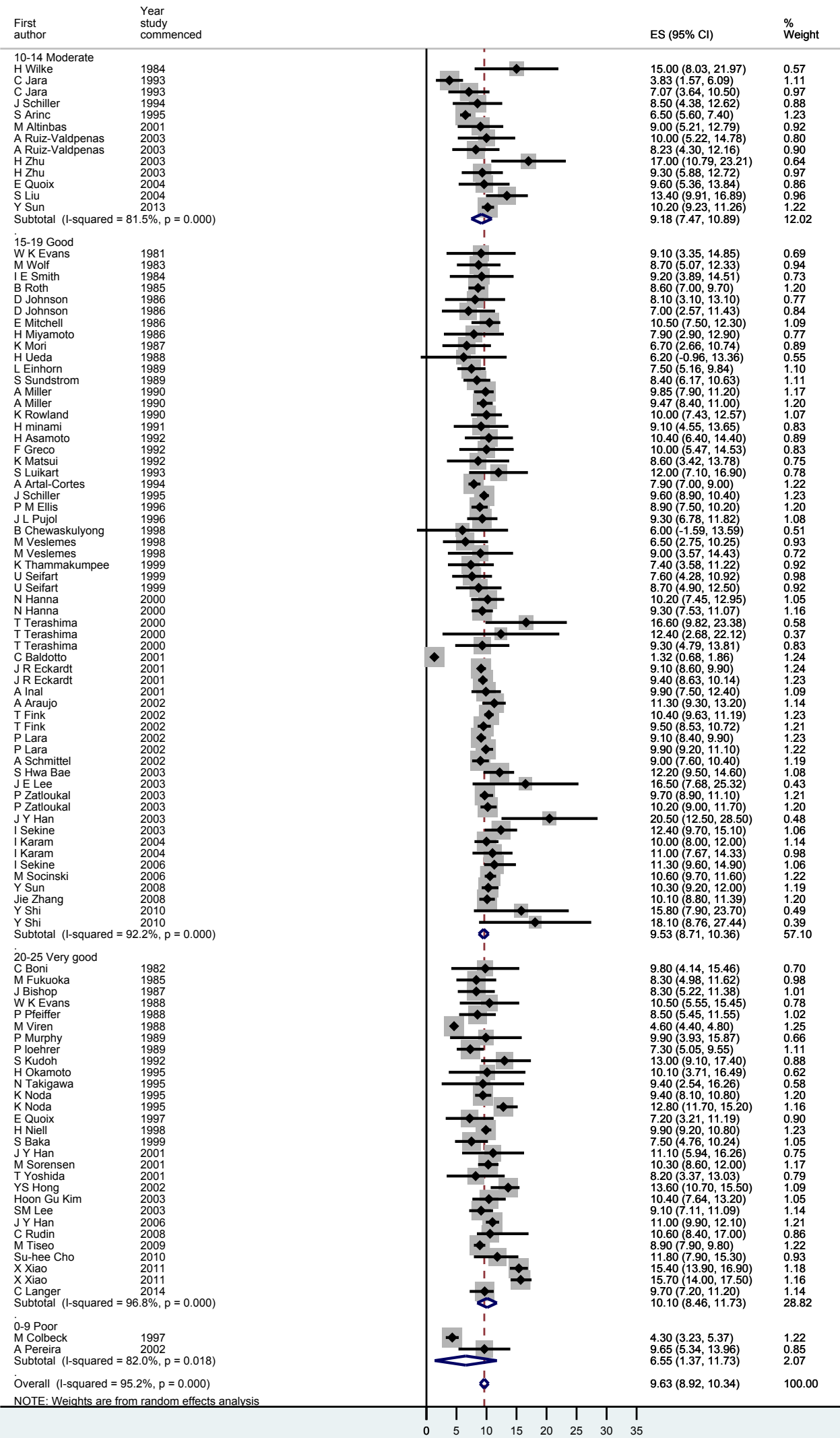


Survival in months for extensive stage by chemotherapy

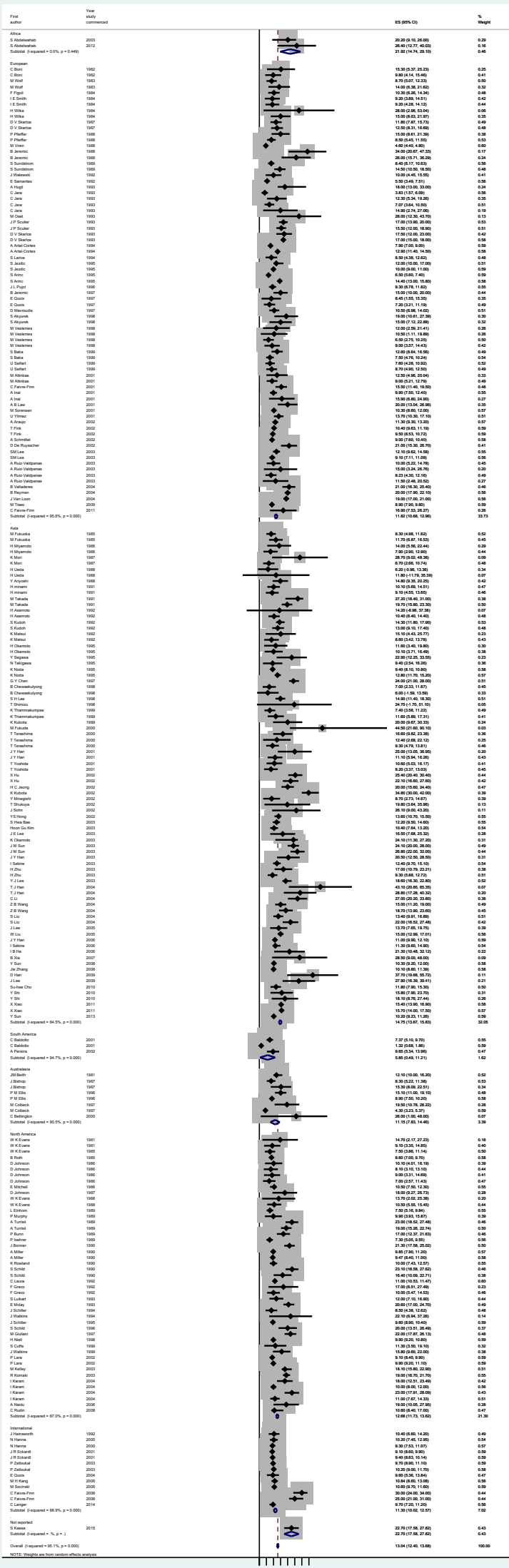


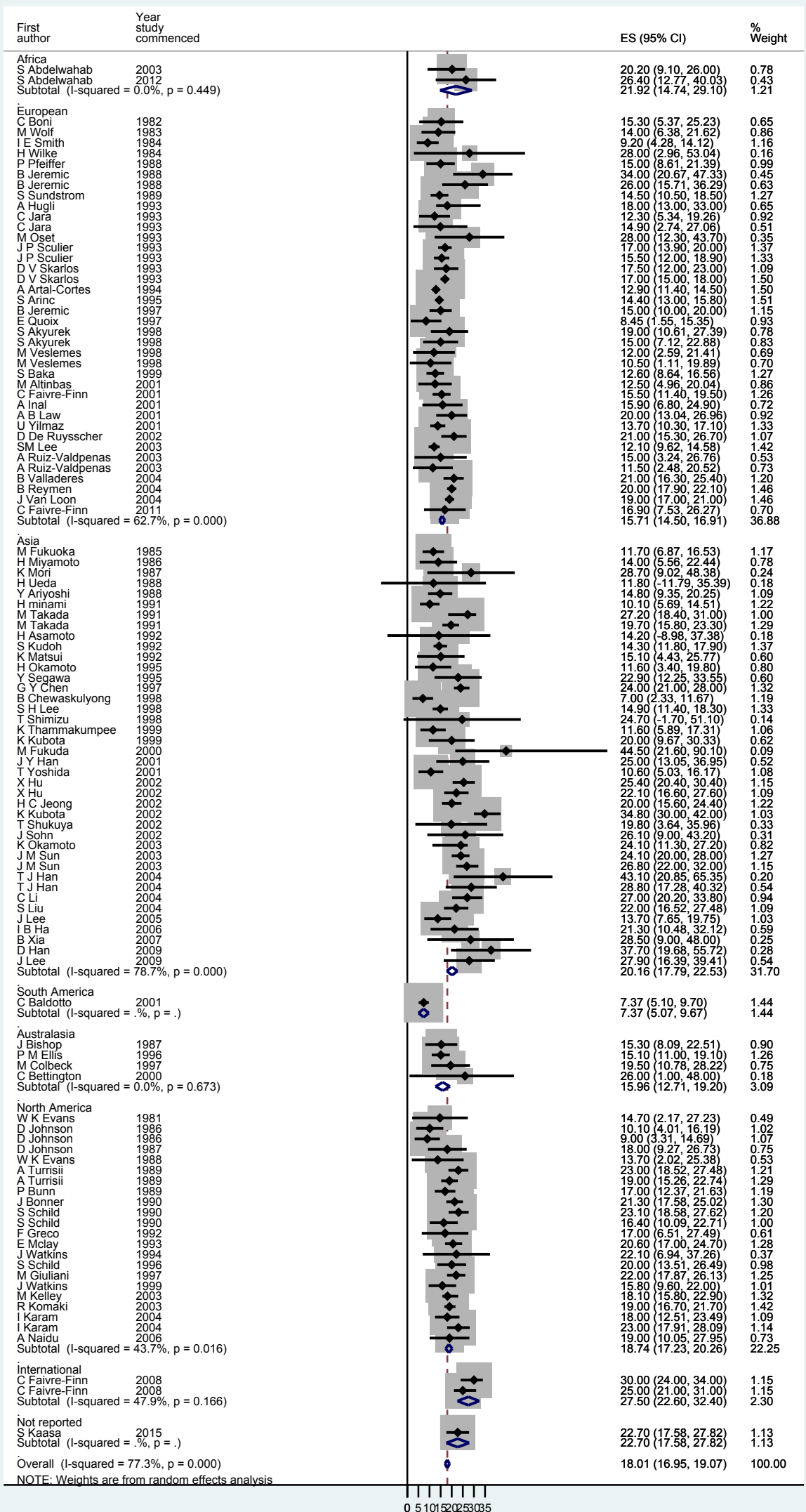


Survival in months for limited stage by quality score

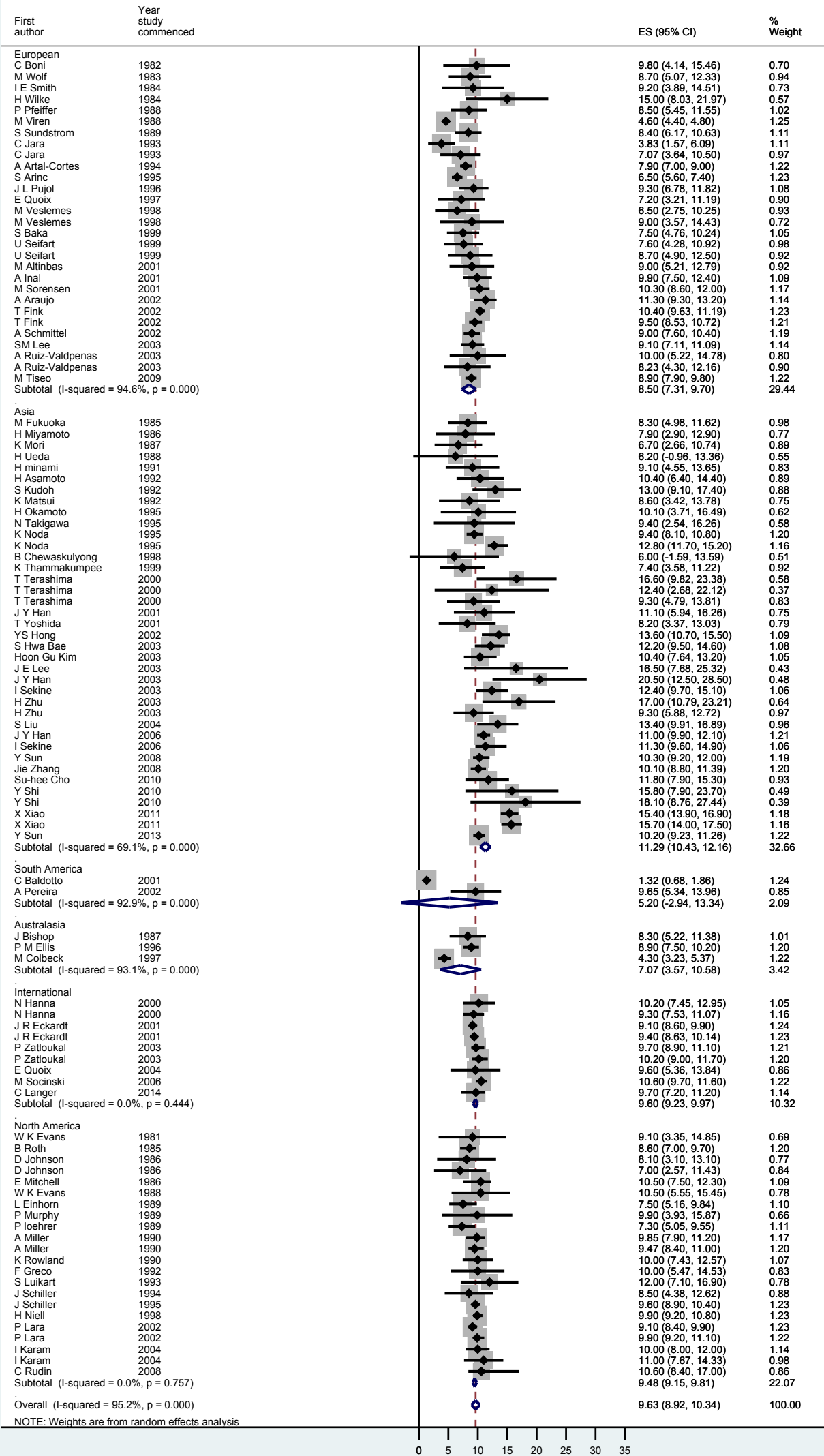


Survival in months for extensive stage by quality score

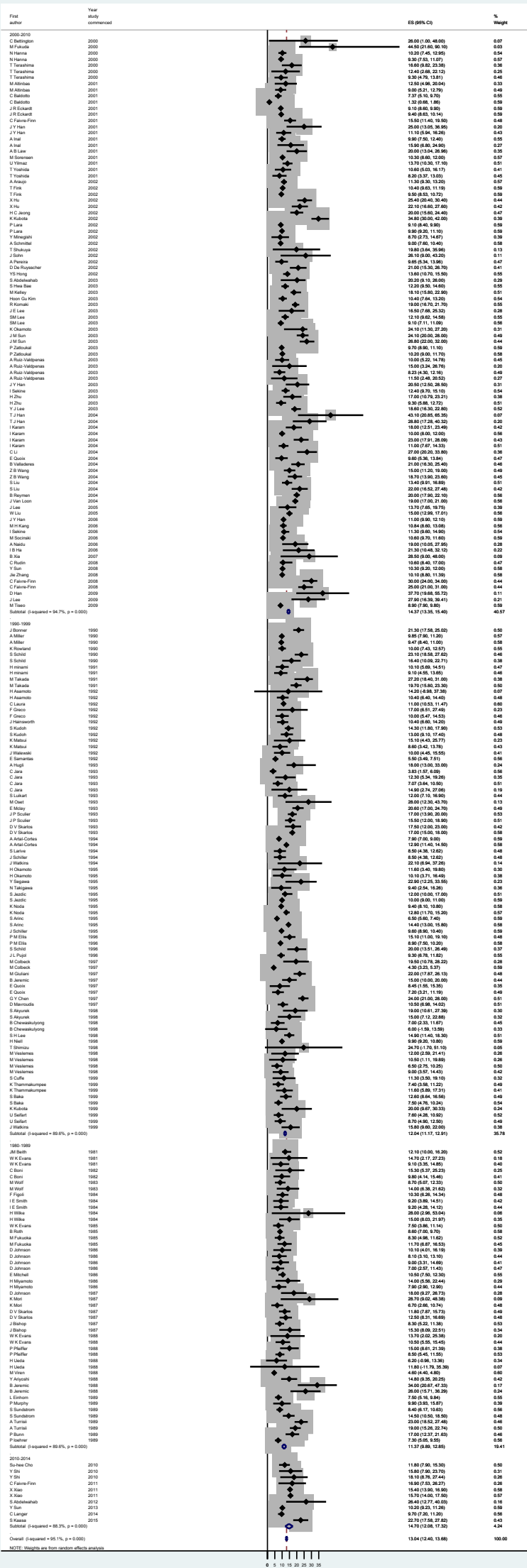


