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Positron Emission Tomography and Computed Tomographic Imaging Prior to Radiotherapy for Lung Cancer

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Positron Emission Tomography and Computed Tomographic Imaging Prior to Radiotherapy for Lung Cancer [PET/CT inför strålbehandling av lungcancer]

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1. Abstract

Background
Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) comprise the great majority of all lung cancer and have a high risk of premature death. Many patients are diagnosed with a severity of their disease that is too advanced for surgery but without distant metastatic spread. They can be treated with curative intent with high dose irradiation and chemotherapy.

A proposed management to better select suitable patients to high dose radiation therapy as well as to increase the likelihood to correctly delineate tumour tissue, is to use the combination of Positron Emission Tomography (PET) and CT (PET/CT) for dose planning purposes in the radiotherapy work-up instead of merely a dose planning CT. The intention is to achieve an improved tumour control and decrease radiation to normal surrounding tissue, and thus minimise side effects and possibly improve survival.

Objective
To evaluate whether the combination of PET and CT is superior to CT alone for target delineation and radiotherapy planning in adult patients with lung cancer suitable for curative radiotherapy treatment, and whether this will lead to improved survival and increased quality of life.

Methods
During March 2015, with an update in November 2015, systematic literature searches were conducted in PubMed, Embase, the Cochrane Library, Centre for Reviews and Dissemination, and in a number of HTA-databases. At least two authors independently screened titles, abstracts, full-text articles and extracted data.

The certainty of evidence was appraised according to GRADE. The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

Main results
Thirty-five cross-sectional studies, one observational study, and one randomised controlled trial (RCT) fulfilled the inclusion criteria. The RCT was published only as an abstract.

- With regard to *target definition and subsequent radiotherapy based on a dose planning PET/CT in comparison with a dose planning CT, with access to a staging PET,* no study reported any data on survival, tumour free or progression free survival, or health related quality of life. The summary estimate of a change in target definition was 36 % (95% CI: 16-62), and of a change in treatment intent from curative to palliative treatment it was 20 % (95% CI: 9-39).
- With regard to *target definition and subsequent radiotherapy based on a dose planning PET/CT in comparison with a dose planning CT, without access to a staging PET* the RCT abstract and the observational study reported survival. The RCT reported a significant improved two-year survival in favour of the PET/CT group (53 % versus 41 %), whereas the difference in survival between the two study groups in the observational study, was not of statistical significance. The summary estimate of a change in target definition was 43 % (95% CI: 35-51), and of a change in treatment intent from curative to palliative treatment it was 22 % (95% CI: 18 - 26) for NSCLC and 9 % (95 % CI: 4-18) for SCLC.

Conclusion
The use of PET/CT (dose planning) may improve survival (GRADE ⊕⊕OO). It probably result in changes in target definition (GRADE ⊕⊕⊕O), and in treatment intent from curative to palliative (GRADE ⊕⊕⊕O). The prognostic impact on quality of life still remains to be clarified.

2. Svensk sammanfattning – Swedish summary

Bakgrund
Icke-småcellig (NSCLC) och småcellig lungcancer (SCLC) utgör majoriteten av all lungcancer. Mortaliteten är hög. Många patienter har vid diagnostillfället en så utbredd sjukdom att de inte är lämpade för kirurgi trots att de inte har någon känd metastatisk spridning. Behandlingen är i dessa fall cytostatika och strålning. Genom att kombinera resultaten från undersökning med "positron emission tomography" (PET) med de från datortomografi (CT), så kallad PET/CT, kan en detaljerad bild av primärtumörens utbredning och förekomst av lymfkörtelengagemang erhållas. Detta kan öka möjligheterna att mer exakt bestämma vilka vävnadsområden som ska ges strålning och vilka delar som inte ska utsättas för strålning. Som konsekvens av detta följer att risken för strålorsakade biverkningar sannolikt minskar, och möjligen kan även överlevnaden förbättras. Tekniken kan sannolikt även förbättra möjligheterna att välja ut de patienter som ska ges strålterapi i botande syfte från de som endast bör ges palliativ terapi.

Syfte
Att utvärdera om kombinationen av PET och CT är bättre än enbart CT avseende bestämning av tumörvolymer och strålfält för behandling hos patienter med lungcancer som primärt bedöms vara kandidater för strålbehandling i kurativt syfte, och om detta leder till en ökad överlevnad och en förbättrad livskvalitet.

Metoder
En systematisk litteratursökning gjordes under mars månad 2015 med en uppdatering i november 2015 i Medline, Embase, Cochrane Library, Centre for Reviews and Dissemination, och ett antal HTA databaser. Två av författarna granskade oberoende av varandra artiklarnas titlar, abstrakts och slutligen utvalda artiklar i fulltext. Endast studier som publicerats efter 2000 på engelska eller något av de skandinaviska språken inkluderades.

Datasammanställning och analys
Två av författarna sammanställde oberoende av varandra resultaten från studierna. Graden av evidens bedömdes därefter enligt GRADE systemet. På samma sätt som vid bedömning av tvärsnittsstudier avseende diagnostiska test startades evidensgraderingen på ⊕⊕⊕⊕ nivån. Två olika huvudanalyser utfördes. Den första (PICO1) avser *definition av tumöromräde aktuellt för bestrålning ("target definition") med efterföljande radioterapi baserad på en dosplanering med PET/CT jämfört med enbart CT, med tillgång till en tidigare PET för stadieindelning,* och den andra (PICO 2) avser *definition av tumöromräde aktuellt för bestrålning ("target definition") med efterföljande radioterapi baserad på en dosplanering med PET/CT jämfört med enbart CT, utan tillgång till en tidigare PET för stadieindelning.*

Resultat
Trettiofem tvärsnittsstudier, en observationsstudie och en randomiserad kontrollerad studie (RCT) identifierades och inkluderades. Den randomiserade studien var endast publicerad i abstraktform.

- PICO1. Ingen studie redovisade effekter på total överlevnad, tumörfri överlevnad eller livskvalitet. Ett sammanvägt estimat för förändring i "target definition" (vävnadsområdet aktuellt för bestrålning) var 36 % (95% KI: 16-62), och i 20% (95 % KI: 9-39) för hur ofta man ändrade beslutet från kurativ till palliativ behandling, när PET/CT jämfördes med enbart CT för dosplanering.
- PICO2. Den randomiserade studien rapporterade en statistiskt signifikant förbättrad överlevnad till fördel för PET/CT (53 % jämfört med 41 %). Däremot var skillnaden i överlevnad mellan studiegrupperna i observationsstudien inte statistiskt signifikant. Ett sammanvägt estimat för förändring i "target definition" (vävnadsområdet aktuellt för bestrålning) var 43 % (95% KI: 35-51), och 22 % (95% KI: 18-26) avseende NSCLC och 9 % (95% KI: 4-18) avseende SCLC för hur ofta man ändrade beslutet från kurativ till palliativ behandling, när PET/CT jämfördes med enbart CT för dosplanering.

Sammanfattande slutsatser
Användningen av PET/CT för dosplanering av strålterapi till patienter med lungcancer"(dose planning") kan resultera i en något bättre överlevnad, GRADE ⊕⊕OO. Effekter på hälsorelaterad livskvalitet kvarstår att utvärdera. PET/CT ändrar troligen definitionen av vävnadsområdet aktuellt för bestrålning ("target definition"), GRADE ⊕⊕⊕◯ och kan ändra beslutet om patienten ska erhålla kurativ eller palliativ behandling, GRADE ⊕⊕⊕O.

The above summaries were written by representatives from the HTA-centrum. The HTA-report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 2016-03-30

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3. Summary of Findings (SoF-table)

Outcomes	Study design No. of studies (No. of patients)	Relative effect	Absolute effect	Certainty of evidence GRADE*
PICO 2 (without staging PET)				
Survival	NSCLC: 1 RCT (n=310) 1 cohort study (n=223)	PET/CT vs. CT alone: HR (mortality)=0.7 95% CI 0.5-1.0, p=0.045	PET/CT vs. CT alone: 2-yrs: 53% vs. 41% 3yrs: 33% vs. 19% p=0.1	⊕⊕◯◯ Low[1] ⊕◯◯◯ Very low[2]
PICO 1 (with staging PET)				
Proportion of patients with change in target definition	NSCLC: 4 cross-sectional studies (n=93)	Not applicable	36% 95% CI 16-62%	⊕⊕⊕◯ Moderate[3]
PICO 2 (without staging PET)				
Proportion of patients with change in target definition	NSCLC: 26 cross-sectional studies (n=1155) SCLC: 3 cross-sectional studies (n=88)	Not applicable	43 % 95% CI 35-51% 26% 95% CI 14-44%	⊕⊕⊕◯ Moderate[4]
PICO 1 (with staging PET)				
Proportion of patients with change in treatment intent (from curative to palliative treatment)	NSCLC: 15 cross-sectional studies (n=102)	Not applicable	20% 95% CI 9-39%	⊕⊕⊕◯ Moderate[5]
PICO 2 (without staging PET)				
Proportion of patients with change in treatment intent (from curative to palliative treatment)	NSCLC: 1 RCT (n=310) 14 cross-sectional studies (n=895) SCLC: 2 cross-sectional studies (n=70)	PET/CT vs. CT alone: RR 5.7 95% CI 2.0-16 Not applicable	PET/CT vs. CT alone: 14% vs. 3%, p<0.05 22% 95% CI 18-26% 9% 95% CI 4-18%	⊕⊕⊕◯ Moderate[6] (RCT) ⊕⊕⊕◯ Moderate[7] (observational)
PICO 1+2 (with and without staging PET)				
Interobserver variability	NSCLC 4 cross-sectional studies (n=92)	Not applicable	Less variability in PET/CT than in CT only	⊕⊕◯◯ Low[8]

Abbreviations: NSCLC= non small cell lung cancer, SCLC= small cell lung cancer, RCT= randomised controlled trial, RR= risk ratio

*The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

[1] Very serious study limitations; very limited information due to abstract only.

[2] Serious study limitations; historical controls, unbalanced study groups in favour of CT only.

[3]Serious study limitations; cut-off level for change in radiation fields not defined in 3/4 of studies.

[4]Some study limitations; cut-off level for change in radiation fields not defined in 16/29 studies.

[5]Some study limitations; time lag between PET1 and PET2 probably affects outcome. Uncertain precision.

[6]Serious study limitations; limited information due to abstract only.

[7]Some study limitations; unclear decision on change of treatment. Heterogeneity between NSCLC and SCLC. Imprecision for SCLC.

[8]Serious indirectness; different measure to study interobserver variability in all four studies. Serious imprecision.

4. Abbreviations

ARR	Absolute risk reduction
CI	Confidence interval
CT	Computed tomography
CTC	Common toxicity criteria
CTV	Clinical target volume
EORTC	European organisation for research and treatment of cancer
EBUS	Endobronchial ultrasound
FDG	^{18}Fluoro-deoxy-glucose
GTV	Gross tumor volume
HRQL	Health Related Quality of Life
HR	Hazard ratio
IAEA	International atomic energy agency
NCCN	National comprehensive cancer network
NSCLC	Non-small cell lung cancer
NCCN	National comprehensive cancer network
PET	Positron emission tomography
PTV	Planning target volume
RCT	Randomised controlled trial
RR	Risk ratio
RTOG	Radiation therapy oncology group
SCLC	Small cell lung cancer
VGR	Region Västra Götaland

5. Background

Lung cancer

Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) comprise the great majority of all lung cancers, and have a high risk of premature death. Around one third of these patients are diagnosed with a severity of their disease that is too advanced for surgery but without distant metastatic spread. They can be treated with curative intent with high dose irradiation and chemotherapy. In the work-up prior to radiotherapy a computed tomography (CT) in a reproducible treatment position is performed to delineate the tumour area. It is crucial for a successful treatment to accurately define the actual tumour tissue. Delineation based on CT slices may be problematic due to e.g. atelectases, and lymph nodes without a pathological increase in size that nonetheless may be malignant.

A proposed management is to use the combination of Positron Emission Tomography (PET) and CT, i.e. PET/CT, for dose planning purposes in the radiotherapy work-up instead of a dose planning CT. The use of PET/CT could better select suitable patients to high dose radiation therapy as well as increase the likelihood to correctly delineate tumour tissue. Hereby, the probability to achieve improved tumour control, and improved survival, may be increased and the radiation to normal tissue, causing side effects, likely will decrease.

The purpose of this HTA was to evaluate whether the use of PET/CT for dose planning purposes improves the radiotherapy for patients suitable for curative treatment with high dose chemoradiotherapy to such a degree that the region of Västra Götaland (VGR) ought to implement the procedure as a standard of practice.

Prevalence and incidence of lung cancer

Lung cancer is the fourth most common cancer in Sweden (following prostate or breast cancer, skin and colorectal cancer). The annual age-standardised incidence rate 2014 was 40.3 per 100,000 for males and 37.0 per 100,000 for females resulting in about 3,800 new cases each year, and a current prevalence of 9,300. It is associated with the highest cancer related mortality with an annual mortality rate of 3,500. In the Region Västra Götaland (VGR) the annual incidence is 560, and the current prevalence 1,300. The subpopulation suitable for high dose radiotherapy with curative intent in VGR constitutes around 80 patients per year (Swedish national board of health and welfare, Cancerincidens, 2015, The Association of the Nordic Cancer Registries, 2016, Regionala cancercentrum i samverkan, 2016b, Data from the Department of Radiotherapy, Sahlgrenska).

Present treatment of lung cancer

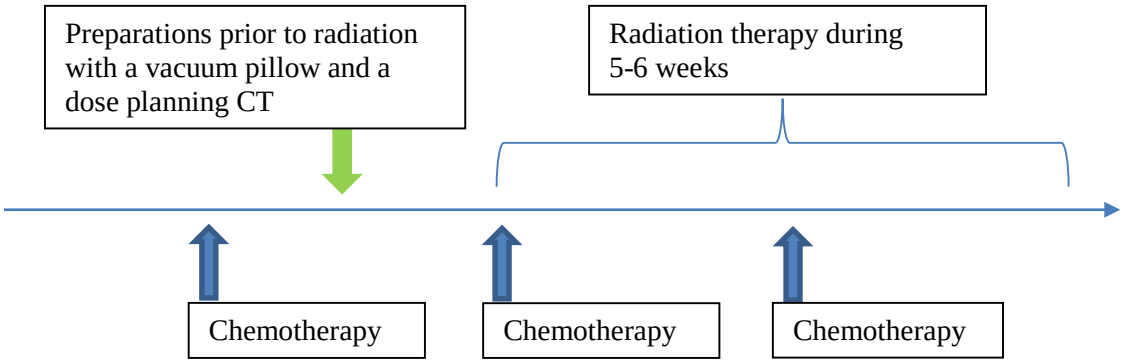
Patients with lung cancer that may be candidates for curative treatment will go through a staging procedure which includes a PET/CT-examination. Those who have stage I or II disease (i.e. tumours confined to the lungs or/and spread to ipsilateral hilar regions) are usually considered for surgery. The majority of patients with stage III disease (i.e. with mediastinal metastases or advanced growth of the primary tumour) are usually referred for high dose chemoradiotherapy.

After a complete clinical work-up and a discussion at a multidisciplinary board a treatment recommendation is made for each patient. The multidisciplinary board include an oncologist, a pulmonologist and a radiologist. Depending on the stage of the disease and the general medical condition of the patient it will then be decided whether he or she should be offered surgery, radiotherapy +/- chemotherapy or palliative systemic treatment.

In the work-up for radiotherapy an individual fixation device is made for each patient, usually a vacuum pillow to keep the patient in the same position for every fraction throughout the treatment period.

A dose planning CT scan is performed with the patient in the treatment position. The tumour area, as well as organs at risk, are delineated on each CT slice, and a calculation of the planned dose is made in three dimensions to optimise the radiation dose to the tumour while minimising the dose to organs at risk. Normally one cycle of chemotherapy is administered prior to the first day of radiation which usually is delivered five days a week for five to six weeks. This period typically includes two additional cycles of chemotherapy (Fig 1).

Fig 1. Schematic figure of the NSCLC treatment course:



The normal pathway through the health care system and current waiting time for medical assessment and treatment

Patients with suspected lung cancer will be referred to the department of Pulmonary Medicine. The diagnostic work-up includes a medical history and a complete physical examination of the patient, histopathology assessment, and tumour staging. Thereafter the patient will be discussed at a multidisciplinary board (see above). Currently (i.e. Feb 2016), the time from the date of treatment decision to the start of radiotherapy is about five weeks. This is considered too long, according to present guidelines being implemented in Sweden ("standardiserade vårdförlopp") but is due to lack of resources (i.e. linear accelerators and time slots to initiate therapy).
After completed therapy the patients will be followed at the department of Oncology (NSCLC) or department of Pulmonary Medicine (SCLC) for five years.

Number of patients per year who undergo chemoradiotherapy for lung cancer.

Approximately 80 patients annually in VGR.