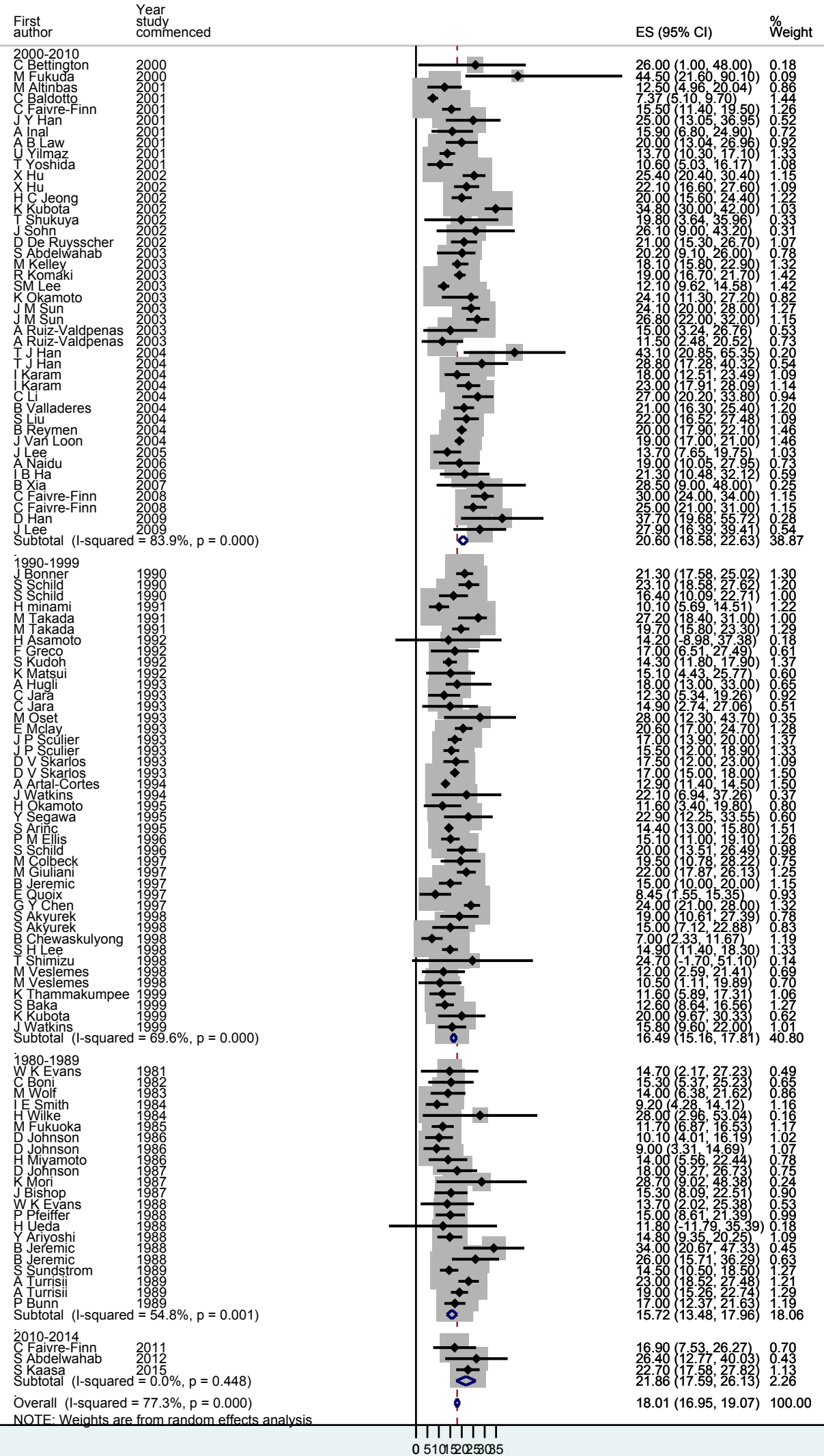


Survival in months for limited stage by region

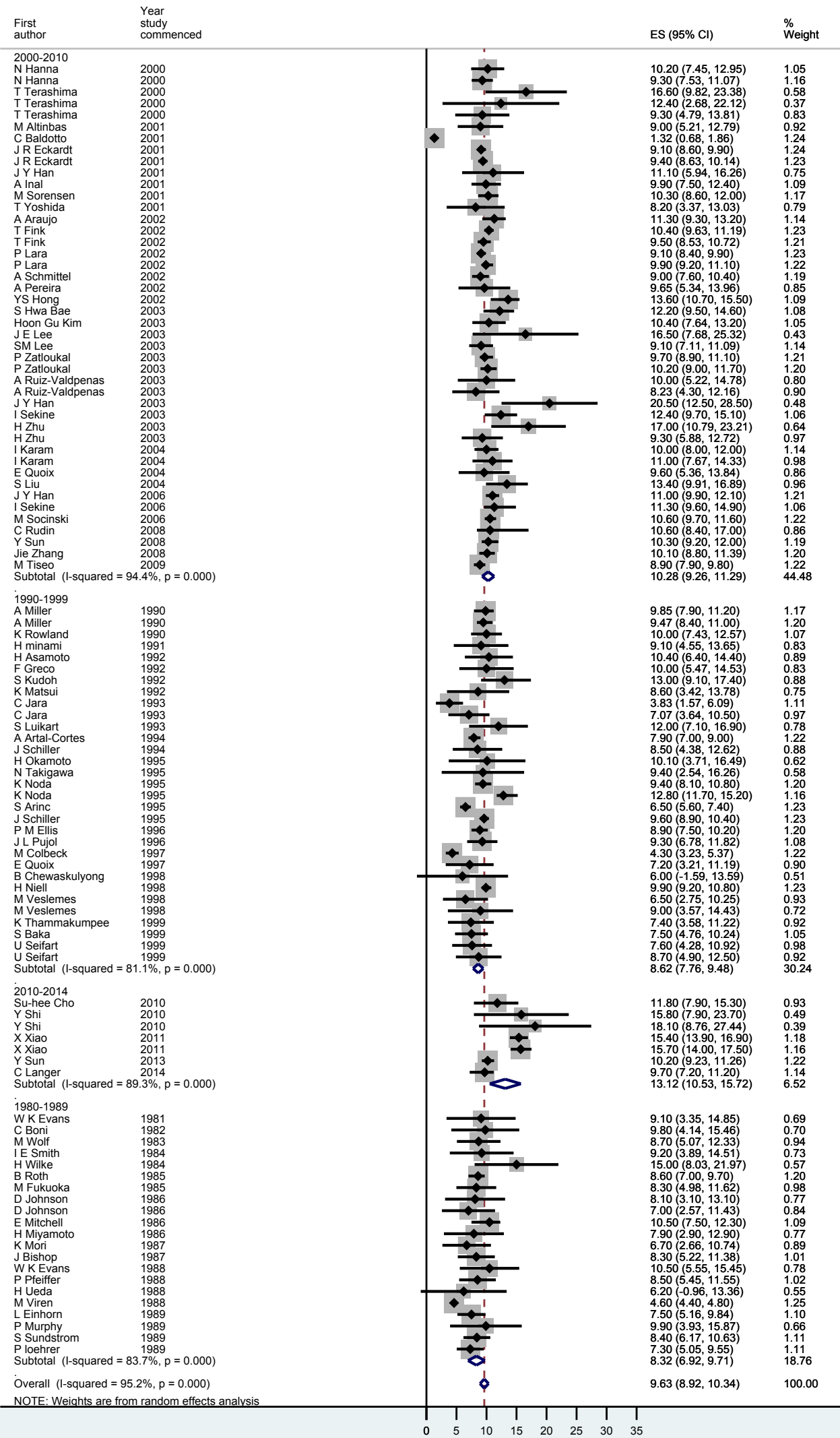


Survival in months for extensive stage by region

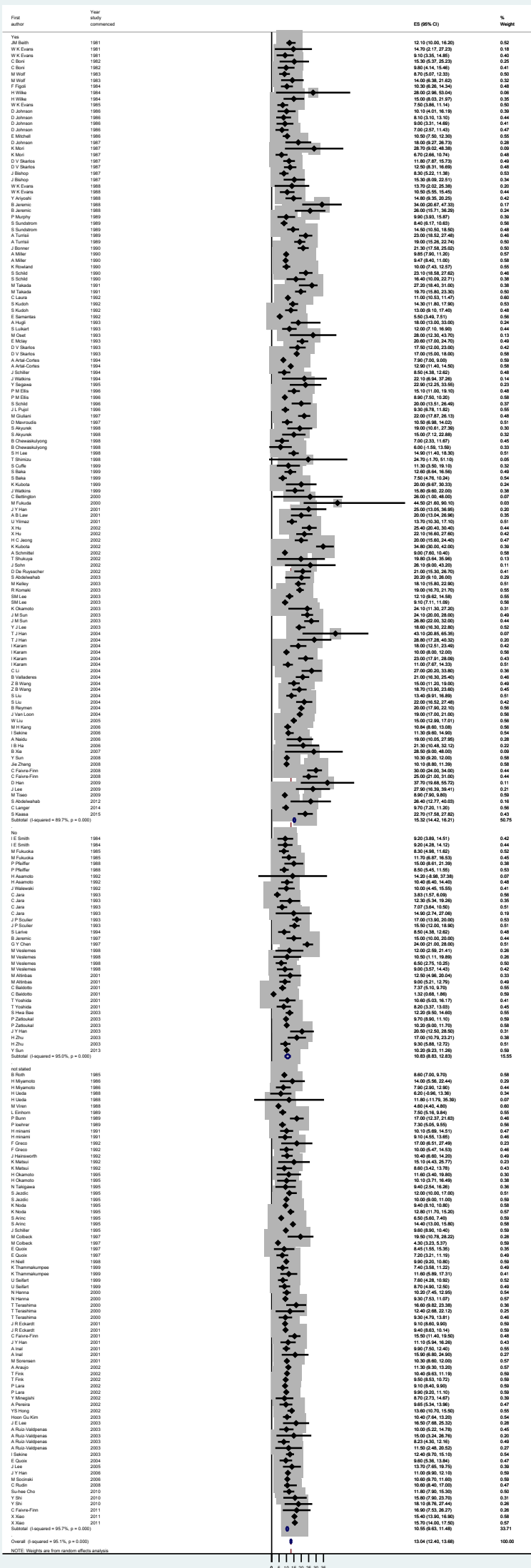


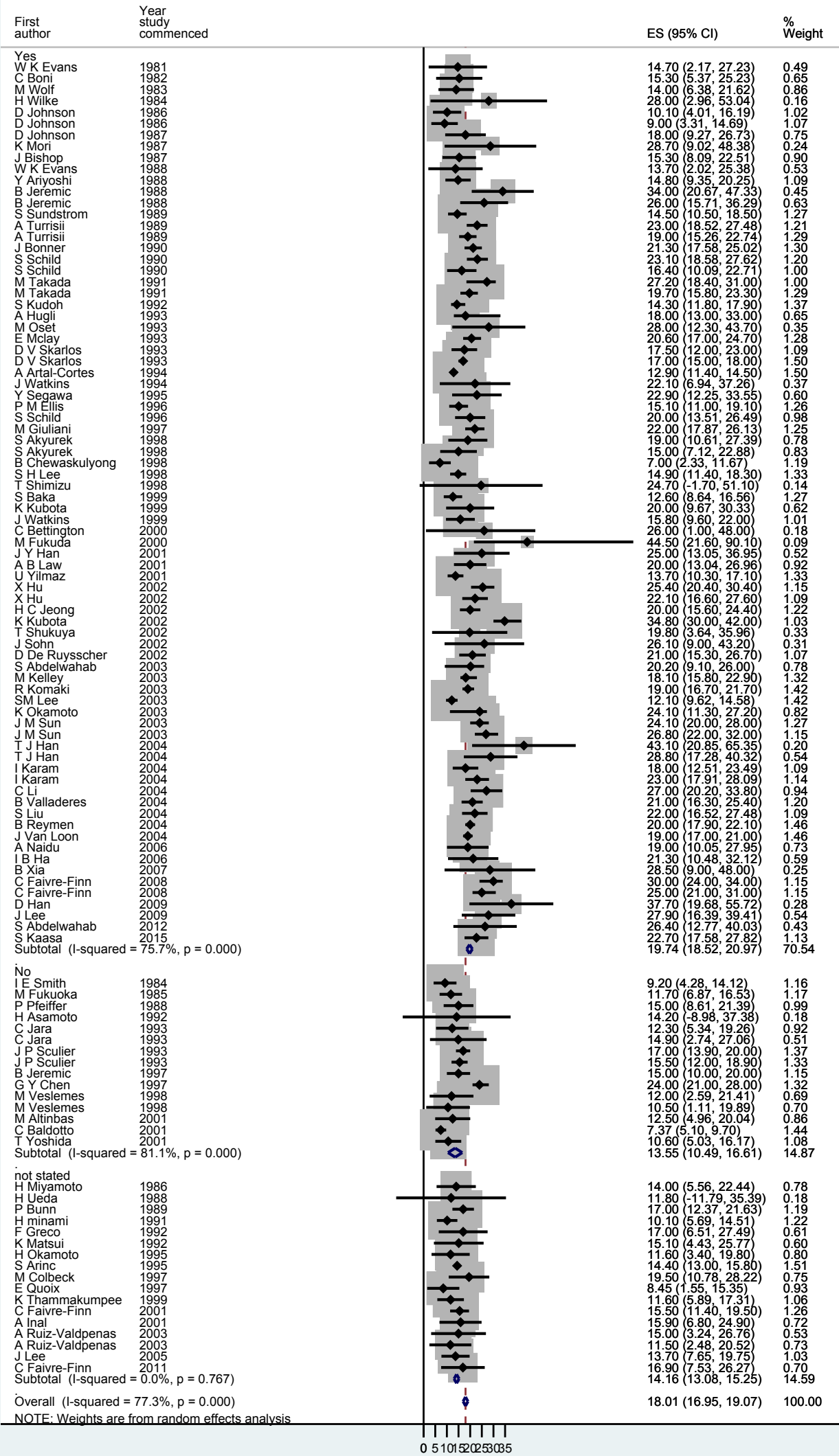


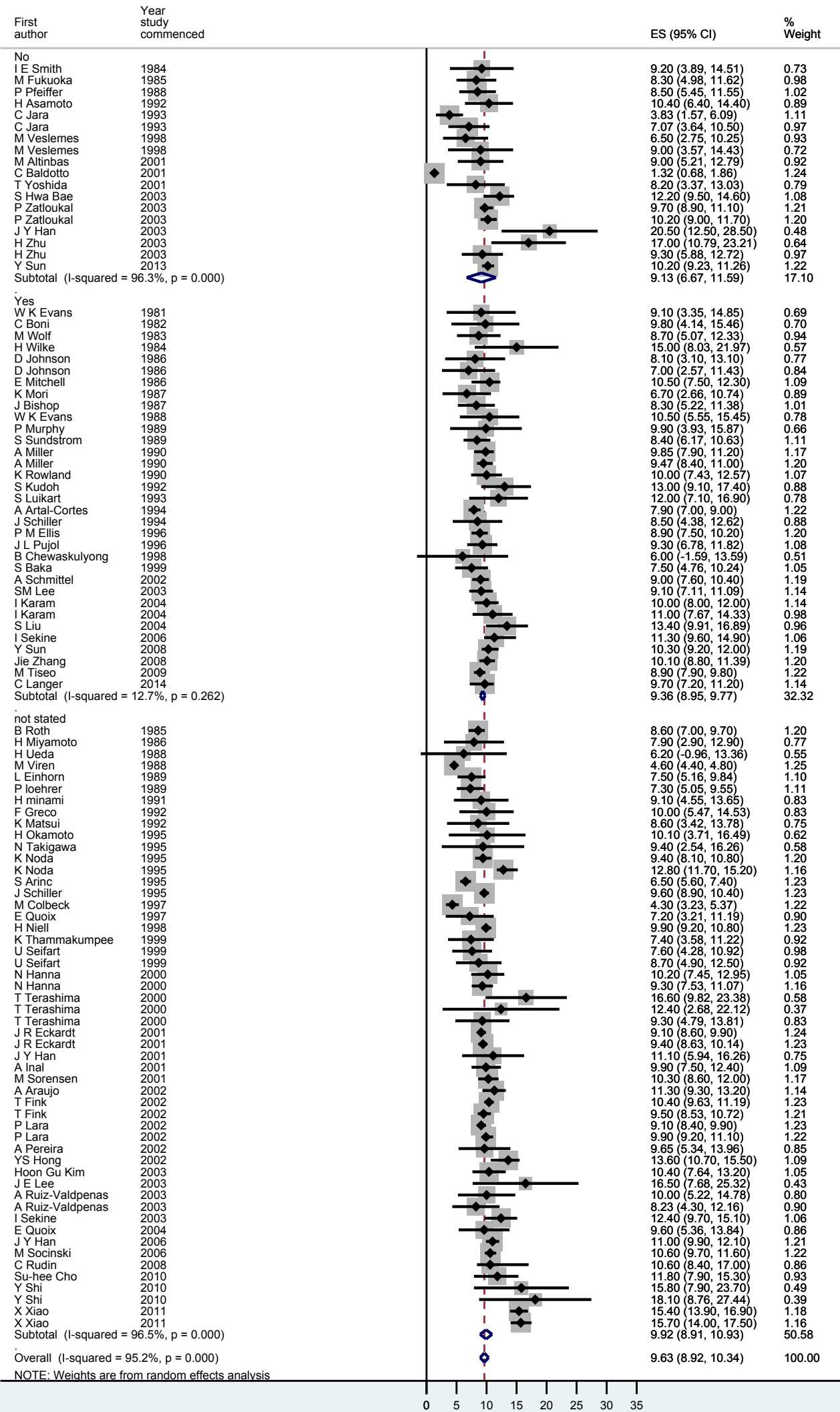
Survival in months for limited stage by study year