Presents recommendations from medical societies or health authorities

Nationella vårdprogrammet: PET/CT is the preferred option for dose planning purposes.
(http://www.cancercentrum.se/samverkan/cancerdiagnoser/lunga-och-lungsack/vardprogram)

Swedish national board of health and welfare: PET/CT is recommended (level 3, where level 10 is the lowest level of recommendation) for planning of radiotherapy in the curative setting (NSCLC stage III).
(http://www.socialstyrelsen.se/nationellariktlinjerforlungcancervard)

European Organisation for Research and Treatment of Cancer (EORTC): FDG-PET is recommended in the process of target delineation (de Ruysscher 2010).

National comprehensive cancer network (NCCN): PET/CT significantly improves target accuracy, should be obtained preferably within four weeks before treatment and ideally in the treatment position. (http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)

International atomic energy agency (IAEA): A combined PET/CT acquisition is now the standard method of acquiring FDG-PET images for the purposes of baseline staging and for radiotherapy treatment planning (RTP) (Konert 2015).

6. Health Technology

Positron emission tomography and computed tomography for dose planning

Positron emission tomography (PET) is a technique that utilises the uptake of sugar in human cells. The glucose molecules are marked with radioactive ^{18}F (2-deoxy-2-[fluorine-18]fluoro- D-glucose; FDG). When the molecules decay they emit positrons, which in turn annihilates into gamma rays that can be detected by a PET-scanner. As cancer cells are highly metabolically active they will incorporate radioactive sugar, and thereby become possible detectable by PET. However, malignant tumours are not the only lesions that may be detected. Foci of infection or inflammation, and healing tissues, can also have an increased FDG uptake (Abouzied 2005). These falsely positive lesions implicate a risk of overestimating the metastatic spread and sometimes necessitate a confirmatory biopsy.

Today the PET technique is used together with computed tomography (”PET/CT”). This combined technique enables the physician to correlate the pathologic uptake to a radiographically visualised anatomical structure. The PET/CT technique has been assessed in a number of studies, and has been shown to improve the staging procedure of lung cancer as compared with CT alone (Fletcher 2008, Liao 2012).

7. Objective

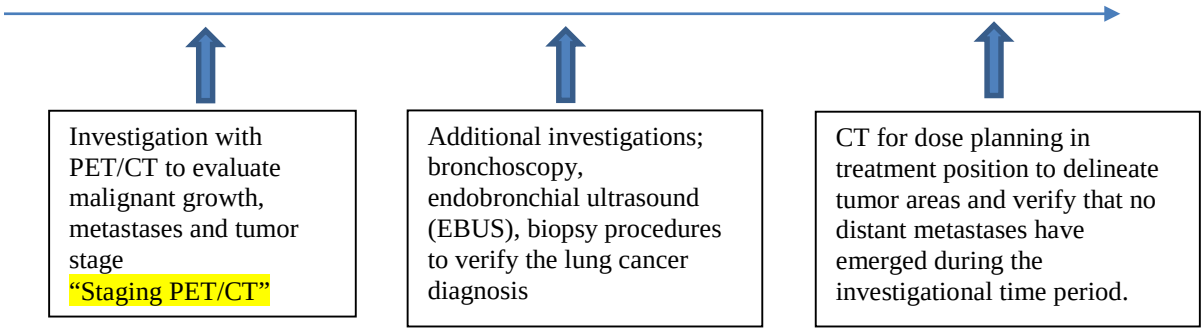
Does dose planning based on 18FDG-PET/CT compared to CT alone, in adult patients with lung cancer, lead to improved survival, increased quality of life, changes in target definition and treatment intention?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

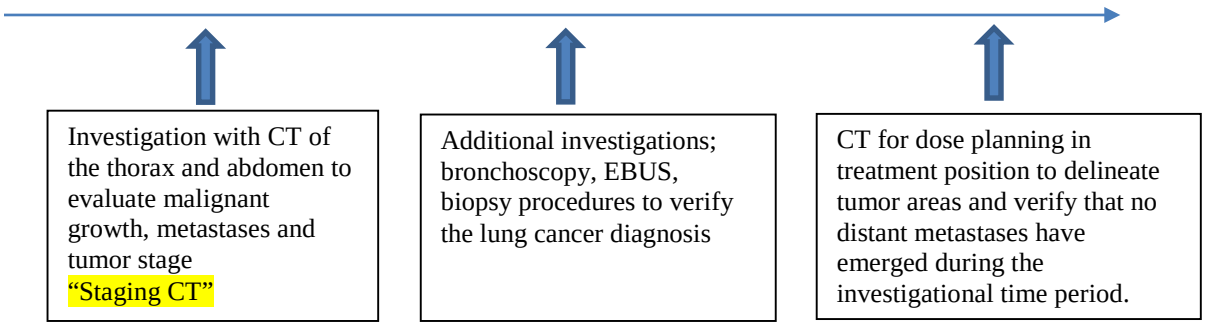
P	Newly diagnosed lung cancer patients suitable for radiotherapy with curative intent
I	Target definition and subsequent radiotherapy based on a dose planning PET/CT
C	C1- Target definition and subsequent radiotherapy based on a dose planning CT with access to a staging PET, see fig. 2A C2- Target definition and subsequent radiotherapy based on a dose planning CT without access to a staging PET, see fig. 2B
O	Critical for decision making Overall survival, tumour free/progression free survival Health Related Quality of Life Important but not critical for decision making Symptom score e.g CTC, RTOG Change in treatment intention (from curative to palliative treatment) Change in target definition Change in interobserver variability Not important for decision making Complications

Fig. 2 Schematic figure of the different work-up procedures C1 and C2.

A: C1



B: C2



8. Methods -

Systematic literature search (Appendix 1)

During March 2015, with an update in November 2015, two librarians (EB, AL) performed systematic searches in Medline, Embase, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 1. The librarians conducted the literature searches, at least two people from the group selected studies and independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. The remaining articles were sent to all the participants of the project group, who read the articles independently and then decided in a consensus meeting which articles that should be included.

An updated search was done in March 2016 in Embase, with limitation to conference abstract and RCT.

Critical appraisal and certainty of evidence

The included studies, their design and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The articles were critically appraised using a slightly modified checklist for case series (Guo et al., 2013), and SBU's checklist regarding cohort studies and randomised trials (SBU 2015). A summary result for the outcome variables and the associated certainty of evidence are presented in a Summary of Findings table (page 8). The certainty of evidence was graded according to the GRADE system (Atkins et al, 2004; GRADE Working group). The grading of the cross-sectional studies started at the ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy with effect measures that may be indirectly important to patients.

Ongoing research

A search in Clinicaltrials.gov (2015-11-26) using the search terms ("Lung cancer" OR "lung carcinoma" OR "lung tumor" OR "lung neoplasm" OR "lung malignancy" OR "lung metastasis" OR "lung adenocarcinoma" OR NSCLC OR SCLC OR "Non-Small Cell Lung Cancer" OR "Small Cell Lung Cancer" OR "Bronchial Cancer" OR "Bronchial carcinoma" OR "Bronchial tumor" OR "Bronchial neoplasm") AND (PET OR PETCT OR PET/CT OR Positron-Emission Tomography OR petscan) identified 287 trials. Nine of these were relevant for the question at issue (see Section 14 - Future perspectives).

9. Results

Literature search (Appendix 1)

The literature search identified a total of 1193 articles (after removal of duplicates). At least two people from the group excluded 1043 articles after reading their abstracts. Another 91 articles were excluded after reading the articles in full text. The remaining 59 articles were sent to the whole project group, and 38 were finally included in the report (Appendix 2). Excluded articles are listed in Appendix 3.

From the updated search in Embase with limitation to conference abstract and RCT 133 abstracts were found. These were either duplicates or did not fulfill the PICO criteria.

Results per outcome

Thirty-seven studies were included in the analysis, one RCT (abstract), one observational study with historical controls and 35 cross-sectional prospective or retrospective studies. In general the directness was high, but a number of studies have enrolled varying proportions of stage I disease which was out of scope for our intended population. There were some study limitations where the different outcomes were assessed in various ways. Cut-offs for significant change regarding target definition (GTV, CTV, PTV) are not always reported and the blinding procedure differs between trials (see Appendices). The RCT is so far only presented in abstract form.

Several studies were rather small with low precision, which however is substantially improved when analysed together. The subset with SCLC in PICO 1 was still accompanied with a relatively low precision due to a limited number of studies.

PICO 1- *Dose planning with PET/CT compared with CT alone for target definition and subsequent radiotherapy with access to a staging PET*

All PICO 1 results concern NSCLC as there were no SCLC trials.

Outcomes critical for decision-making

No study reported survival or health related quality of life.

Outcomes important for decision-making

Change in target definition (Appendix 4.2a, a denotes PICO 1**)**

Change in target definition was reported in four cross-sectional trials with 93 patients in total. All studies had some limitations. The proportion of patients with a change in target definition varied between 16% and 71% with a summary estimate of 36% (95% CI 16-62).

Conclusion: The use of PET in addition to CT for dose planning probably changes target definition (⊕⊕⊕◯).

Change in treatment intent (Appendix 4.3a, a denotes PICO 1**)**

Change in treatment intent from curative to palliative treatment was reported in four cross-sectional studies with 102 patients in total. All studies had some limitations. The proportion of patients with a change in treatment intent varied between 4% and 37% with a summary estimate of 20% (95% CI 9-39).

Conclusion: The use of PET in addition to CT for dose planning probably alters the decision to change the treatment intent from curative to palliative (⊕⊕⊕◯).

PICO 2-

Dose planning with PET/CT compared with CT alone for target definition and subsequent radiotherapy without access to a staging PET

Outcomes critical for decision-making

Survival (Appendix 4.1)

Survival was reported in one RCT and one observational study. The RCT was only available in abstract form published in 2011. A full manuscript is under preparation and will be submitted during 2016 (personal communication, Mark Levine, November 17 2015). The observational study had major limitations with historical controls and patients in the intervention group had more severe disease at baseline. The RCT reported a survival difference of 53% vs. 41% in favour of the PET/CT group (HR=0.7, 95%CI 0.5-1.0, p=0.045). The observational trial reported a median survival of 17 months in both groups and a non-significant survival difference at three years of 33% vs. 19% (p=0.1).
Conclusion: The use of PET/CT compared with CT alone for dose planning may improve survival (⊕⊕◯◯).

Outcomes important for decision-making

Change in target definition (Appendix 4.2b, b denotes PICO 2**)**

Change in target definition was reported in 29 cross-sectional trials (26 NSCLC, 3 SCLC) with 1,243 patients in total. Most of the studies had some study limitations. The change in target definition varied between 9% and 75% with a summary estimate of 43% (95%CI 35-51) for NSCLC and 26% (95% CI 14-44) for SCLC.
Conclusion: The use of PET in addition to CT for dose planning probably changes target definition (⊕⊕⊕◯).

Change in treatment intent (Appendix 4.3b, b denotes PICO 2**)**

Change in treatment intent was reported in the RCT and 16 cross-sectional trials (14 NSCLC, 2 SCLC). The RCT reported a difference between groups of 14% vs. 3% (RR 5.7 (95%CI 2-16), ARR 11% (95%CI 5.6-18.6), p<0.05. The change in treatment intention in the cross-sectional trials varied between 8% and 33% with a summary estimate of 22% (95%CI 18-26) for NSCLC and 9% (95%CI 4-18) for SCLC.
Conclusion: The use of PET/CT compared with CT alone for dose planning probably changes the decision to change the treatment intent from curative to palliative (⊕⊕⊕◯).

PICO 1 and 2

Outcomes important for decision-making

Change in interobserver variability (Appendix 4.4)

Change in interobserver variability was assessed in four cross-sectional trials. All studies had some limitations and all used different measures to study interobserver variability. They report decreased standard deviation, increased concordance index and decreased volume discrepancy with PET/CT.
Conclusion: The use of PET/CT (dose planning) may results in an reduced interobserver variability (⊕⊕◯◯).

10. Ethical consequences

There are no obvious ethical concerns for the individual patients with replacing a dose planning CT with a dose planning PET/CT. Ethical consequences are further explored in Appendix 5. As the time slots on the single PET/CT-scanner at the department of Nuclear Medicine in VGR are limited for the time being, there is a risk of causing longer waiting times for other patients in need of the same technique. However a capacity increase is already scheduled at the department of Nuclear Medicine with a second PET/CT scanner being delivered in May 2016 and a third in 2017.

11. Organisation

Time frame for the putative introduction of the new health technology

PET/CT is already available at the Sahlgrenska University Hospital/Sahlgrenska at the Department of Nuclear Medicine. A second PET/CT scanner will be delivered in May 2016 and a third in 2017.

Present use of the technology in other hospitals in Region Västra Götaland

PET/CT is only available at the Sahlgrenska University Hospital/Sahlgrenska. The use of PET/CT for dose planning purposes varies throughout the country and is e.g. used at Karolinska University Hospital in Stockholm.

Consequences of the new health technology for personnel

A change of routine from CT to PET/CT before treatment planning will impact on where and on which scanner the patient is prepared for radiotherapy. Radiotherapy nurses and radiology nurses will perform part of the radiotherapeutic work-up, and assist the patients, at another facility (department of Nuclear Medicine) more often than today.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

If PET/CT for dose planning purposes is introduced for all patients with lung cancer with curative intent it would mean approximately 80 patients per year. Initially this will influence patients who receive the irradiation at Sahlgrenska University Hospital (n=60). A minority of patients treated at South Älvsborg Hospital will be transferred to Sahlgrenska University Hospital and perform the entire PET/CT based work-up and treatment in Gothenburg. Ultimately, with increasing capacity, all patients in the region will have the same pre-radiotherapeutic work-up.

12. Economic aspects

Present costs of currently used technologies

Radiotherapy is performed at Sahlgrenska University Hospital and South Älvsborg Hospital in VGR. The number of lung cancer patients accepted for treatment with high dose irradiation with curative intent is around 60 patients per year in Gothenburg and 20 patients per year in Borås. The calculated cost for a standard treatment course for these patients, including patient visits, chemotherapy, radiotherapy planning and treatment, body scans, hospitalisation time, and follow up for three months is 218,300 SEK. In VGR with 80 patients treated annually the present total cost sums up to 17,464,000 SEK per year.

Expected costs of the new health technology

At present there is only one PET/CT scanner in VGR, located at the Department of Nuclear Medicine at Sahlgrenska University Hospital. The cost in 2015 for a PET/CT examination was 22,604 SEK. For 2016, an expected increase by 2 % would result in a cost of 23,000 SEK. With 80 patients treated per year the total cost of PET/CT for dose planning would be an additional 1,840,000 SEK annually.

Total change of cost

The cost for the use of PET/CT for dose planning is an additional 23,000 SEK to the standard treatment course of 218,300 SEK per patient. This is a relative increase of 10.6 % and adds up to a total cost of 241,300 SEK per patient. With 80 patients treated per year the new total cost in VGR can be estimated to 19,304,000 SEK. The cost per treatment course might be somewhat less than 241,300 SEK as the present CT for dose planning is included in the sum but will be replaced by the PET/CT. By performing a PET/CT before dose planning the number of patients accepted for treatment with high dose irradiation with curative intent will be reduced by around 20 %, as shown in this report. The radiotherapy given to this palliative patient cohort is not as advanced or protracted as the high dose curative treatment course resulting in a decreased cost. The actual cost per palliative treatment will vary substantially between patients, and is difficult to estimate on group level due to the individualised strategy. However, the net effect will be a total cost less than the calculated 19,304,000.

Possibility to adopt and use the new technology within the present budget

The present budget at the Department of Oncology at Sahlgrenska University Hospital does not allow for the additional PET/CT-dependent costs since the Department of Nuclear Medicine charges the cost for each PET/CT-examination.

Available analyses of health economic or cost advantages or disadvantages

Remonnay et al. (2008) estimated the cost for CT alone in comparison with CT associated with PET. The cost estimation was made in the French setting during 2005 including 112 patients with non-small cell lung cancer. The additional use of PET resulted in both increases and decreases of costs in the mean cost per patient. The total increase in cost per patient was €889 of which the cost of the radionuclide, FDG, accounted for 45%. Additional tests were performed for eight percent of the patients, which resulted in an extra cost per patients of €57. Changes in radiotherapy following PET resulted in a cost-saving of €521. In total, there was an increase in the net cost of €425 per patient.

13. Discussion

To our knowledge, this is presently the largest systematic assessment of PET/CT for dose planning purposes prior to radiation of lung tumours encompassing 37 trials and one previous systematic review from year 2000 and onwards. The data on the considerable proportion of patients who will have a meaningful change in the tumour target volume and a change of treatment intent from curative to palliative are solid. Around two in five patients will have a significant change in target definition and one in five will receive palliative treatment instead of high dose radiation. The numbers might be somewhat less with regards to SCLC of which there are fewer studies and more uncertainties. Interestingly the magnitudes of the proportions of patients with changes in target volumes and treatment intention seem to be similar regardless of the availability of a previous staging-PET. These results are definitely influenced by the time interval between the staging PET and subsequent dose planning PET, but this issue is not very well studied. Even with a rather narrow interval in the clinical practice of three to four weeks, studies have detected distant metastases in one third of the patients (Everitt 2013, Lin 2011).