Survival in months by study year

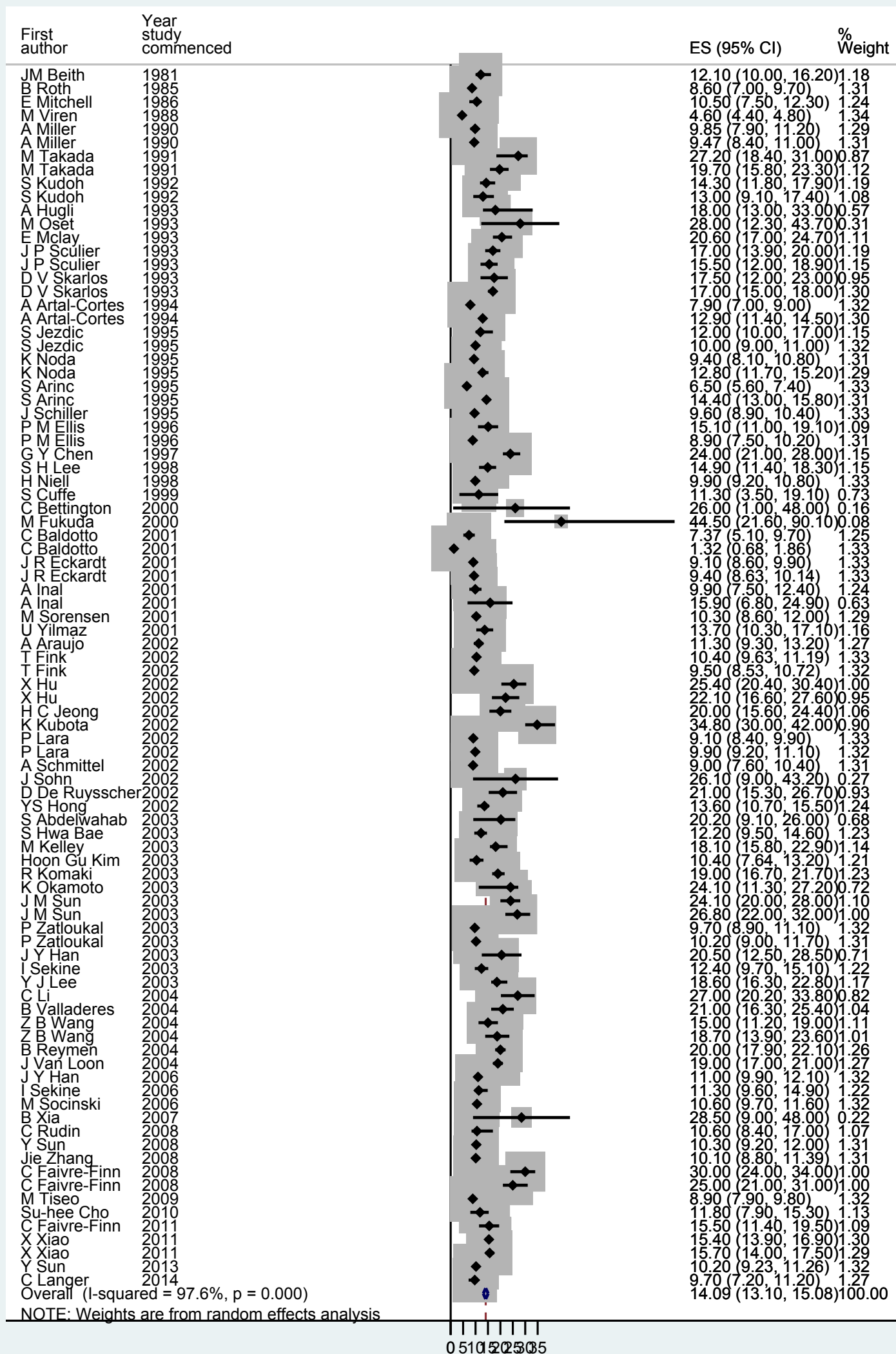




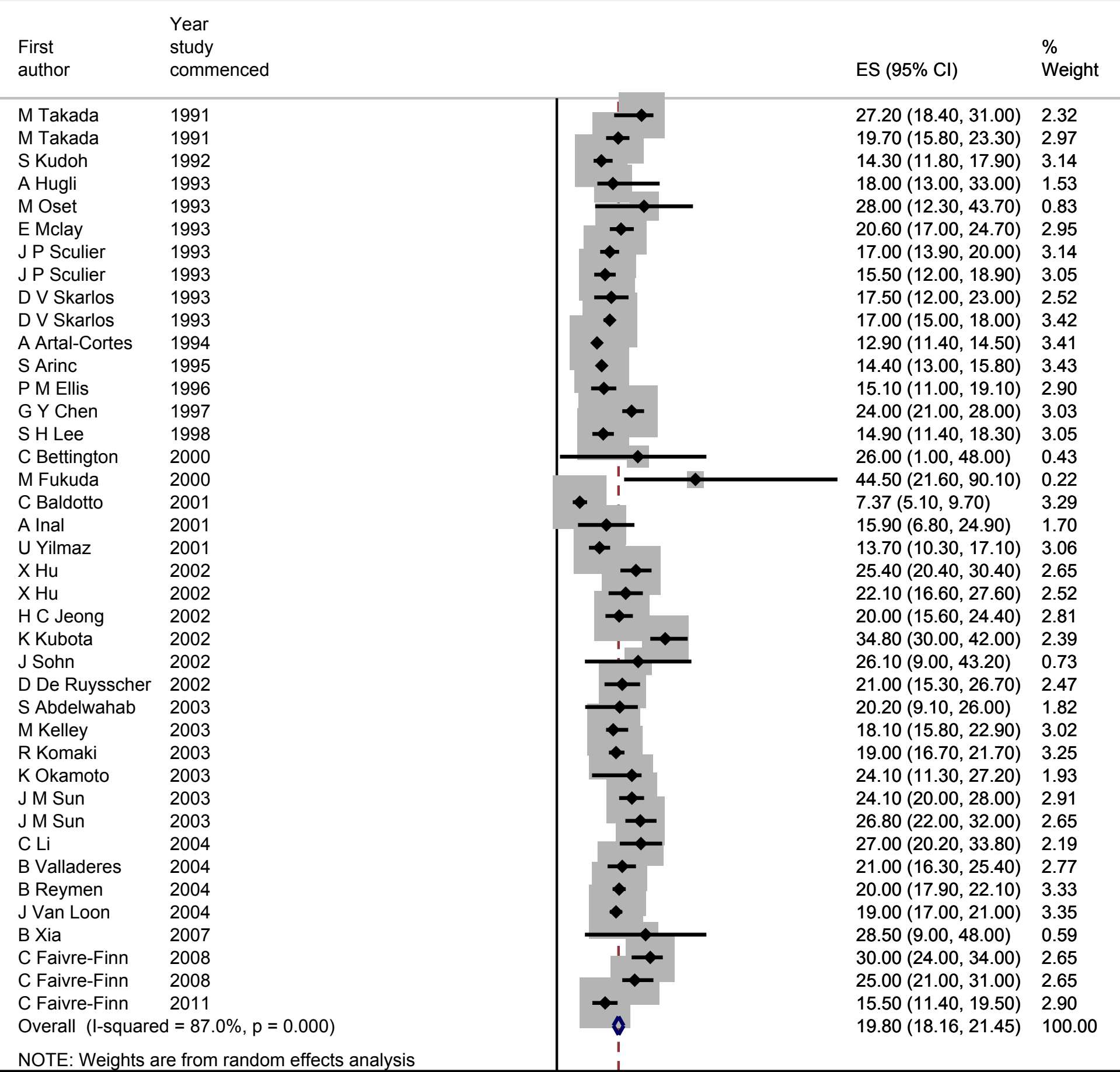


Survival in months for extensive stage by PCI

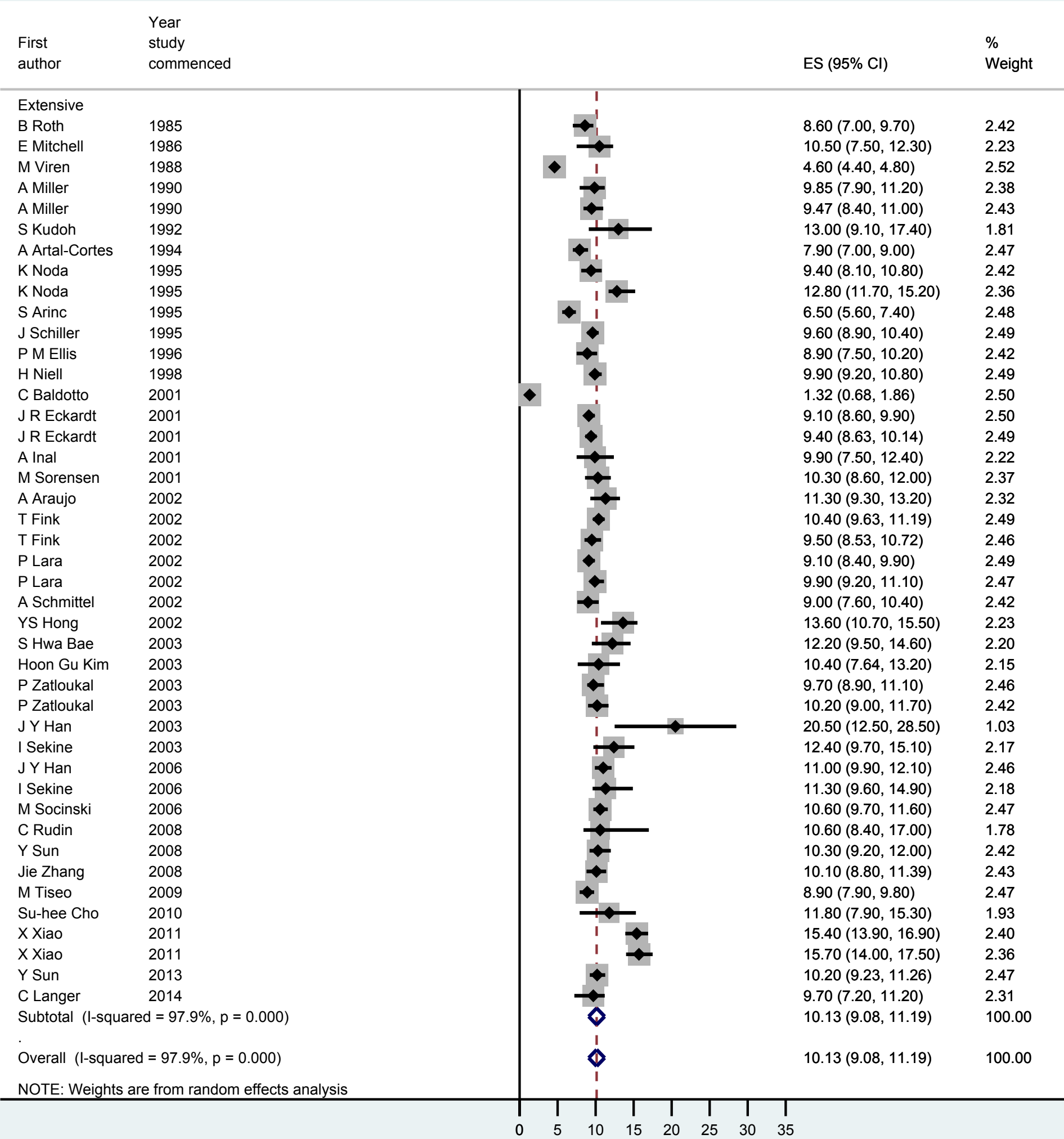
Median survival (sensitivity analysis)