The findings of changes of tumour target volume and changes of treatment intent are in line with a previously reported systematic review by Ung (2011a) in which they concluded that PET/CT leads to substantial modifications of target volumes and changes in treatment intention. They pointed out that it was uncertain whether these changes also will result in better clinical outcome. To what extent the changes in delineation of target structures influence the clinical and patient reported outcomes (i.e. survival, side effects, HRQL) are still not definitely clarified. Ung et al. (2011b) have performed the only RCT in the field and they reported a significantly improved survival. This seems logical as targeting the correct areas with irradiation is a prerequisite for tumour control and survival, and PET/CT has been shown to more accurately detect tumour areas compared to CT in a number of staging trials (Fletcher 2008, Liao 2012). In spite of the superiority of PET/CT there still is a risk to wrongly refer patients to a palliative treatment course due to falsely positive PET findings when implementing PET/CT before dose planning. If there are doubts regarding distant spread the PET positive lesion should be verified with a histopathological examination.

On-going research will add some knowledge with regard to clinical outcomes as locoregional progression rate, time to progression and survival in the phase II setting when using PET/CT. However there are no further phase III trials, on-going or planned, and it is not likely that another large controlled trial will be performed with the comparison of CT and PET/CT as objective. The hitherto accumulated data accounted for in this report has been considered robust and convincing enough for clinical societies to recommend PET/CT based dose planning for lung cancer (EORTC, NCCN, IAEA).

14. Future perspective

Scientific knowledge gaps

The studies are almost exclusively reporting surrogate endpoints like changes in treatment intent or changes in volumes irradiated that probably would influence tumour control, survival and side effect from normal tissue but data on actual patient outcome are scarce.

Ongoing research

There are in all nine trials listed in www.clinicaltrials.gov investigating PET/CT prior to radiotherapy. They are studying treatment volumes, locoregional progression rate and time to progression. Some are interventional and randomised but none are phase III trials and the likelihood that they will bring about more substantial data regarding survival and HRQL is rather low (Appendix 6).

Interest at the clinic/research group/organisation to start studies/trials within the research field at issue

We do not think it would be feasible to perform another trial comparing CT and PET/CT for dose planning purposes due to available data and ethical concerns.

15. Participants in the project

The question was nominated by

Marie Lindh, Head of the Department of Oncology, Sahlgrenska University Hospital, Göteborg, Sweden.
Thomas Björk-Eriksson MD, Associate professor,
on demand of the Regional Advisory Board for priority setting (PPR), Region Västra Götaland.

Participants from the clinical departments

Per Albertsson, MD, Associate professor, Consultant,
Andreas Hallqvist, MD, PhD, Consultant,
Charlotte Månsson, MD, Resident,
all at the Department of Oncology, Sahlgrenska University Hospital, Göteborg, Sweden.

Participants from the HTA-centrum

Annika Strandell, MD, Associate professor, HTA-centrum, VGR, Göteborg, Sweden.
Ola Samuelsson, MD, Associate professor, HTA-centrum, VGR, Göteborg, Sweden.
Ann Liljegren, librarian, Medical Library, Sahlgrenska University Hospital, Göteborg, Sweden.
Emil Björkander, librarian, Medical Library, Sahlgrenska University Hospital, Göteborg, Sweden.

External reviewers

Michael Breimer, MD, professor, Department of Surgery, Sahlgrenska University Hospital, Göteborg, Sweden.
Christian Rylander, MD, Associate professor, Department of Anaestesiology, Sahlgrenska University Hospital, Göteborg, Sweden.

Conflicts of interest

None

Project time

The HTA was accomplished during the period of 2015-02-19 – 2016-03-30
Literature searches were made in March 2015, and updated in November 2015.

Appendix 1 – search strategy, study selection and references

Question at issue:
Does dose planning based on 18FDG-PET/CT compared to CT alone, in adult patients with lung cancer, lead to improved survival, increased quality of life, changes in target definition and treatment intention?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

P	Newly diagnosed lung cancer patients suitable for radiotherapy with curative intent
I	Target definition and subsequent radiotherapy based on a dose planning PET/CT
C	C1- Target definition and subsequent radiotherapy based on a dose planning CT with access to a staging PET C2- Target definition and subsequent radiotherapy based on a dose planning CT without access to a staging PET
O	<u>Critical for decision making</u> Overall survival, tumor free/progression free survival Health Related Quality of Life <u>Important but not critical for decision making</u> Symptom score e.g. CTC, RTOG Change in treatment intention (from curative to palliative treatment) Change in target definition Change in interobserver variability <u>Not important for decision making</u> <u>Complications</u>

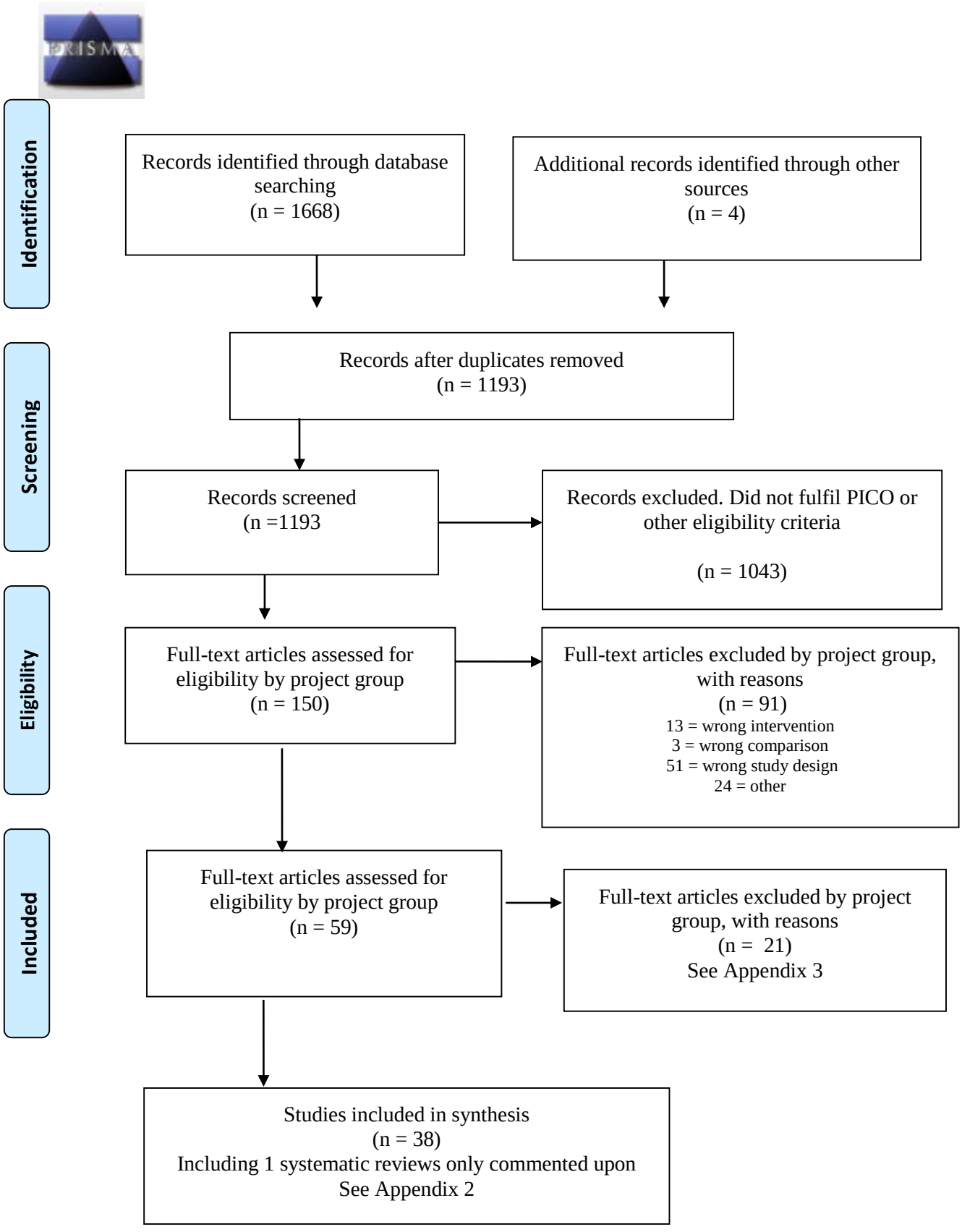
<u>Eligibility criteria</u>

Study design:
- Systematic reviews
- Randomised controlled trials
- Non-randomised controlled studies
- Case series minimum 10 patients

Publication year: 2000-

Language: English, Danish, Norwegian, Swedish

Selection process – flow diagram



Database: MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Date: 2015-03-09
No of results: 436
Search updated: 2015-11-19, 44 results