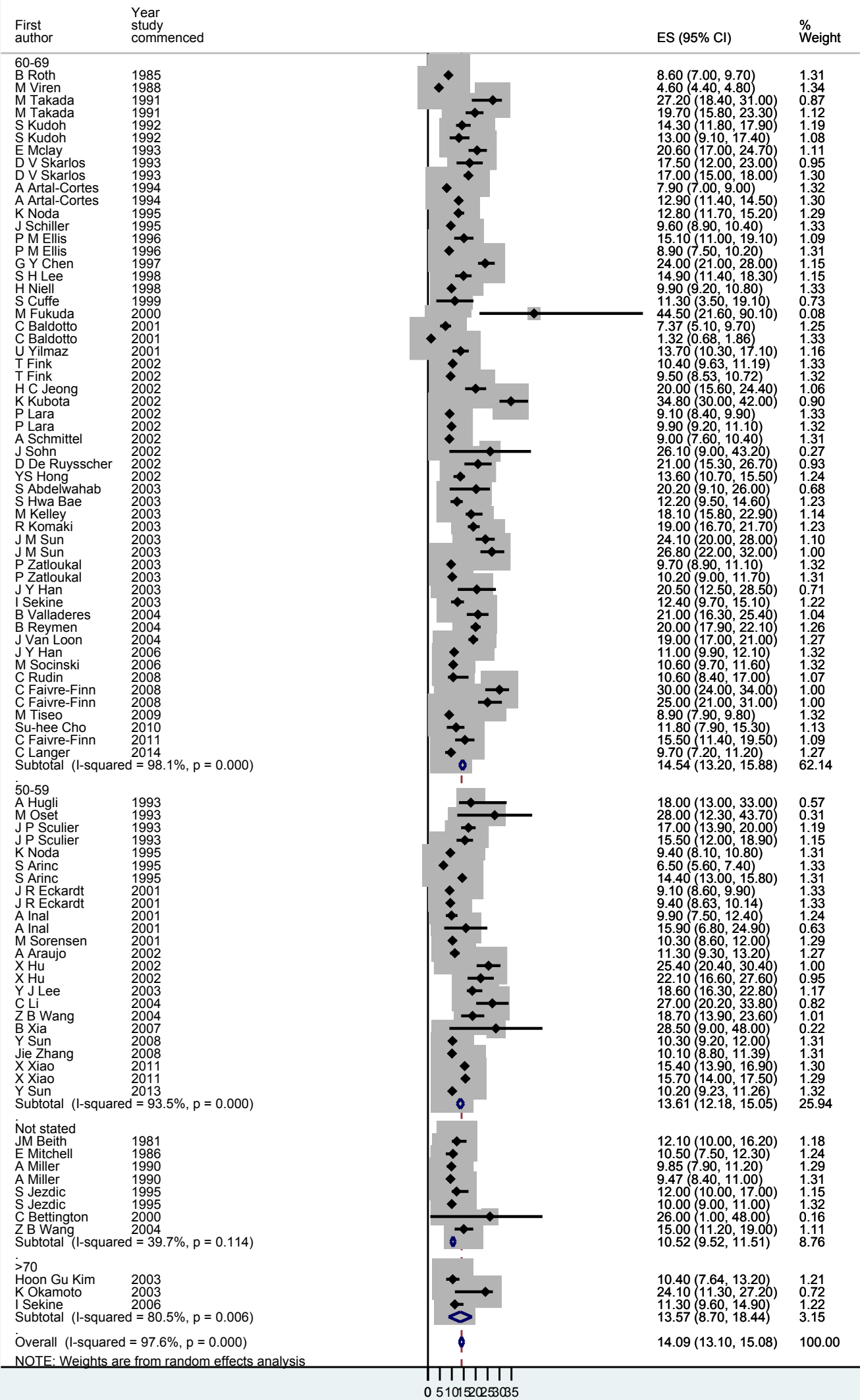
Median survival in months



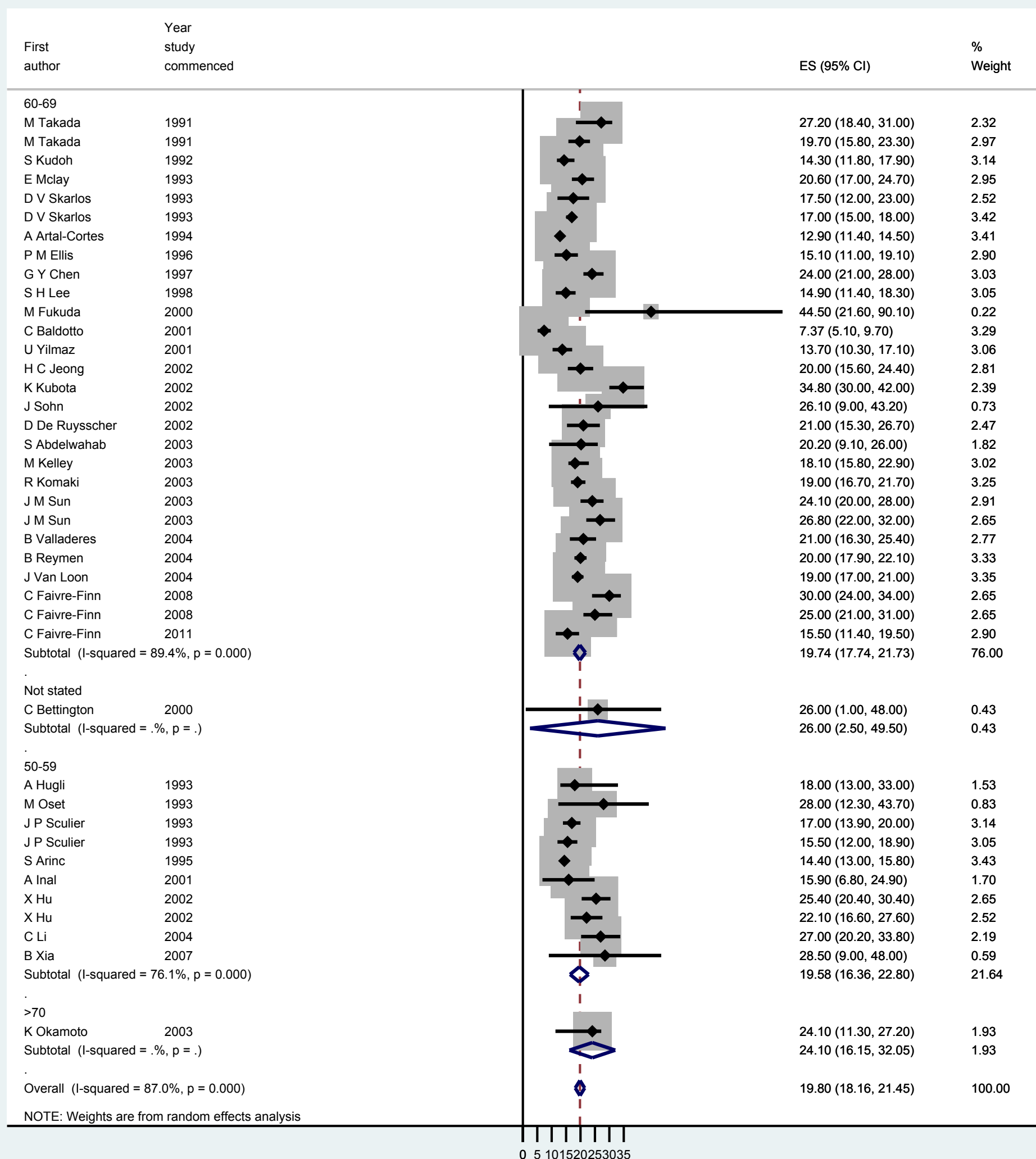
Survival in months for limited stage



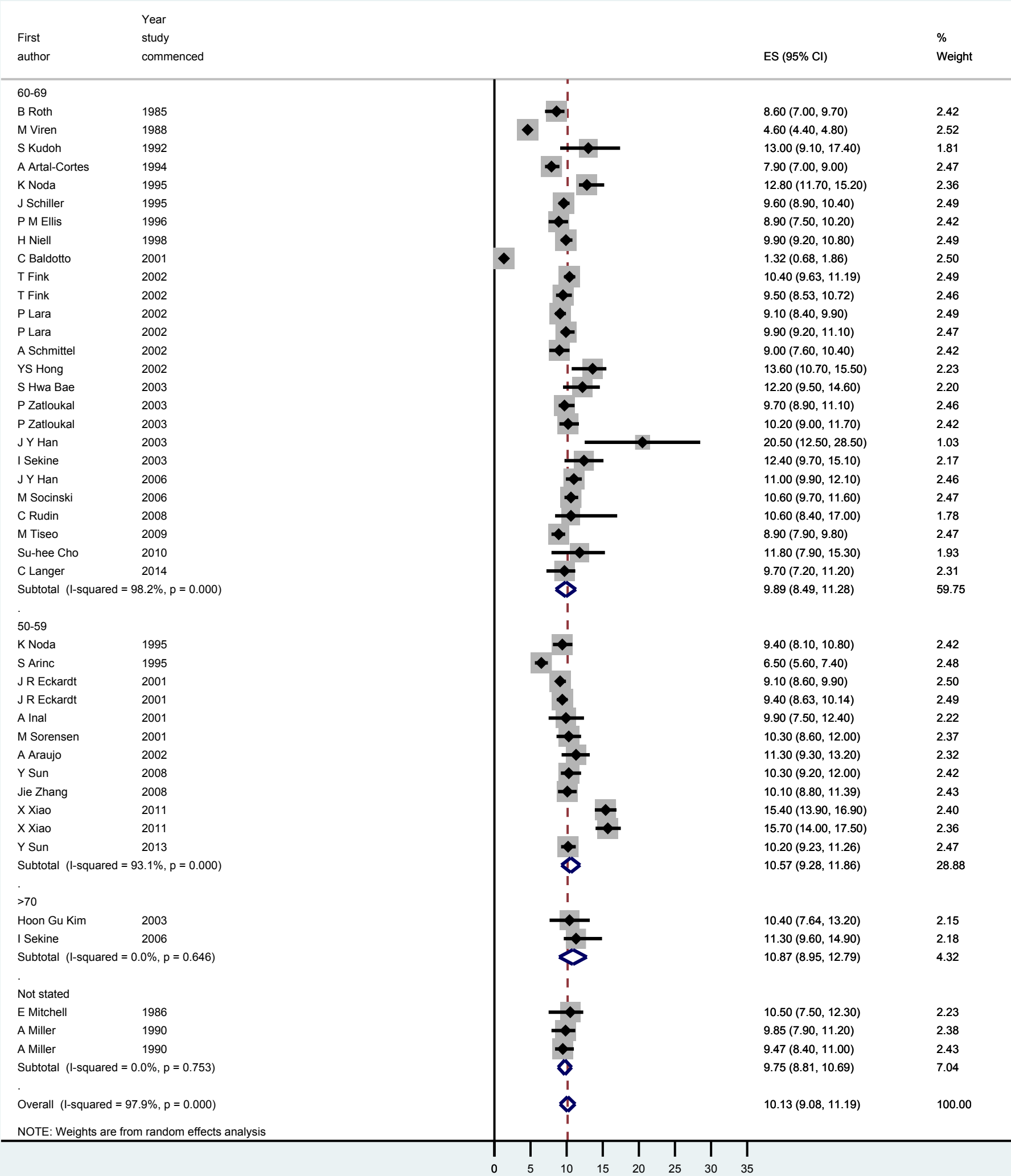
Survival in months for extensive stage



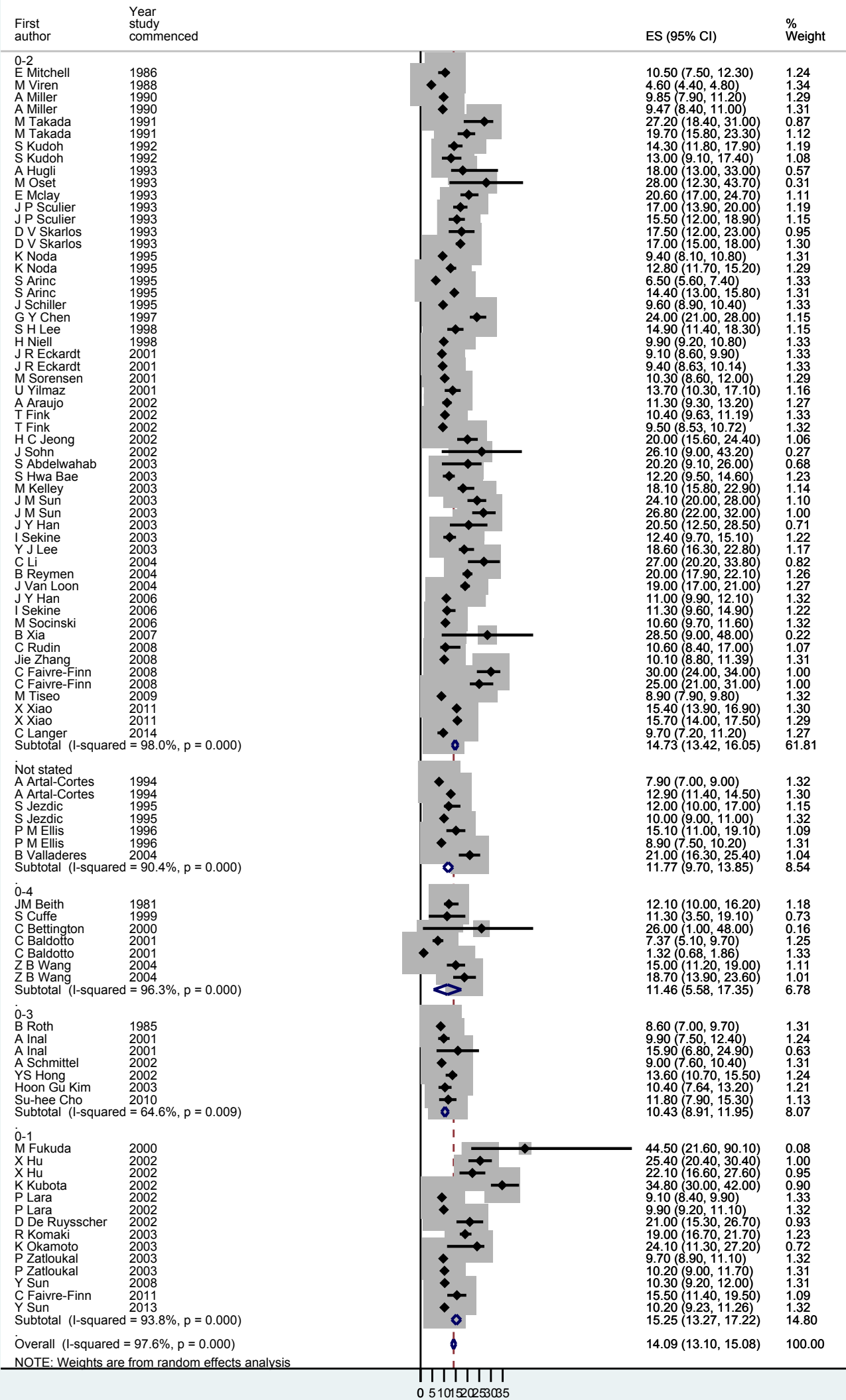
Median survival in months by median participant age



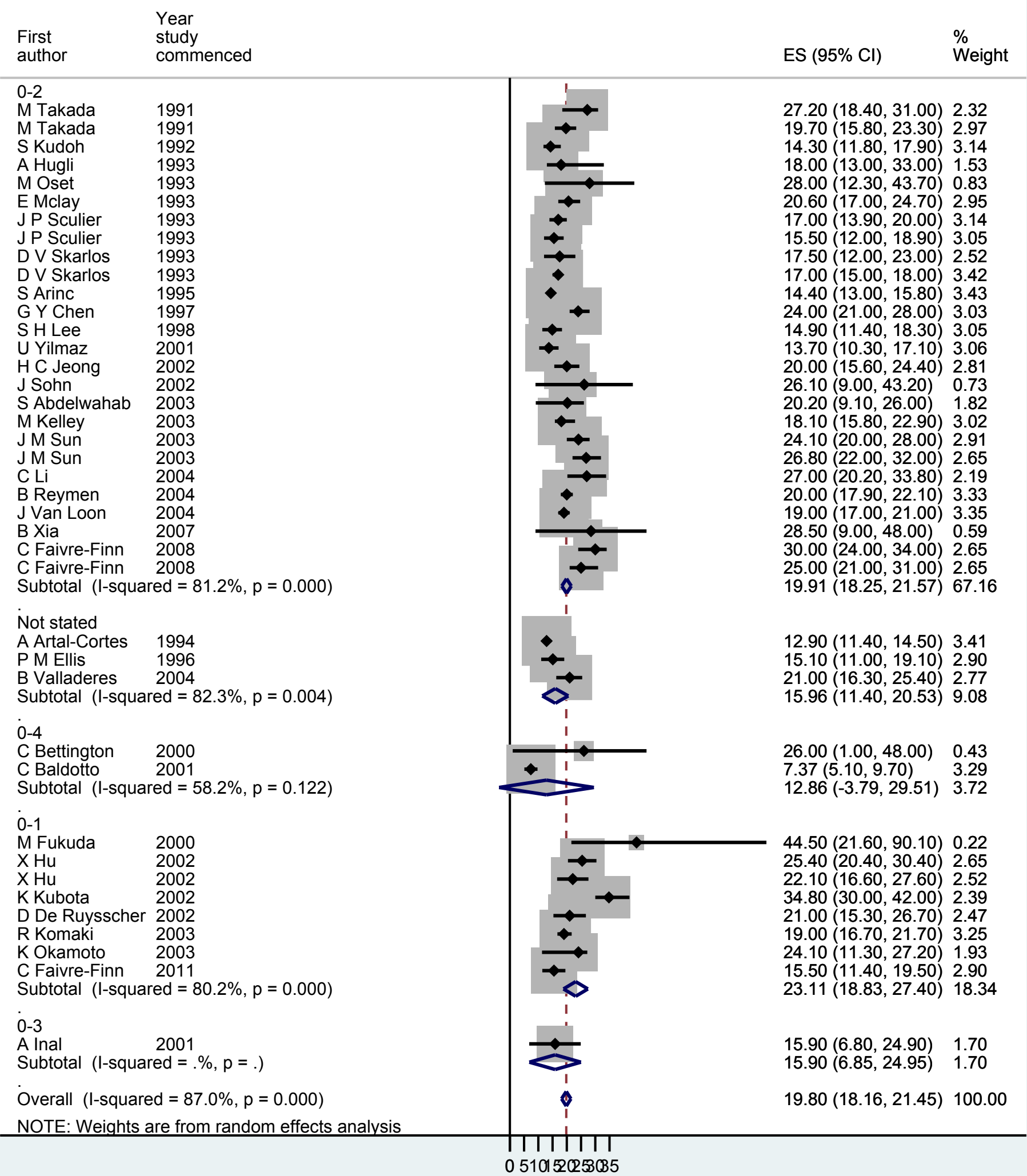
Survival in months for limited stage by median participant age



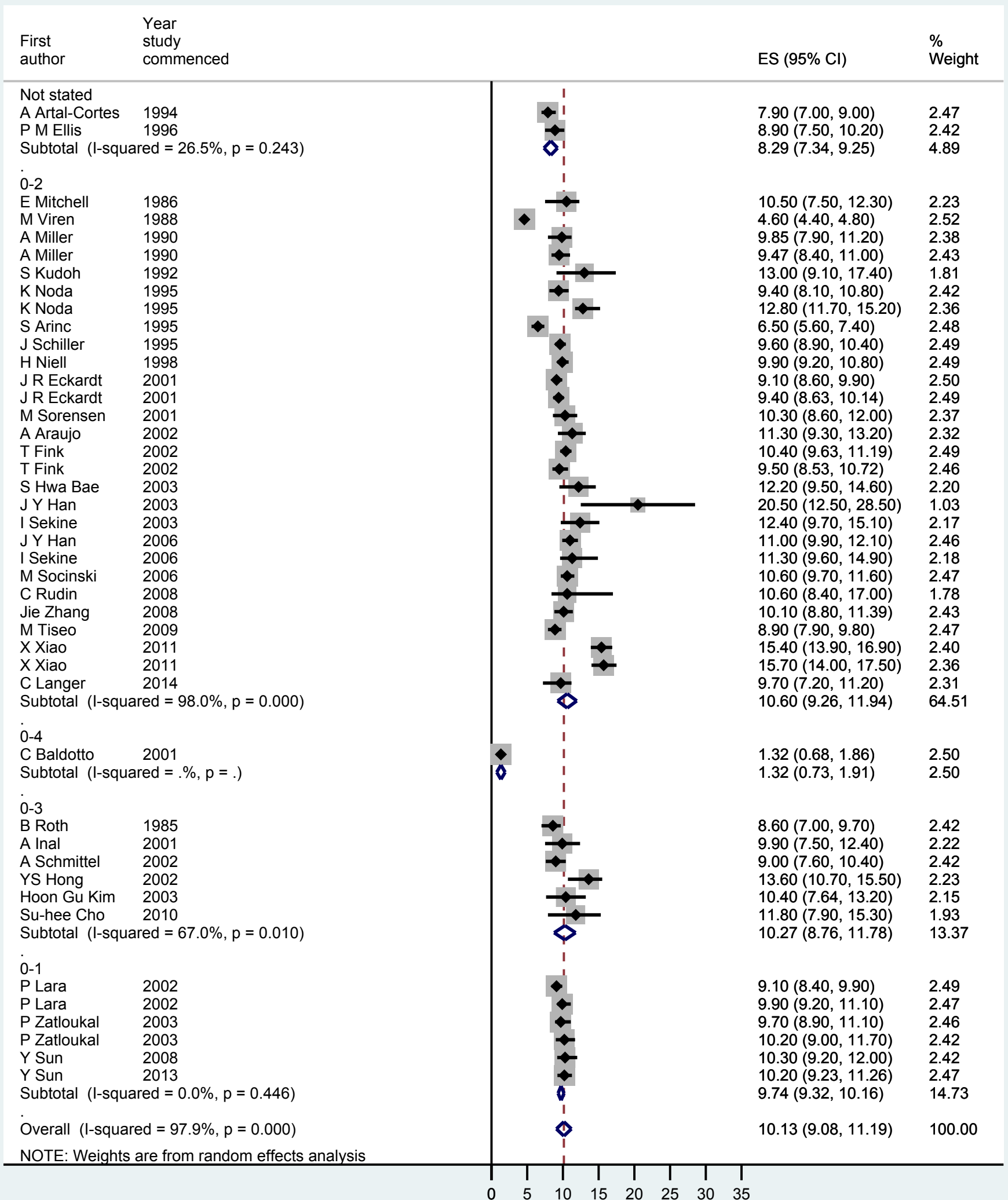
Survival in months for extensive stage by median participant age



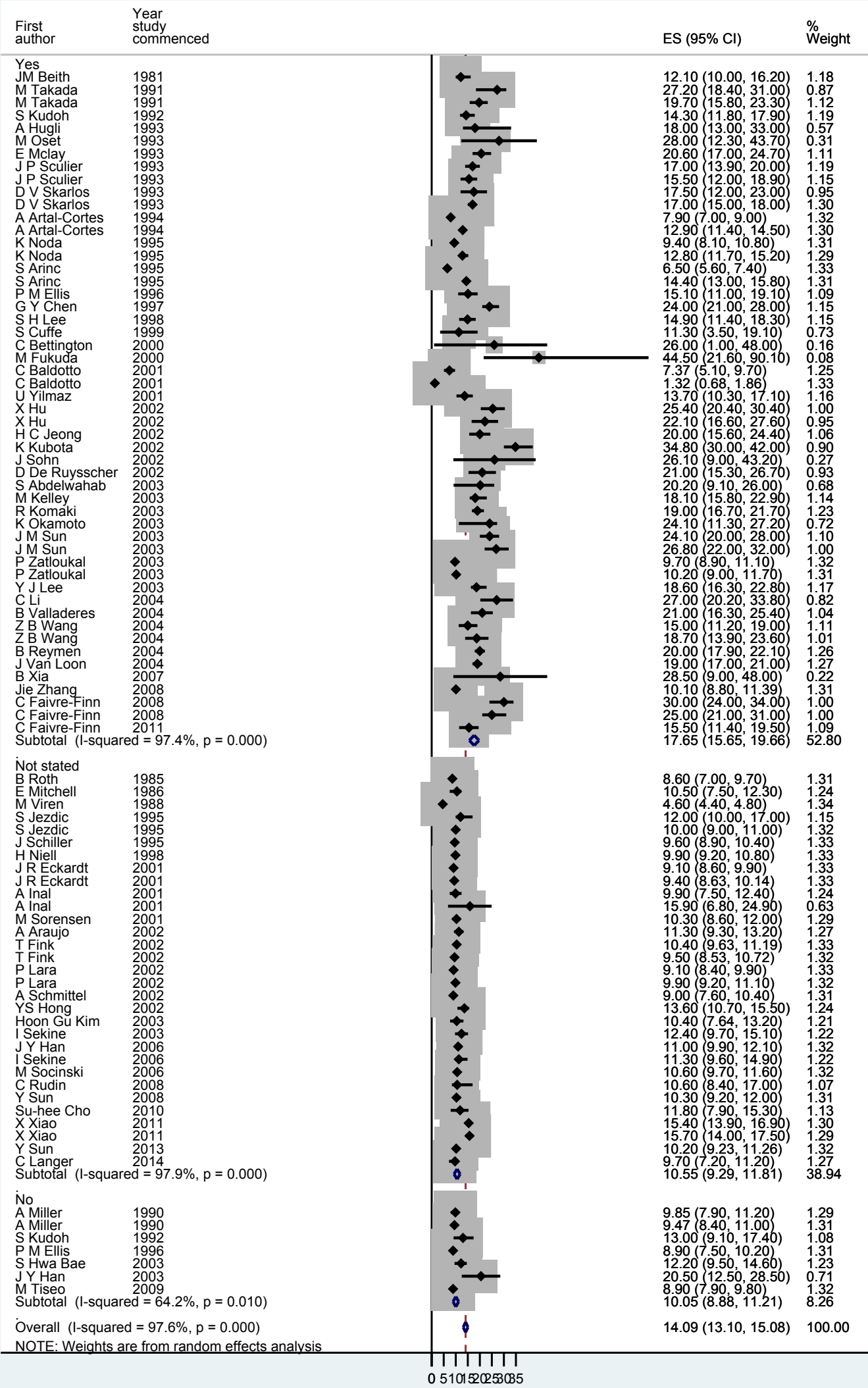
Median survival in months by PS



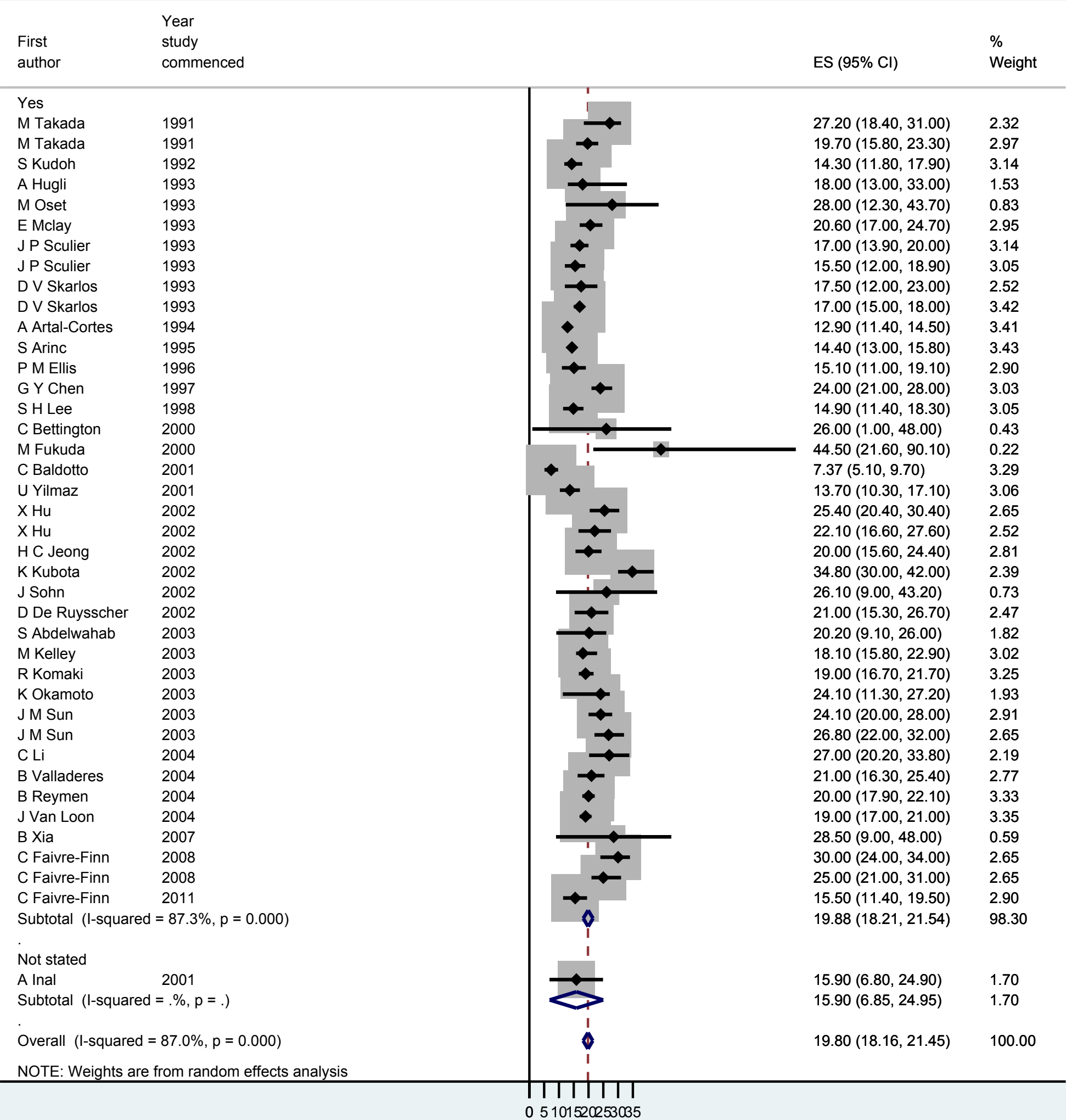
Survival in months for limited stage by PS