#	Searches	Results
1	exp Lung Neoplasms/	178072
2	((Lung or lungs or pulmonar$ or bronch$ or small cell) adj5 (cancer$ or carcinoma$ or tumor or tumors or tumour or tumours or neoplas$ or malignan$ or metasta$ or sarcoma$ or adenocarcinoma$ or adeno?carcinoma$ or adenoma$)).ab,ti.	191875
3	(NSCLC or SCLC).ab,ti.	25483
4	1 or 2 or 3	244159
5	exp Positron-Emission Tomography/	34217
6	exp Tomography, Emission-Computed/	80640
7	(Pet or petscan$).ab,ti.	59235
8	(emission$ adj10 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ab,ti.	51589
9	5 or 6 or 7 or 8	110904
10	exp Tomography, X-Ray Computed/	312970
11	(comput$ adj8 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ab,ti.	200199
12	(CT or CAT).ab,ti.	306477
13	10 or 11 or 12	559438
14	9 and 13	43250
15	"'pet/ct'".ab,ti.	12259
16	PETCT.ab,ti.	20
17	15 or 16	12266
18	14 or 17	43251
19	exp Radiation/	336102
20	exp Radiotherapy/	142328
21	(Radiation$ or Radiotherap$ or x-ray$ or x ray$).ab,ti.	571541
22	19 or 20 or 21	868206
23	(Defining or Define$ or delineat$ or Target$ or planning$ or target definition$ or paint$ or contour$).ab,ti.	1737688
24	4 and 18 and 22 and 23	499
25	(animals not (animals and humans)).sh.	3906384
26	24 not 25	496
27	(comment or editorial or letter).pt.	1386399
28	26 not 27	490
29	**limit 28 to (danish or english or norwegian or swedish)**	**436**

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The Cochrane Library
Date: 2015-03-10
No of results: 225
Cochrane reviews 1
Other reviews 28
Trials 149
Technology assessments 16
Economic evaluations 31
Search updated: 2015-11-19, 10 results
Trials 10

ID	Search	Hits
#2	MeSH descriptor: [Lung Neoplasms] explode all trees	5017
#3	((Lung or lungs or pulmonar* or bronch* or small cell) near/5 (cancer* or carcinoma* or tumor or tumors or tumour or tumours or neoplas* or malignan* or metasta* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenoma*)):ti,ab,kw (Word variations have been searched)	10454
#4	NSCLC or SCLC:ti,ab,kw (Word variations have been searched)	3536
#5	#2 or #3 or #4	10662
#6	MeSH descriptor: [Positron-Emission Tomography] explode all trees	1035
#7	MeSH descriptor: [Tomography, Emission-Computed] explode all trees	2631
#8	Pet or petscan*:ti,ab,kw (Word variations have been searched)	2220
#9	(emission* near/10 (Tomograph or Tomographs or tomographic* or tomography or tomographies)):ti,ab,kw (Word variations have been searched)	3794
#10	#6 or #7 or #8 or #9	4400
#11	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	4107
#12	(comput* near/8 (Tomograph or Tomographs or tomographic* or tomography or tomographies)):ti,ab,kw (Word variations have been searched)	9816
#13	CT or CAT:ti,ab,kw (Word variations have been searched)	40981
#14	#11 or #12 or #13	46670
#15	#10 and #14	2869
#16	pet/ct:ti,ab,kw (Word variations have been searched)	392
#17	PETCT:ti,ab,kw (Word variations have been searched)	4
#18	#16 or #17	394
#19	#15 or #18	2870
#20	MeSH descriptor: [Radiation] explode all trees	3422
#21	MeSH descriptor: [Radiotherapy] explode all trees	5314
#22	Radiation* or Radiotherap* or x-ray* or x ray*:ti,ab,kw (Word variations have been searched)	26692
#23	#20 or #21 or #22	29160
#24	#5 and #19 and #23	108
#25	**#5 and #19**	**225**

Database: CRD
Date: 2015-03-10
No of results: 105
Search updated: 2015-11-19, 1 result

Line	Search	Hits
1	MeSH DESCRIPTOR Lung Neoplasms EXPLODE ALL TREES	1072
2	(((Lung or lungs or pulmonar* or bronch* or small cell) near5 (cancer* or carcinoma* or tumor or tumors or tumour or tumours or neoplas* or malignan* or metasta* or sarcoma* or adenocarcinoma* or adeno?carcinoma* or adenoma*)))	1384

3	((NSCLC or SCLC))	251
4	#1 OR #2 OR #3	1399
5	MeSH DESCRIPTOR Positron-Emission Tomography EXPLODE ALL TREES	407
6	MeSH DESCRIPTOR Tomography, Emission-Computed EXPLODE ALL TREES	643
7	((Pet OR petscan*))	509
8	((emission* near10 (Tomograph or Tomographs or tomographic* or tomography or tomographies)))	672
9	#5 OR #6 OR #7 OR #8	776
10	MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES	979
11	((comput* near8 (Tomograph or Tomographs or tomographic* or tomography or tomographies)))	1382
12	((CT or CAT))	1487
13	#10 OR #11 OR #12	2339
14	#9 AND #13	468
15	(pet-ct)	196
16	(petct)	0
17	#15 OR #16	196
18	#14 OR #17	468
19	**#4 AND #18**	**105**

Database: EMBASE 1980 to present (OVID SP)
Date: 2015-03-09
No of results: 749
Search updated: 2015-11-19, 92 results
2016-03-29 133 reults, an updated search with limitation to Conference abstract and RCT.

#	Searches	Results
1	exp lung tumor/	219256
2	((Lung or lungs or pulmonar$ or bronch$ or small cell) adj5 (cancer$ or carcinoma$ or tumor or tumors or tumour or tumours or neoplas$ or malignan$ or metasta$ or sarcoma$ or adenocarcinoma$ or adeno?carcinoma$ or adenoma$)).ti,ab.	245776
3	(NSCLC or SCLC).ti,ab.	42412
4	1 or 2 or 3	315925
5	exp positron emission tomography/	88706
6	exp computer assisted emission tomography/	17907
7	(Pet or petscan$).ti,ab.	92073
8	(emission$ adj10 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ti,ab.	63228
9	5 or 6 or 7 or 8	156475
10	exp Tomography, X-Ray Computed/	638136
11	(comput$ adj8 (Tomograph or Tomographs or tomographic$ or tomography or tomographies)).ti,ab.	235257
12	(CT or CAT).ti,ab.	416995
13	10 or 11 or 12	859235

14	9 and 13	83130
15	"'pet/ct'".ti,ab.	23337
16	petct.ti,ab.	293
17	15 or 16	23448
18	14 or 17	83202
19	(Defining or Define$ or delineat$ or Target$ or planning$ or target definition$ or paint$ or contour$).ti,ab.	2181764
20	exp radiation/	422651
21	exp radiotherapy/	391604
22	(Radiation$ or Radiotherap$ or x-ray$ or x ray$).ti,ab.	667662
23	20 or 21 or 22	1102482
24	4 and 18 and 19 and 23	1541
25	(animal not (animal and human)).sh.	1209342
26	24 not 25	1539
27	limit 26 to (article or conference paper or note or "review")	842
28	**limit 27 to (danish or english or norwegian or swedish)**	**749**

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen** were visited 2015-03-09
Six relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 4 new records

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Included studies:

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Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2a – Characteristics of included studies PICO 1 (with staging PET)

* Blinding
0. Not blinded or not reported.
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded.
3. Both target delineation and dose planning is done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
Everitt 2013 Australia	Prospective cross-sectional	0	2004-2007	21	Median 68	67%	NSCLC I - 29% II - 9% III - 62%	Median 23 days between PET1 and PET2 (range 8–176 days)	Change in treatment intention Change in target definition
Grills 2007 USA	Retrospective cross-sectional	0	2002-2003	21	Not reported	Not reported	NSCLC I- 48% III- 52%		Change in target definition
Hanna 2010 Ireland	Retrospective cross-sectional	1	2004-2007	28	Mean 69	79%	NSCLC I- 32% II- 14% III- 54%		Interobserver variability
Lin 2011 Australia	Retrospective cross-sectional	1	2007-2010	26	Median 69	69%	NSCLC I- 19% II- 19% III- 62%	Scan interval 40 ±12 days	Change in target definition Change in treatment intention
McManus 2013 Australia	Prospective cross-sectional	1	2004-2007	30	Not reported	68%	NSCLC I-III Majority stage III	The trial also included patients without a staging PET (Appendix 2b)	Change in treatment intention
Pommier 2010 France	Prospective cross-sectional	1	2004-2006	25	Mean 61	82%	NSCLC I- 13% II- 8% III- 79%	The trial also included patients without a staging PET (Appendix 2b)	Change in target definition Change in treatment intention

NSCLC= non small cell lung cancer

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2b- Characteristics of included studies, PICO 2 (without staging PET)