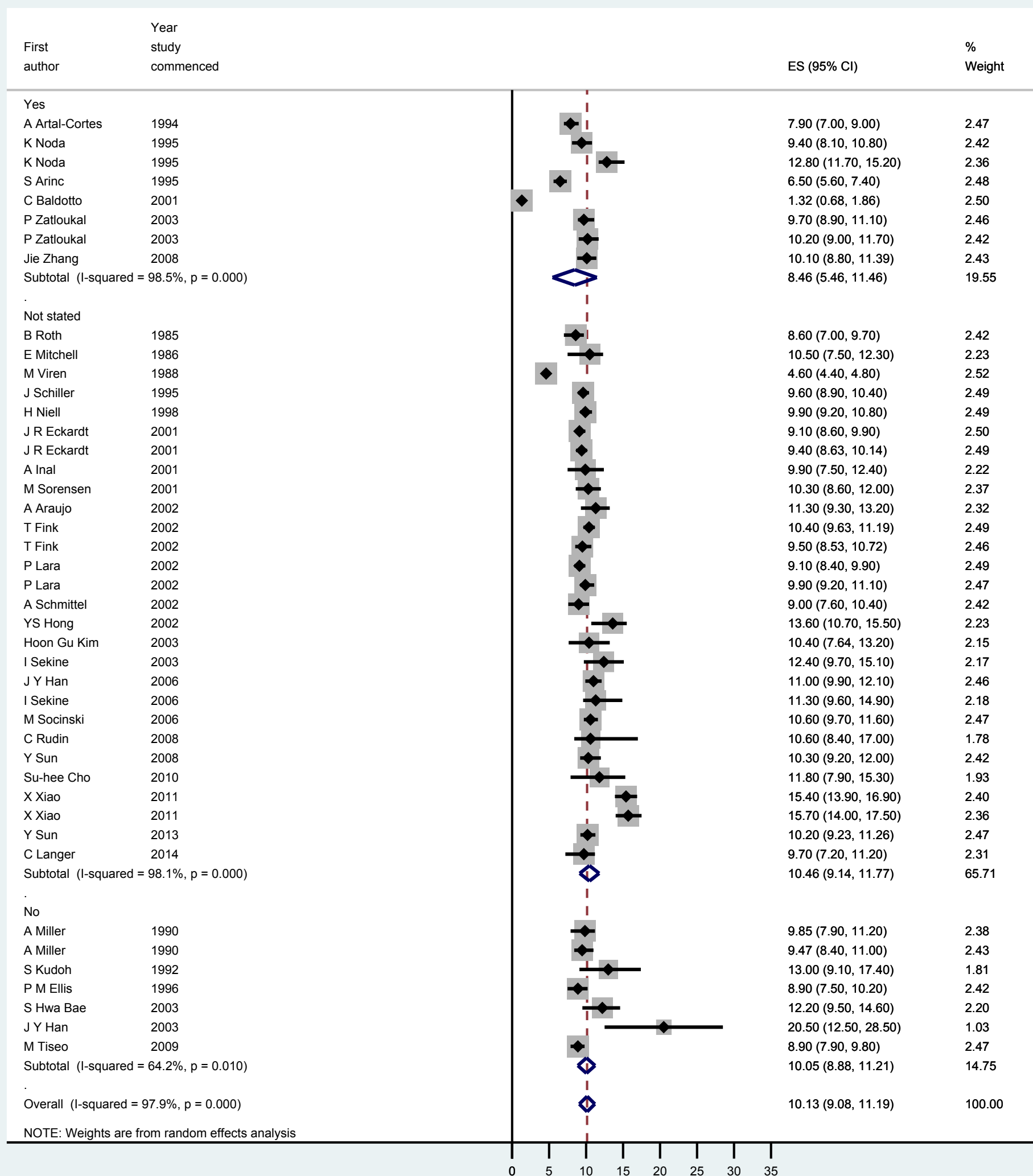
Survival in months for extensive stage by PS



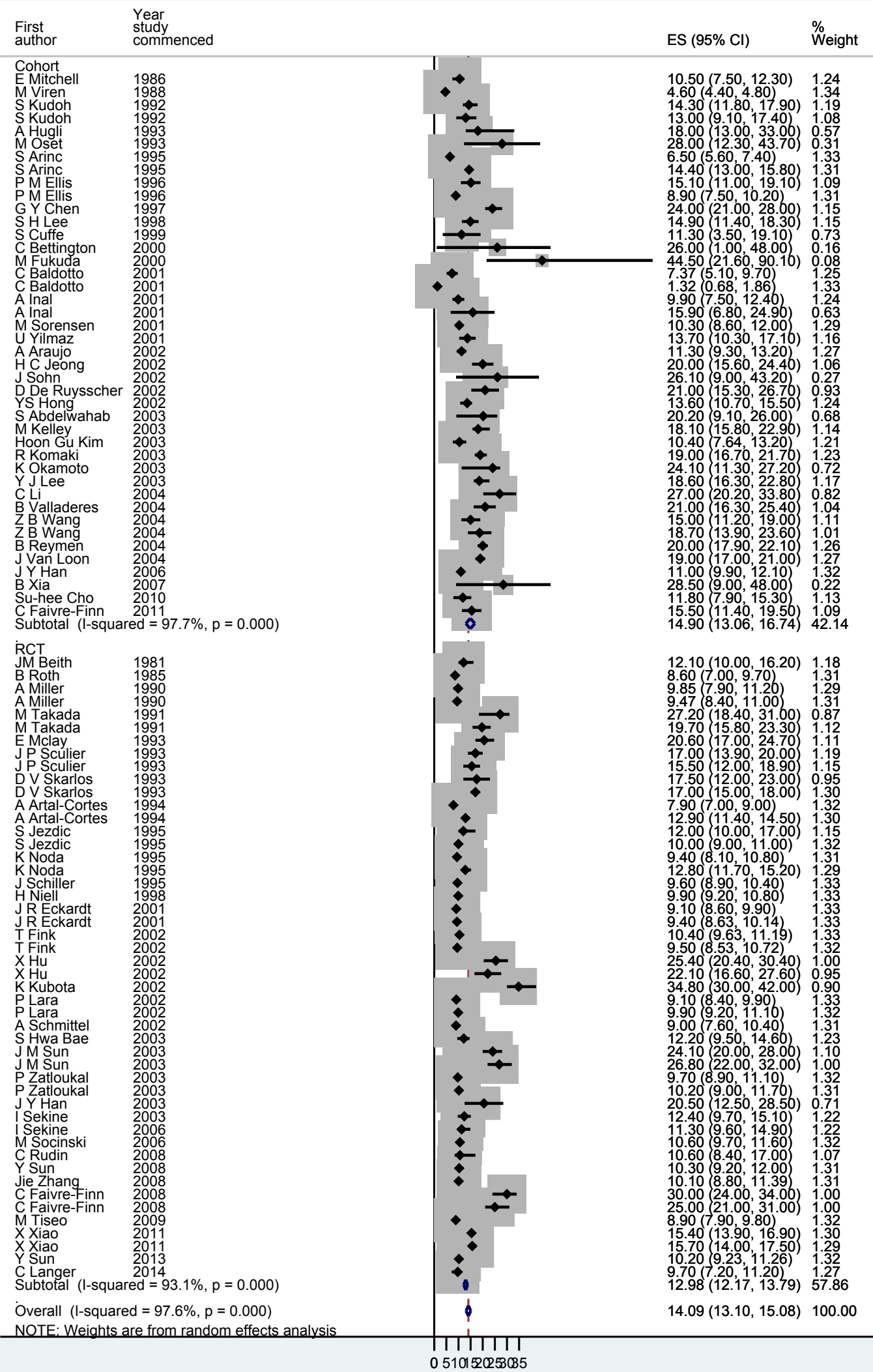
Median survival in months by radiotherapy



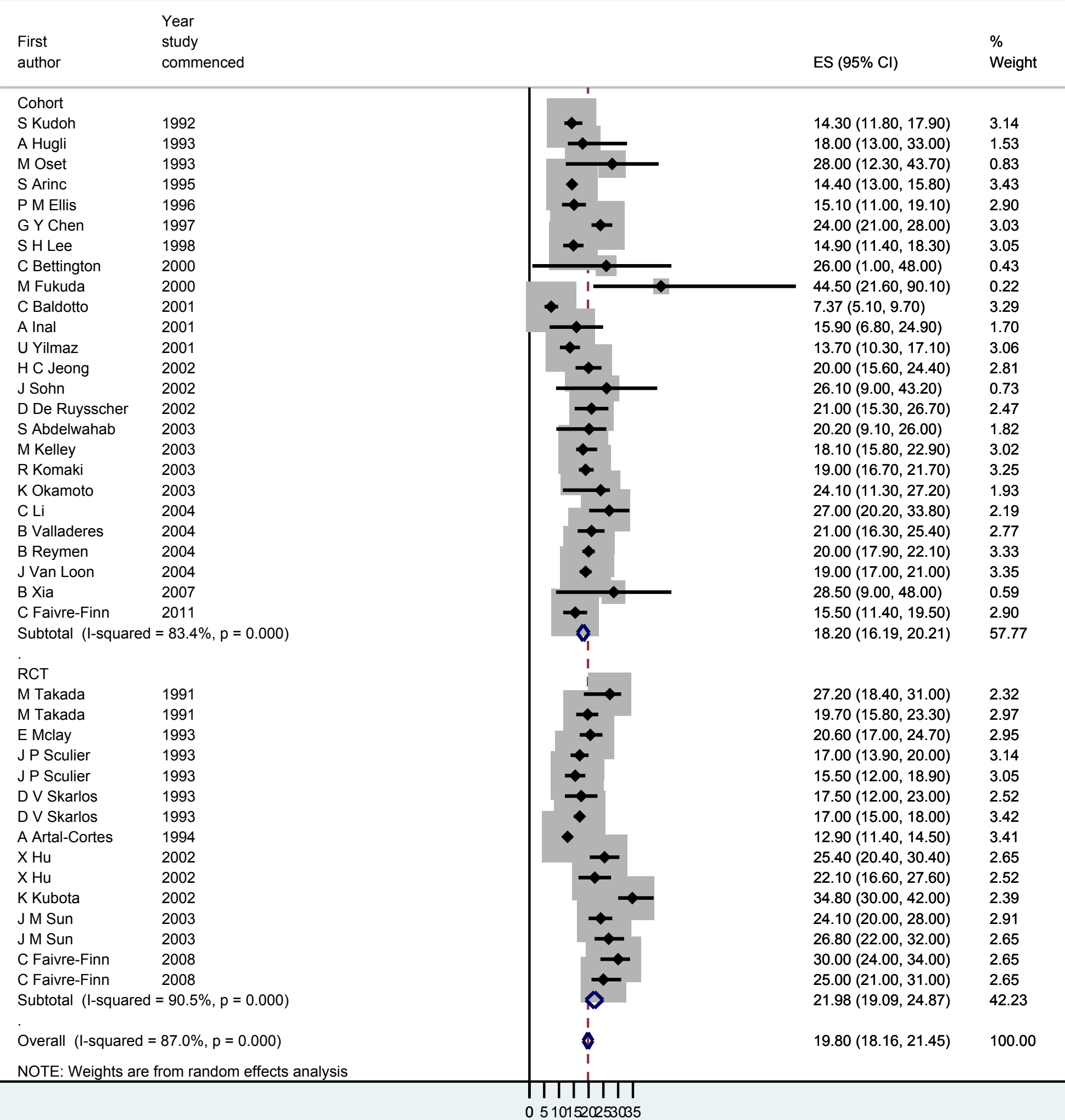
Survival in months for limited stage by radiotherapy



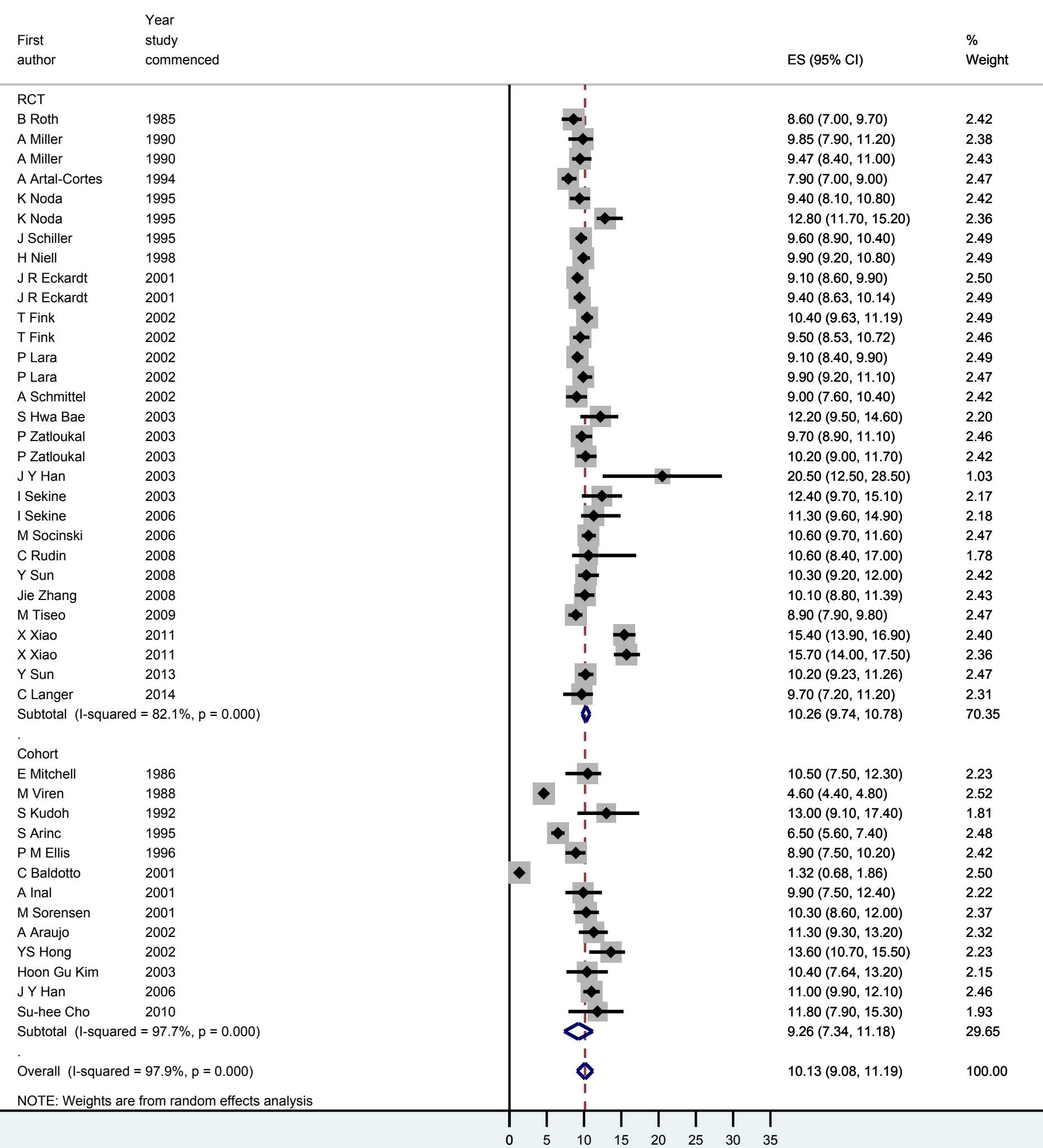
Survival in months for extensive stage by radiotherapy