*
0. Not blinded or N.R
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded
3. Both target delineation and dose planning are done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
NSCLC									
Ung 2011b Canada	Randomised controlled trial (abstract)	0	NR	310	NR	NR	NSCLC III- 100%	Abstract	Change in treatment intention Survival
Socha 2013 Poland	Retrospective cross-sectional (a) and Case-series with historical controls (b)	0	NR	a: 100 b: 223	Median 64	76%	a: NSCLC I- 17% II- 6% III- 77% b: NSCLC III- 100%	a: Cross-sectional b: Case-series with historical control (cohort)	a: Change in treatment intention b: Survival
Abramyuk 2012 Germany	Retrospective cross-sectional	1	2005-2008	104	Median 72	83%	NSCLC I- 22% II- 13% III- 59% IV- 6%	Median interval between CT and PET/CT 19 days	Change in treatment intention
Ashamalla 2005 USA	Prospective cross-sectional	1	2004	19	Median 74	N.R	NSCLC II-III Proportions not reported		Change in target definition Interobserver variability
Bradley 2012 USA	Prospective cross-sectional	3	2006-2008	47	Median 64	64%	NSCLC II- 6% III- 97%		Change in target definition
Bradley 2004a USA	Prospective cross-sectional	3	2001-2003	26	NR	NR	NSCLC I- 23% II- 8% III- 65% IV- 4%		Change in target definition Change in treatment intention
Ceresoli 2007 Italy	Retrospective cross-sectional	1	2002-2003	21	Median 65	86%	NSCLC I- 5% III- 76% Recurrence- 19%		Change in target definition Change in treatment intention

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, NR = not reported

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2b- Characteristics of included studies, PICO 2 (without staging PET)

*
0. Not blinded or N.R
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded
3. Both target delineation and dose planning are done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
Davis 2015 Canada	Prospective cross-sectional	1	NR	36	NR	61%	NSCLC I-28% II-14% III-50% IV-8%	The study included both NSCLC (n=36) and Head and neck cancer patients (n=53). Mean age in the whole population was 64	Change in target definition Change in treatment intention
De Ruysscher 2005 Netherlands	Prospective cross-sectional	1	NR	21	NR	NR	NSCLC II- 5% III- 95%		Change in target definition
Deniaud-Alexandre 2005 France	Retrospective cross-sectional	1	2000-2004	101	Median 66	82%	NSCLC I- 15% II- 4% III- 63% Recurrence- 18%		Change in target definition Change in treatment intention
Erdi 2002 USA	Retrospective cross-sectional	0	NR	11	Mean 72	27%	NSCLC I-III Proportions not reported		Change in target definition
Faria 2008 Canada	Retrospective cross-sectional	0	NR	32	NR	NR	NSCLC Stages not reported		Change in target definition
Fitton 2008 Netherlands	Retrospective cross-sectional	1	NR	22	Mean 72	77%	NSCLC Localised- 100%		Interobserver variability
Giraud 2001 France	Retrospective cross-sectional	0	NR	12	NR	67%	NSCLC I- 42% II- 16% III- 42%		Change in target definition
Gondi 2007 USA	Retrospective cross-sectional	1	2001-2004	14	NR	NR	NSCLC I- 7% II- 7% III- 65% IV- 14% Recurrence- 7%		Change in target definition

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, NR = not reported

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2b- Characteristics of included studies, PICO 2 (without staging PET)

*
0. Not blinded or N.R
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded
3. Both target delineation and dose planning are done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
Gregory 2012 Australia	Prospective cross-sectional	1	2002-2003	49	NR	68%	NSCLC I- 50% II- 10% III- 34% IV- 6%		Change in target definition Change in treatment intention
Kalff 2001 Australia	Prospective cross-sectional	1	1997-1998	34 105	Mean 64	58%	NSCLC I-IV Proportions not reported	Partly same population as in Mac Manus 2001?	Change in target definition (n=34) Change in treatment intention (n=105)
Kolodziejczyk 2011 Poland	Prospective cross-sectional	0	2008-2009	100	Median 67	78	NSCLC I- 21% II- 9% III- 70%		Change in target definition Change in treatment intention
Kruser 2009 USA	Prospective cross-sectional	2	2004-2006	38	NR	NR	NSCLC I- 13% II- 13% III- 58% IV- 5% SCLC- 11%	Results are based on the whole population (n=38)	Change in target definition
Lewandovska 2006 Poland	Retrospective cross-sectional	1	2003-2005	20	Mean 60	90%	NSCLC I- 15% II- 5% III- 75% IV- 5%		Change in target definition
McManus 2001 Australia	Prospective cross-sectional	0	1996-1999	153	Median 67	70%	NSCLC I- 24% II- 15% III- 61%		Change in target definition Change in treatment intention
McManus 2013 Australia	Prospective cross-sectional	1	2004-2007	46	NR	68%	NSCLC I-III Majority stage III	This trial also included patients with a staging PET (see appendix 2a)	Change in treatment intention

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, NR = not reported

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2b- Characteristics of included studies, PICO 2 (without staging PET)

*
0. Not blinded or N.R
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded
3. Both target delineation and dose planning are done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
Mah 2002 Canada	Prospective cross-sectional	1	1999-2000	30	Mean 67	53%	NSCLC I-13% II-23% III-60% Recurrence-4%		Change in target definition Change in treatment intention
Marta 2011 Brazil	Retrospective cross-sectional	1	2003-2007	23	NR	56%	Subgroup or stages not reported		Change in target definition
Nawara 2012 Austria	Prospective cross-sectional	0	2003-2008	91	Mean 67	79%	NSCLC I-21% II-4% III-75%		Change in target definition
Pommier 2010 France	Prospective cross-sectional	1	2004-2006	109	Mean 61	82%	NSCLC I-13% II-8% III-79%	The trial also included patients with a staging PET (see appendix 2a)	Change in target definition Change in treatment intention
Spratt 2010 USA	Retrospective cross-sectional	1	2005-2006	11	Mean 71	NR	NSCLC I-18% II-18% III-46% Recurrence-18%		Change in target definition Change in treatment intention
Vanuytsel 2000 Belgium	Retrospective cross-sectional	0	N.R	73	N.R	NR	NSCLC N0-7% N1-8% N2-77% N3-8%		Change in target definition
Vojtisek 2014 Chech Republic	Retrospective cross-sectional	1	2009-2012	31	Median 68	84%	NSCLC I-6% II-3% III-78% IV-13%		Change in target definition Change in treatment intention
Yin 2013 China	Retrospective cross-sectional	0	2010-2012	30	Median 71	63%	NSCLC III-100%	Only patients with atelectasis	Change in target definition

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, NR = not reported

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 2b- Characteristics of included studies, PICO 2 (without staging PET)

*
0. Not blinded or N.R
1. Investigator delineates a separate CT-based target without access to PET and then delineates a PET/CT based target.
2. Different investigators delineate CT and PET/CT-based targets but dose planning is not blinded
3. Both target delineation and dose planning are done by separate investigators.

Author Year Country	Study Design	Blinding*	Study period (years)	Patients (n)	Age (years)	Men (%)	Lung cancer subgroup and stage	Comments	Outcome variables
Zheng 2014 China	Retrospective cross-sectional	0	2006-2007	23	Median 63	83%	NSCL I-9% II-17% III-74%		Change in target definition Change in treatment intention Interobserver variability
SCLC									
Azad 2010 Australia	Retrospective cross-sectional	2	1993-2008	26	Mean 63.5	52%	SCLC LD-100%	Only PET no PET/CT	Change in target definition Change in treatment intention
Bradley 2004b USA	Prospective cross-sectional	1	2001-2003	24	Mean 60	46%	SCLC LD-100%	Only PET no PET/CT	Change in target definition Change in treatment intention
Kruser 2009 USA	Prospective cross-sectional	2	2004-2006	38	NR	NR	NSCLC I-13% II-13% III-58% IV-5% SCLC-11%	Results are based on the whole population (n=38)	Change in target definition

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, NR = not reported

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Ciernik 2003	N (NSCLC + SCLC) < 10 patients
De Ruysscher 2010	Guidelines from The European Organization for Research and Treatment of Cancer (EORTC)
Duan 2014	Incorrect PICO (compares 4DCT and 3DPET/CT)
Fox 2005	Incorrect PICO (compares registered and non-registered PET/CTs)
Hicks 2001	Duplicate (Mac Manus 2001)
Igdem 2010	N< 10 patients (8 NSCLC, 3 SCLC)
Mac Manus 2007	N<10
Morarji 2012	N<10
Messa 2005	Duplicate (Ceresoly 2007)
Nestle 2005	Incorrect PICO (compares delineation by different SUV cut-offs on PET/CT)
Nestle 2007	Incorrect PICO (compares delineation of mediastinal lymph nodes by different SUV cut-offs on PET/CT)
Okubo 2010	Incorrect PICO (compares delineation by different SUV cut-offs on PET/CT)
Reyman 2013	Incorrect PICO (dose not compare PET/CT- and CT-based radiotherapy)
Roberts 2005	Incorrect PICO (evaluates PET/CT in residual disease)
Roman 2001	Incorrect PICO (evaluates PET/CT in the staging procedure)
Steenbakkers 2006	Duplicate (Fitton 2008)
Steenbakkers 2007	Duplicate (Fitton 2008)
van Der Wel 2005	Duplicate (de Ruysscher 2005)