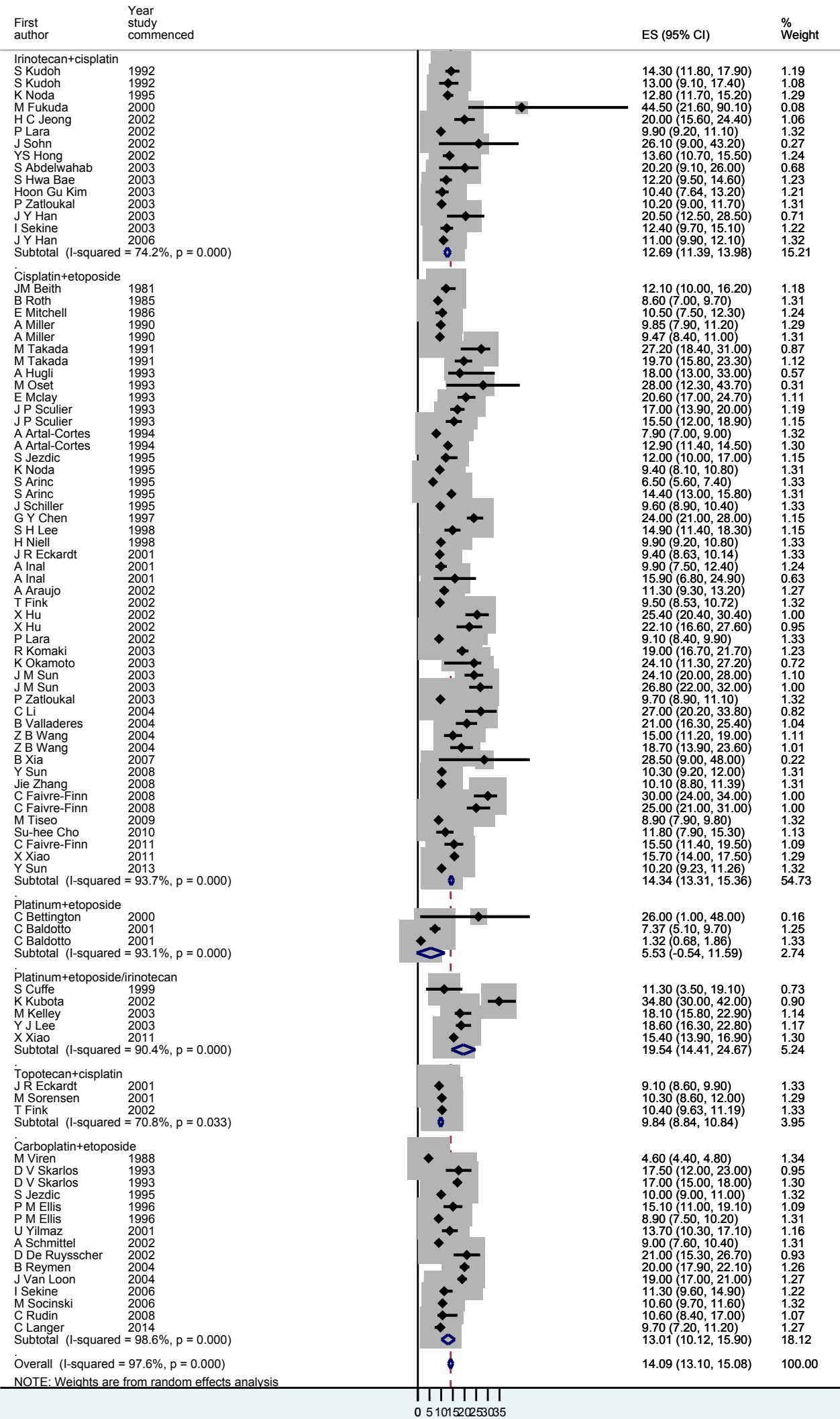
Median survival in months by study design



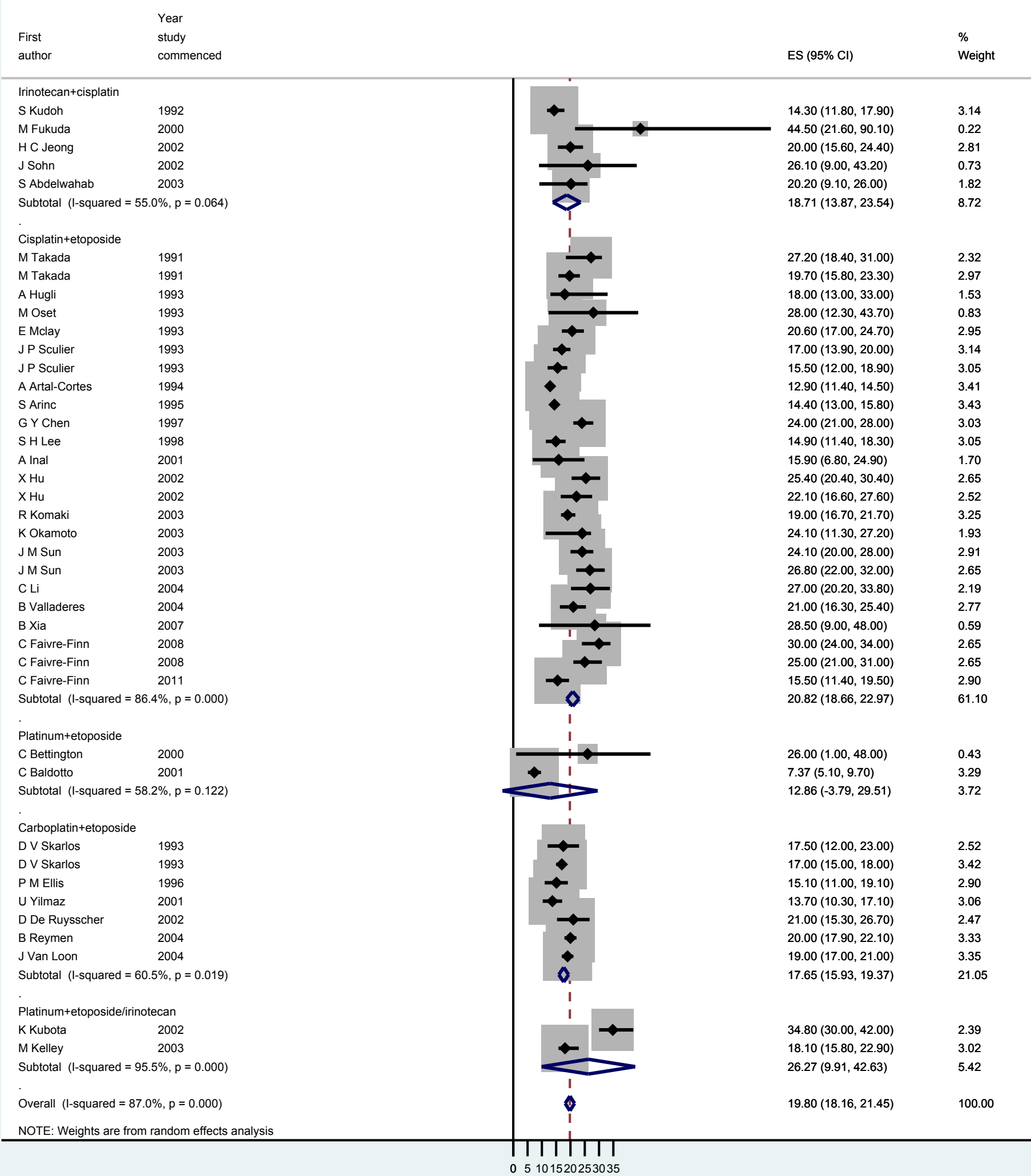
Survival in months for limited stage by study design



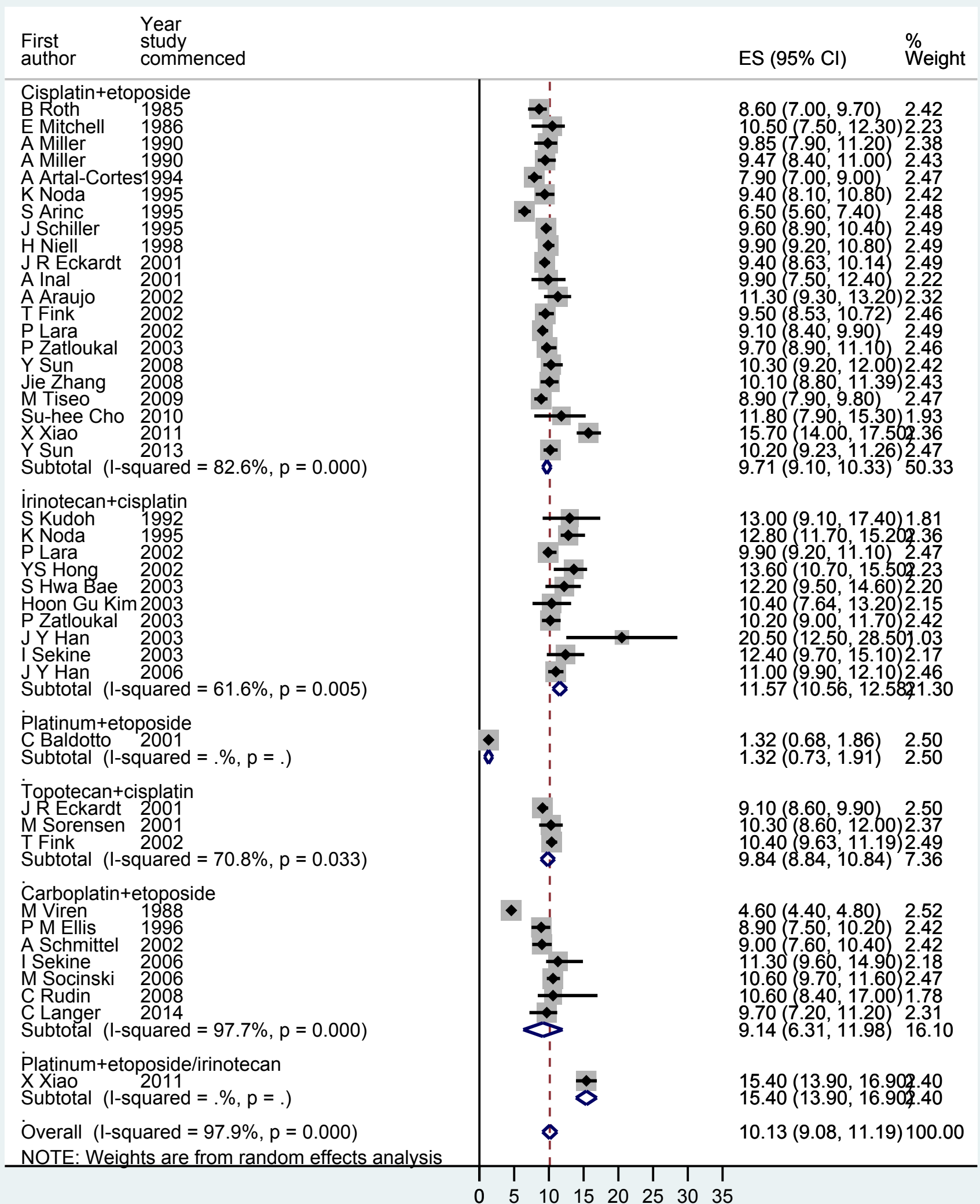
Survival in months for extensive stage by study design



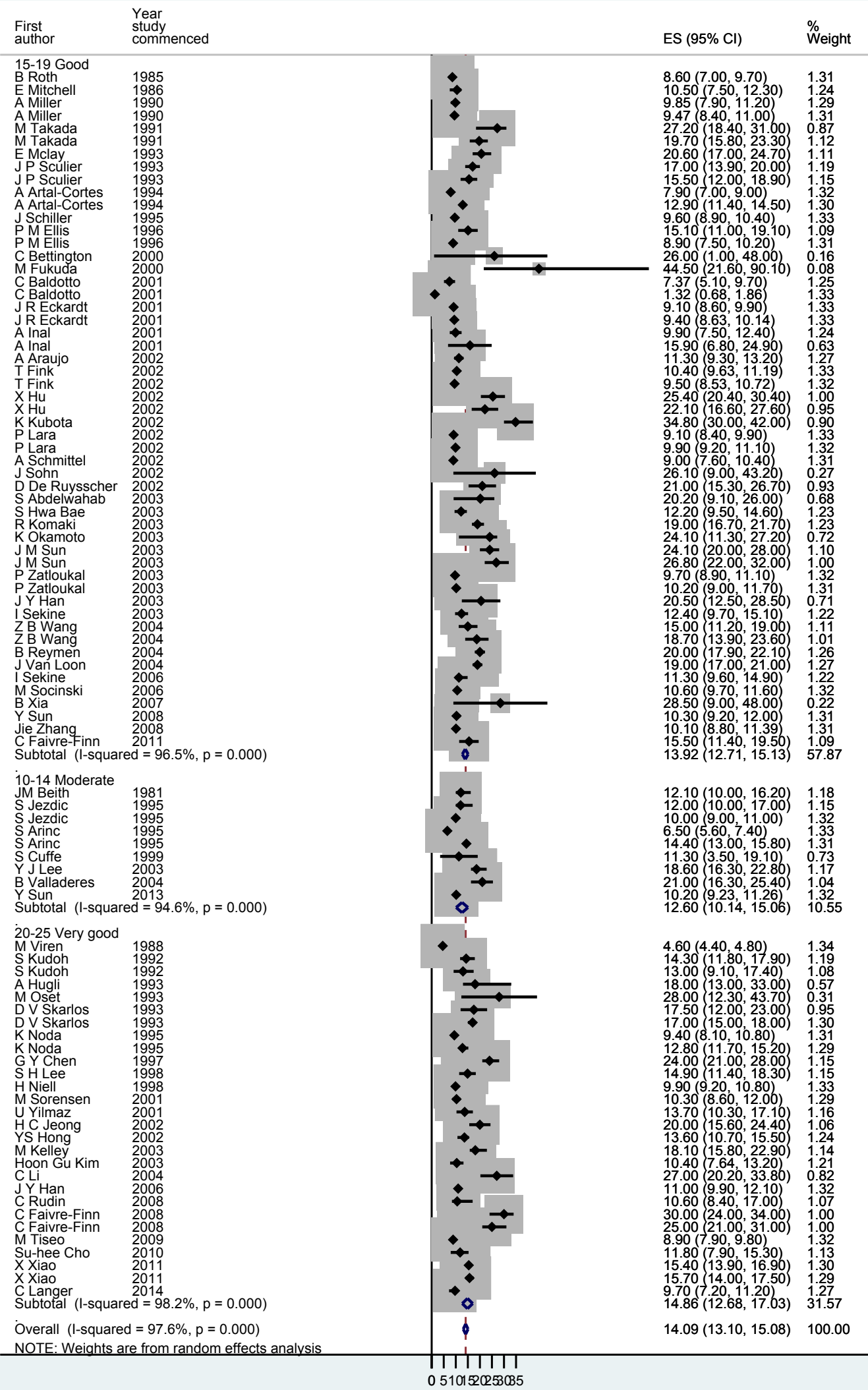
Median survival in months by chemotherapy



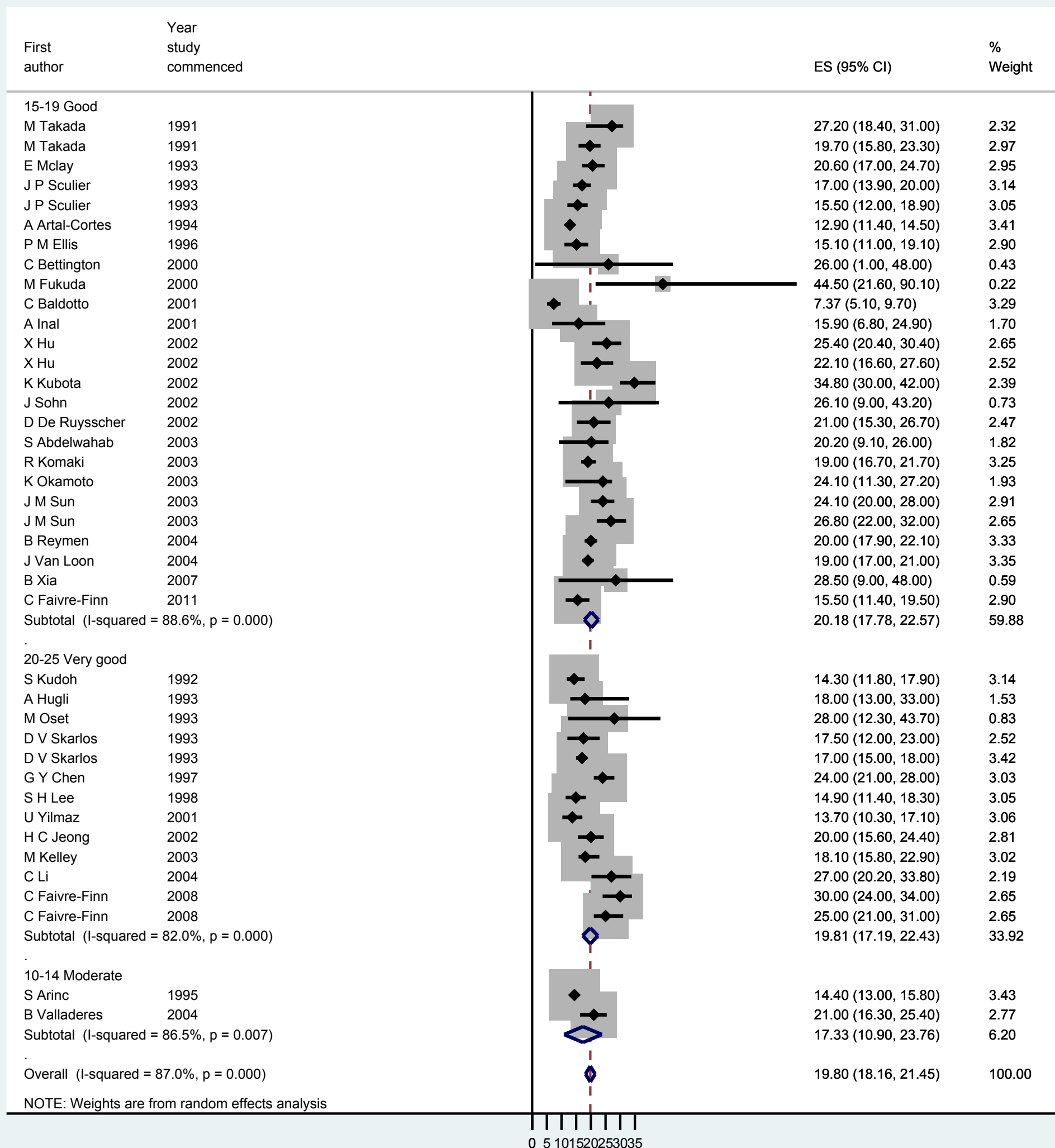
Survival in months for limited stage by chemotherapy



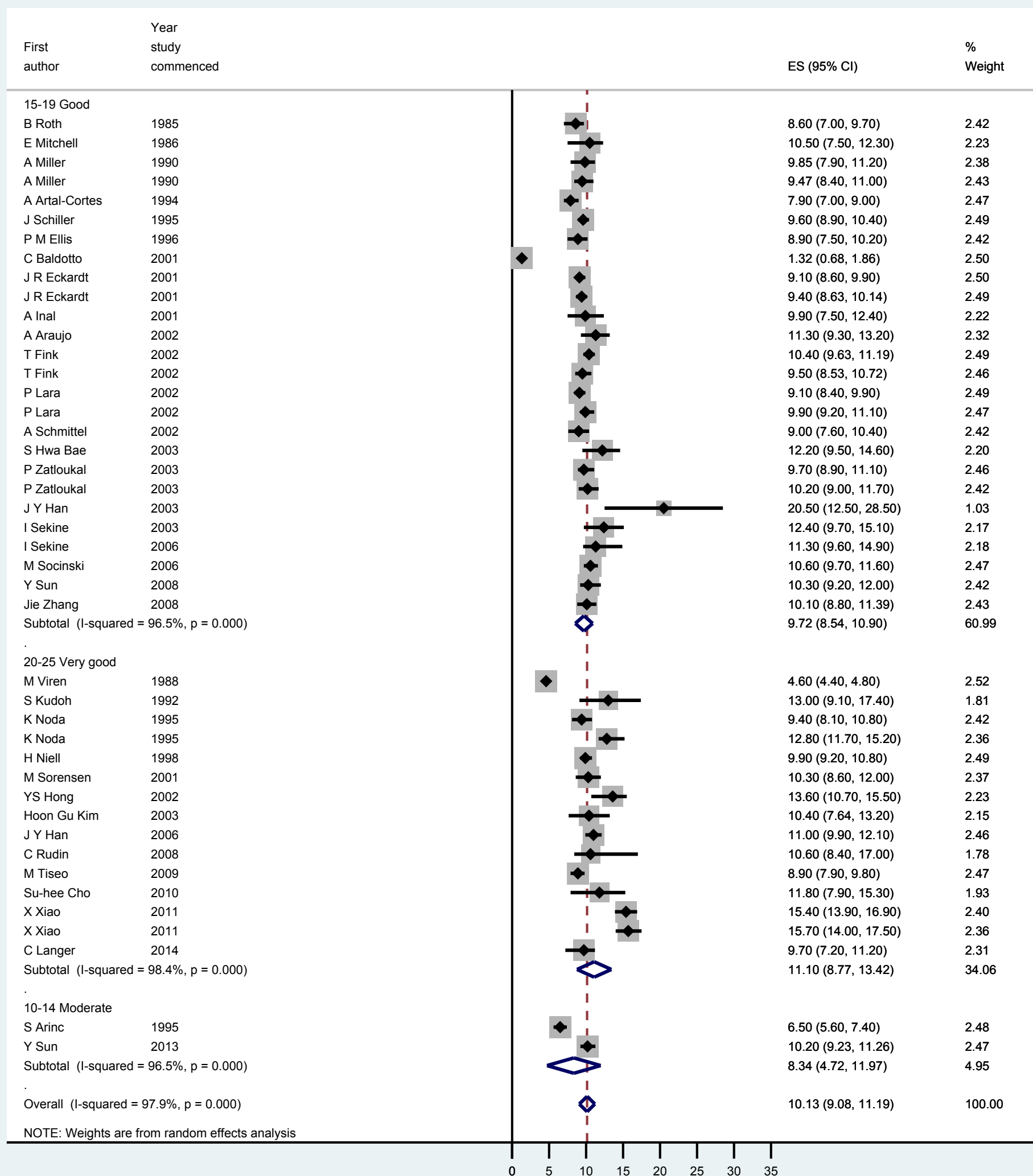
Survival in months extensive stage by chemotherapy



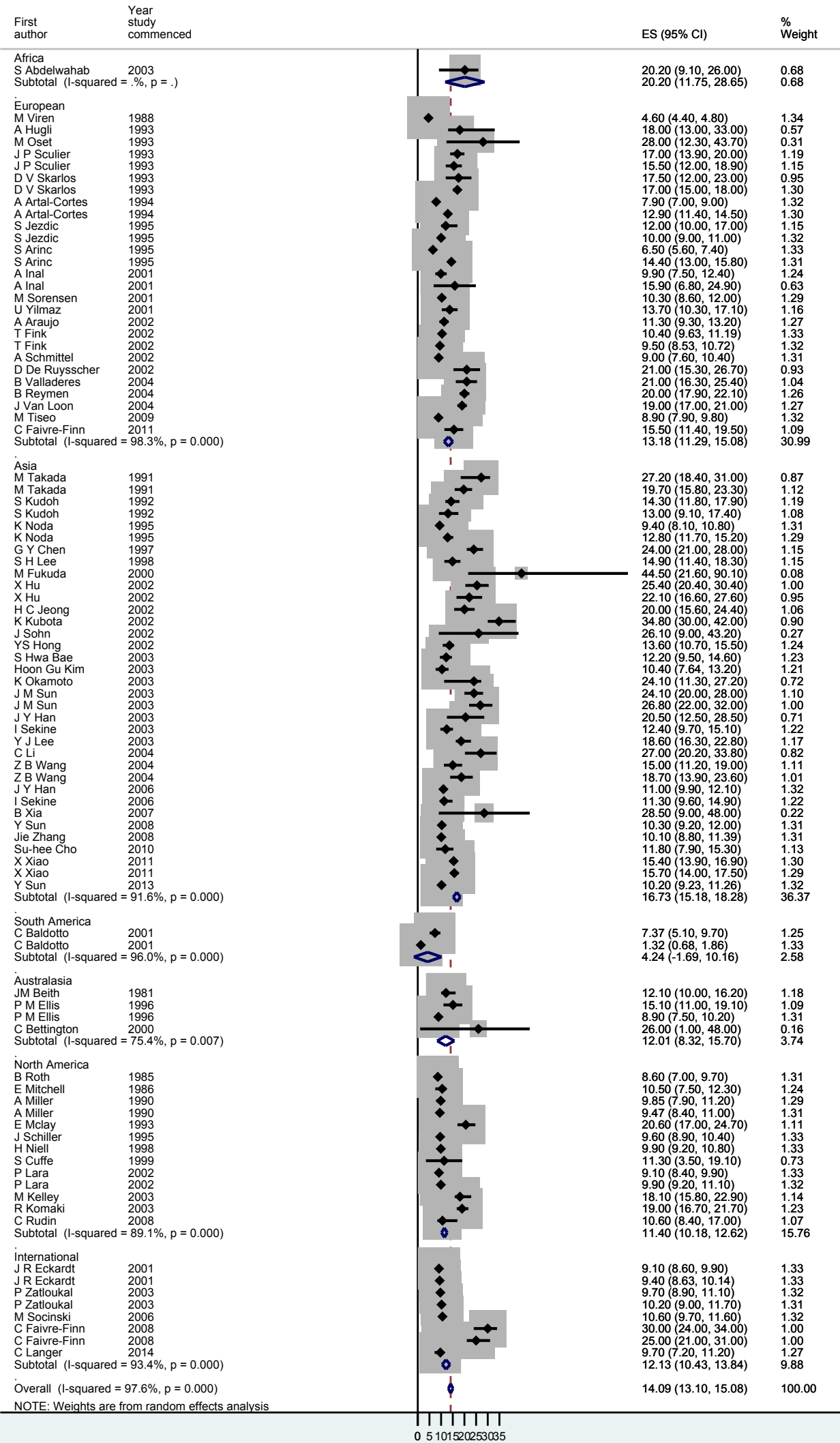
Median survival in months by quality score



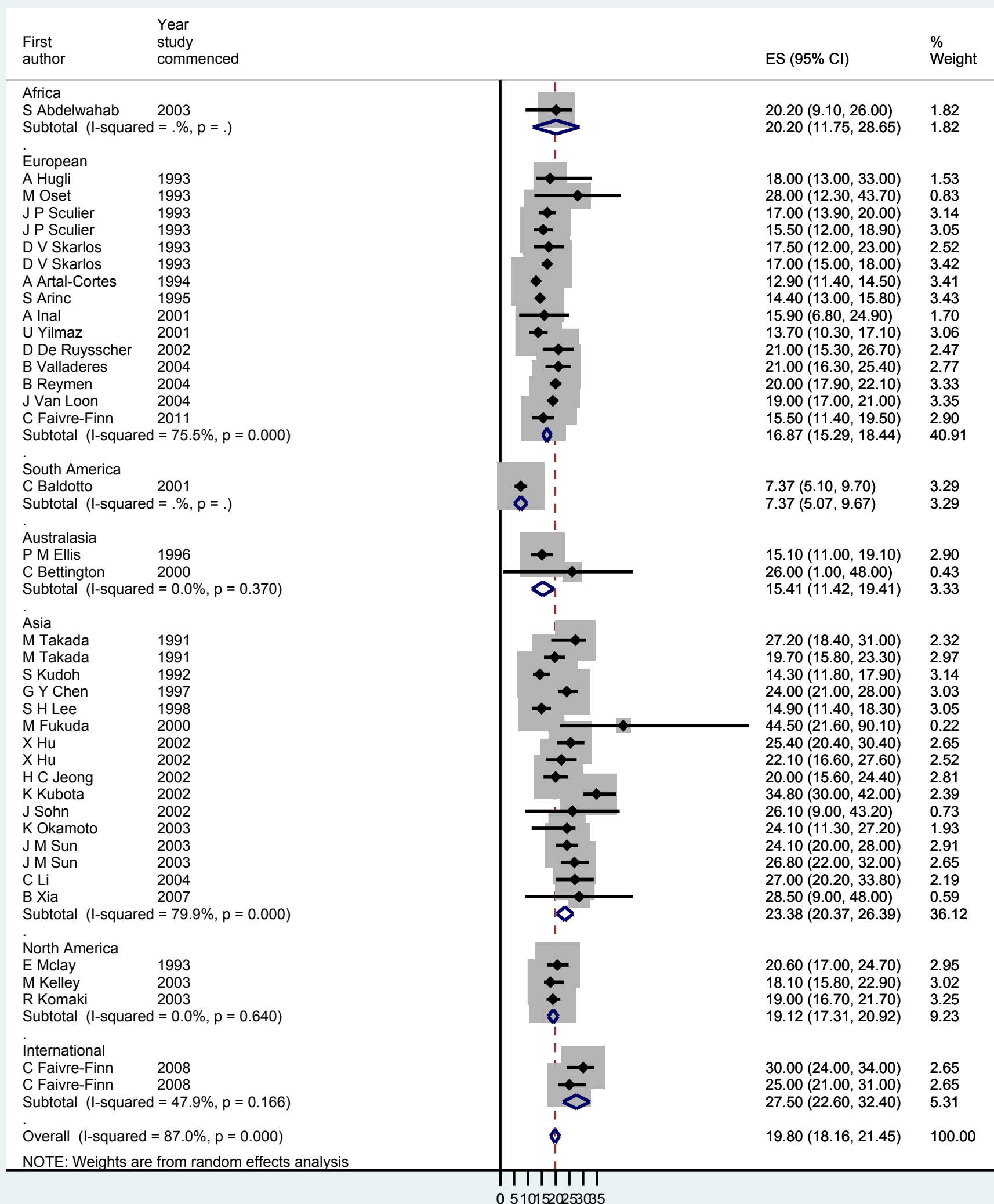
Survival in months for limited stage by quality score



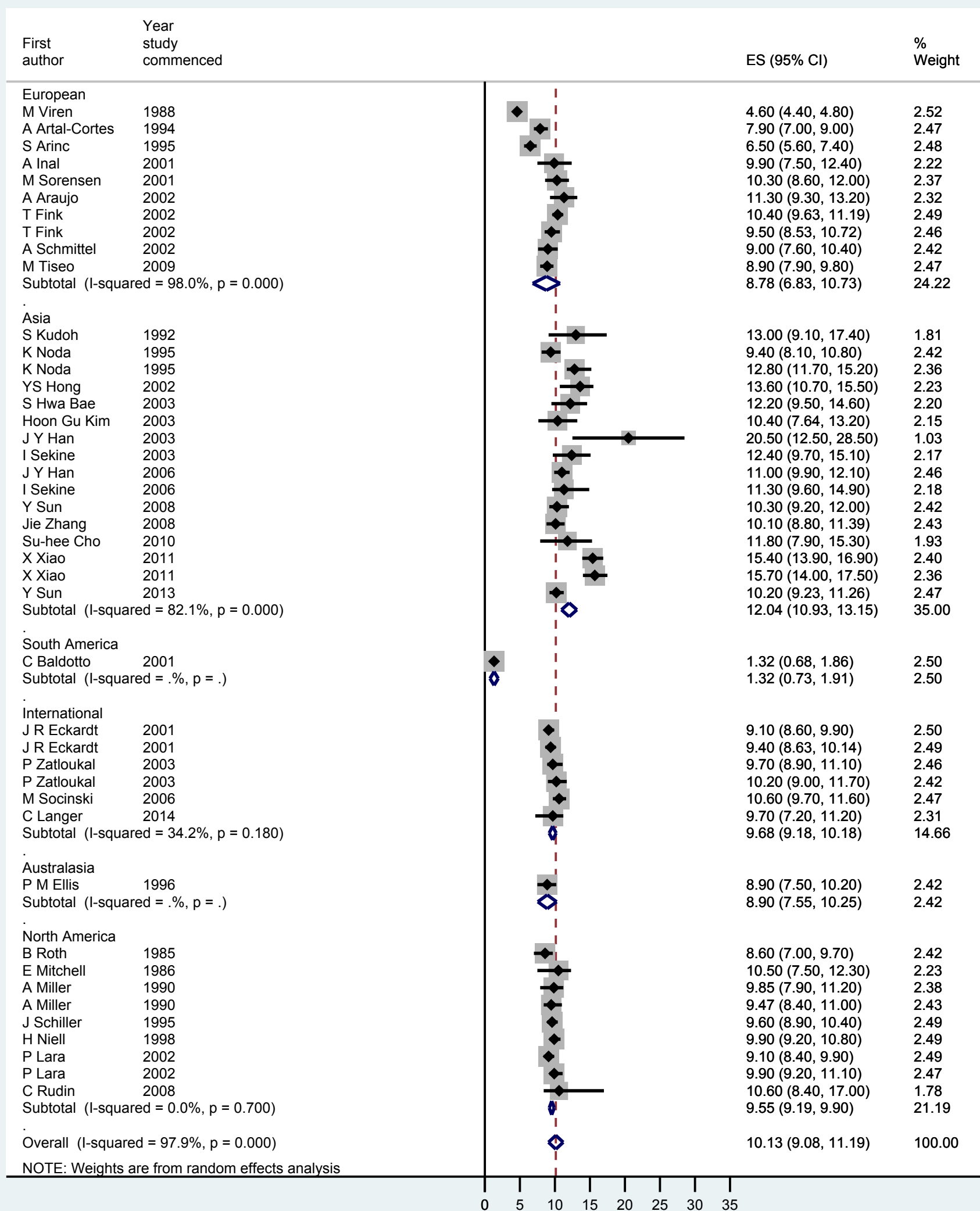
Survival in months for extensive stage by quality score



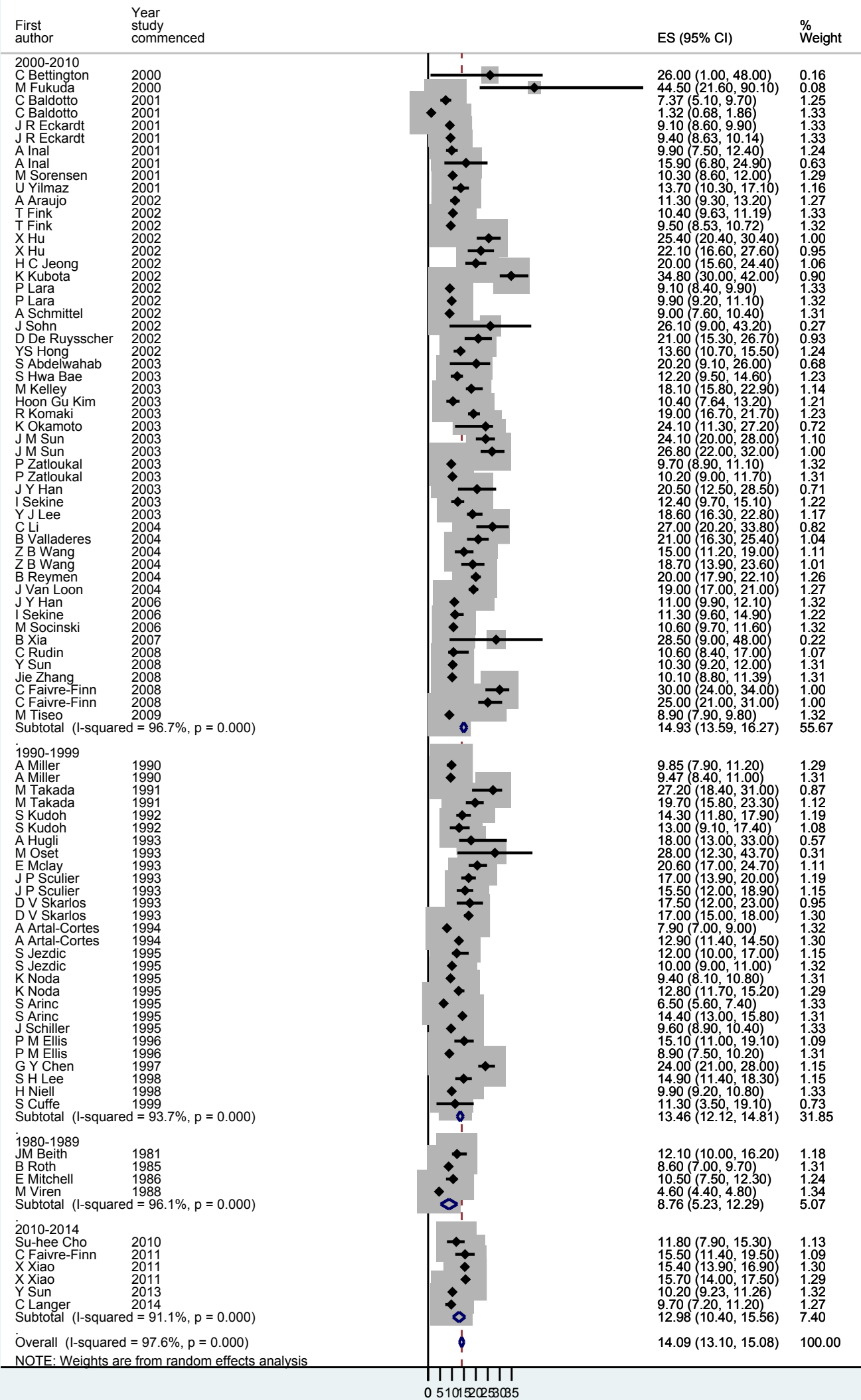
Median survival in months by region



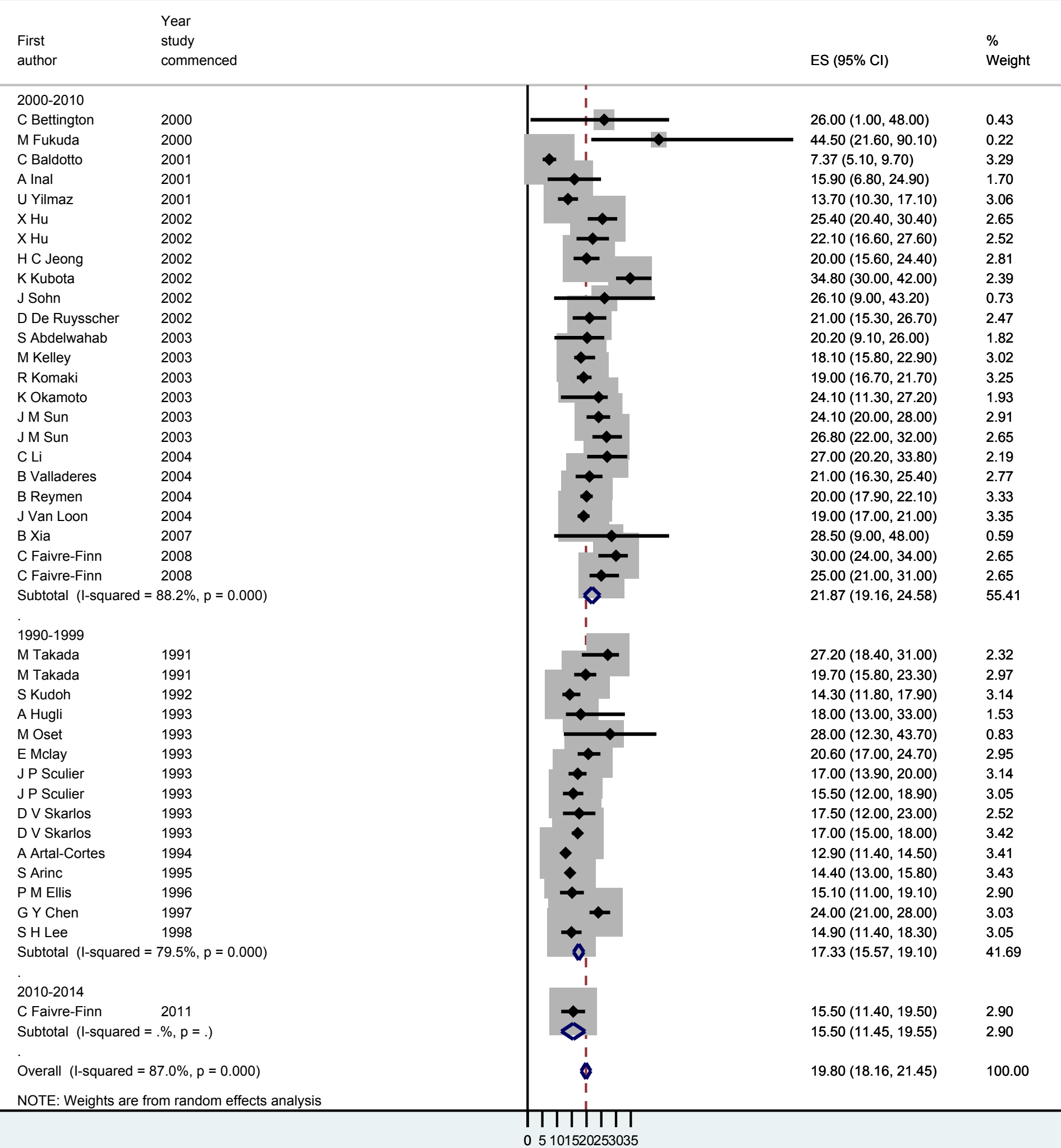
Survival in months for limited stage by region



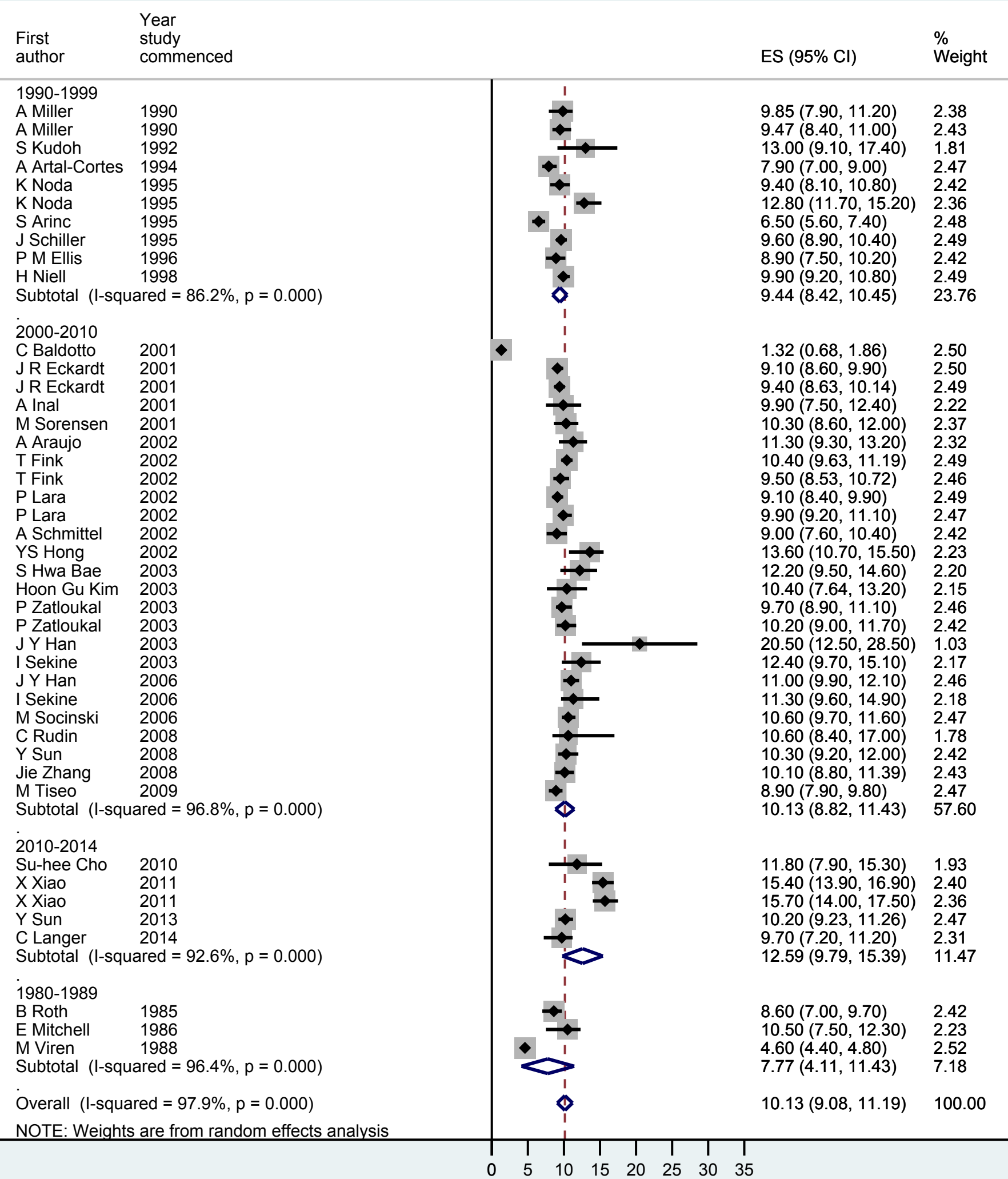
Survival in months for extensive stage by region



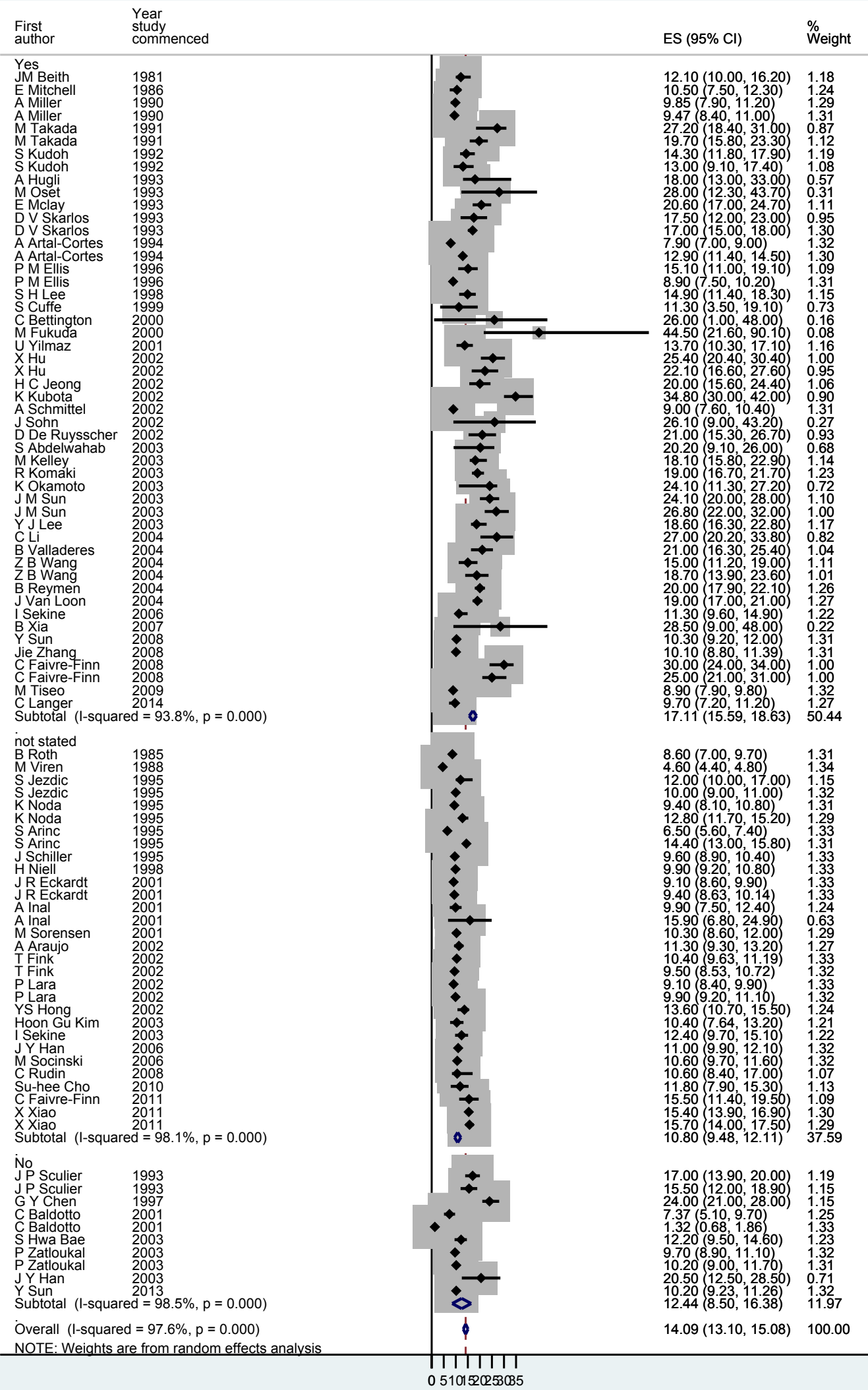
Median survival in months by study year



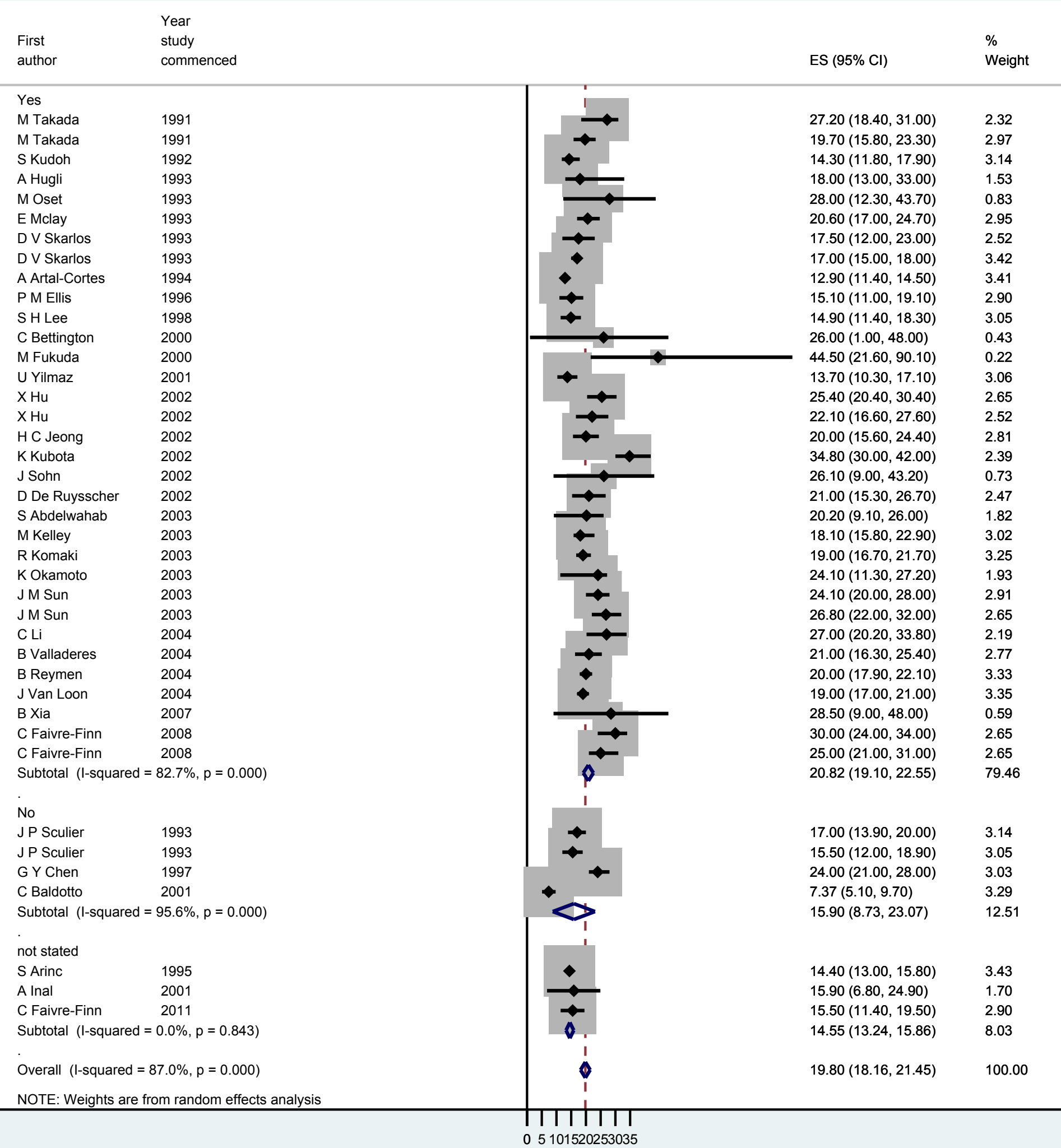
Survival in months for limited stage by study year



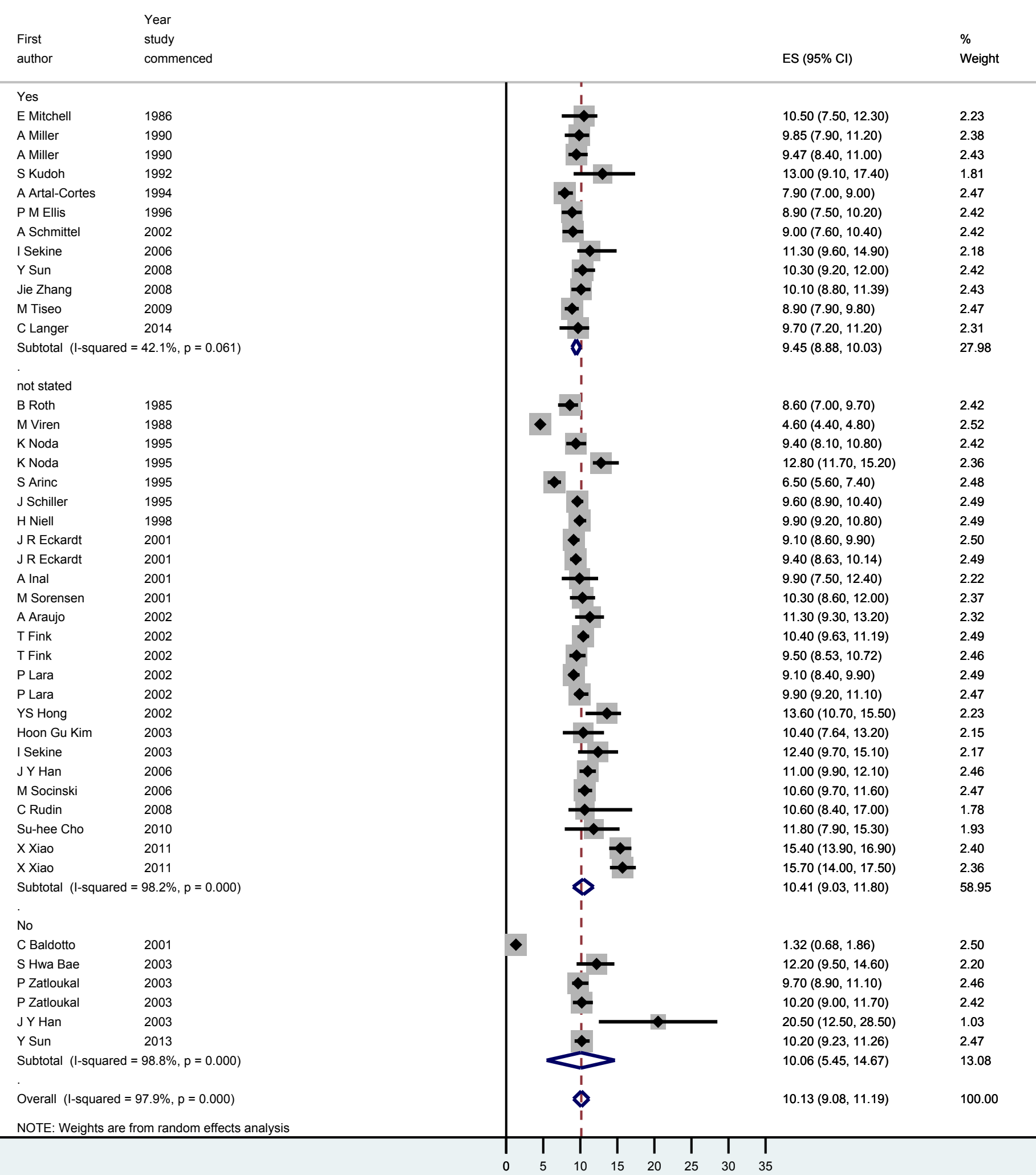
Survival in months for extensive stage by study year



Median survival in months by PCI



Survival in months for limited stage by PCI



Survival in months for extensive stage by PCI

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