Appendix 3. Excluded articles

Study (author, publication year)	Reason for exclusion
Ung 2011c	Duplicate (Ung 2011b)
Vinod 2010	N<10
Yu 2009	Incorrect PICO (compares PET/CT-based volumes with histopathology after surgery)

NSCLC = non small cell lung cancer, SCLC = small cell lung cancer, SUV= standardized uptake values

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.1 PICO 2 (without staging PET)
Outcome variable: Survival

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results Survival		Comments	Directness *	Study limitations*	Precision *
			Intervention PET/CT	Control CT				
NSCLC								
Ung 2011b Canada	Randomised controlled Trial (abstract)	310	2-year survival: 53% HR (mortality)=0.7 (95% CI 0.5-1.0 p=0.045	2-year survival: 41%	Abstract	?	-	?+
Socha 2013 Poland	Cohort	223	Median survival: 17 months 3-year survival: 33% p=0.1	Median survival: 17 months 3-year survival: 19%	Case series with historical controls. Not corrected for stage imbalance (more stage IIIB in interventional group, favouring CT only)	?	-	?

NSCLC = non small cell lung cancer, HR=Hazard ratio, CI=confidence interval

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.2a PICO 1 (with a staging PET)
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Number of patients n=	Results		Comments	Directness *	Study limitations	Precision *
			Change in radiation fields	Cut-off level for change in volume				
NSCLC								
Everitt 2013 Australia	Prospective cross-sectional	21	15/21 (71%)	Cut-off not known (PTV)		+	?	-
Grills 2007 USA	Retrospective cross-sectional	21	8/21 (38%)	Cut-off not known		?	-	-
Lin 2011 Australia	Retrospective cross-sectional	26	6/26 (23%)	Cut-off not known (defined as "upstaging")		+	?	-
Pommier 2010 France	Prospective cross-sectional	25	4/25 (16%)	Change in CTV >25%		+	+	+
		Summary ratio:	33/93					
		Summary estimate of ratios from individual articles:	36% (95%CI 16-62%)	Meta-analysis conducted in the software R, applying a random effects model.				

PTV= planning target volume, CTV= clinical target volume

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.2b PICO 2 (without a staging PET)
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results		Comments	Directness *	Study limitations	Precision *
			Change in radiation fields	Cut-off level for change in volume				
NSCLC								
Ashamalla 2005 USA	Prospective cross-sectional	19	8/19 (42 %)	Change in PTV >20%		?	+	?
Bradley 2012 USA	Prospective cross-sectional	47	24/47 (51 %)	Cut-off not known (defined as “disagreement between nodal stations”)		+	+	+
Bradley a 2004 USA	Prospective cross-sectional	26	14/26 (54 %)	Cut-off not known (defined as “clear GTV decrease or increase”)		?	?	?
Ceresoli 2007 Italy	Retrospective cross-sectional	21	7/21 (33 %)	Change in GTV >25%		-	?	-
Davis 2015 Canada	Prospective cross-sectional	36	10/36 (28 %)*	Defined as failure to meet constraint: 100 % of PTV volume should receive ≥ 95 % of the dose	* 5 patients missing			
De Ruysscher 2005 Netherlands	Prospective cross-sectional	21	14/21 (67 %)	Cut off not known (PTV)		+	?	-
Deniaud-Alexandre 2005 France	Retrospective cross-sectional	101	45/101 (45 %)	Change in GTV >25%		+	?	+
Erdi 2002 USA	Retrospective cross-sectional	11	5/11 (45 %)	Cut-off not known (defined as “significantly change in PTV”)		-	-	-

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer, PTV= planning target volume, GTV= gross tumor volume, CTV= clinical target volume

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.2b PICO 2 (without a staging PET)
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results		Comments	Directness *	Study limitations	Precision *
			Change in radiation fields	Cut-off level for change in volume				
Faria 2008 Canada	Retrospective cross-sectional	32	16/32 (50 %)	Change in GTV >30%		-	-	-
Giraud 2001 France	Retrospective cross-sectional	12	5/12 (41 %)	Cut-off not known		-	?	-
Gondi 2007 USA	Retrospective cross-sectional	14	11/14 (79 %)	Change in GTV >5%		-	?	-
Gregory 2012 Australia	Prospective cross-sectional	49	7/49 (14 %)	Cut-off not known	49 patients considered for radical radiotherapy, 168 patients totally in study	+	+	+
Kalff 2001 Australia	Prospective cross-sectional	34	22/34 (65 %)	Cut-off not known		?	?	+?
Kolodziejczyk 2011 Poland	Prospective cross-sectional	100	40/100 (40 %)	Cut-off not known (defined as “change in radiotherapy schedule”)		+	+	+
Kruser 2009 USA	Prospective cross-sectional	38	14/38 (37 %)	Change in GTV >20%		?	-	?
Lewandovska 2006 Poland	Retrospective cross-sectional	20	15/20 (75 %)	Change in GTV >20 %		-	?	-
McManus 2001 Australia	Prospective cross-sectional	153	41/153 (27 %)	Cut-off not known		+	?	+
Mah 2002	Prospective cross-sectional	30	5/30 (17 %)	Cut-off not known	17-29% of patients would have their PTV underdosed without planning-	?	?	-

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer, PTV= planning target volume, GTV= gross tumor volume, CTV= clinical target volume

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.2b PICO 2 (without a staging PET)
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results		Comments	Directness *	Study limitations	Precision *
			Change in radiation fields	Cut-off level for change in volume				
Canada					PET			
Marta 2011 Brazil	Retrospective cross-sectional	23	18/23 (78 %)	Cut-off not known		-	-	-
Nawara 2012 Austria	Prospective cross-sectional	91	8/91 (9 %)	Cut-off not known		+	?	+
Pommier 2010 France	Prospective cross-sectional	109	23/109 (21 %)	Change in CTV >25%		+	+	+
Spratt 2010 USA	Retrospective cross-sectional	11	7/11 (64 %)	Change in GTV >15%		+	?	-
Vanuytsel 2000 Belgium	Retrospective cross-sectional	73	45/73 (62 %)	Change in PTV >12%		-	-	?
Vojtisek 2014 Chech Republic	Retrospective cross-sectional	31	13/31 (42 %)	Cut-off not known	Decrease in median PTV from 320 cm^3 (CT) to 263 cm^3 (PET/CT) p<0.001	?	?	-
Yin 2013 China	Retrospective cross-sectional	30	12/30 (40 %)	Change in GTV >25 %		?	?	-
Zheng 2014 China	Retrospective cross-sectional	23	12/23 (52 %)	Change in GTV >11%		+	-	-
		Summary ratio:	440/1155					
		Summary estimate of ratios from individual articles	43% (95% CI 35-51%)		Meta-analysis conducted in the software R, applying a random effects model.			

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer, PTV= planning target volume, GTV= gross tumor volume, CTV= clinical target volume

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.2b PICO 2 (without a staging PET)
Outcome variable: Change in target definition

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results		Comments	Directness *	Study limitations	Precision *
			Change in radiation fields	Cut-off level for change in volume				
SCLC								
Azad 2010 Australia	Retrospective cross-sectional	26	3/26 (12 %)	Cut-off not known	Only SCLC LD included n=46 patients totally in study	?	?	?
Bradley b 2004 USA	Prospective cross-sectional	24	7/24 (29%)	Cut-off not known		?	+	?
Kruser 2009 USA	Prospective cross-sectional	38	14/38 (37 %)	Change in GTV >20%		?	-	?
		Summary ratio:	24/88					
		Summary estimate of ratios from individual articles:	26% (95% CI 14-44%)		Meta-analysis conducted in the software R, applying a random effects model.			

Summary estimate NSCLC and SCLC: 41%, 95% CI 34-48%

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer, PTV= planning target volume, GTV= gross tumor volume, CTV= clinical target volume

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.3a PICO 1 (with staging PET)
Outcome variable: Change in treatment intent (change from curative to palliative treatment)

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Number of patients n=	Results: Change in treatment intention	Comments	Directness *	Study limitations	Precision *
NSCLC							
Everitt 2013 Australia	Prospective cross-sectional	21	6/21 (29 %)	Median 23 days between PET1 and PET2 (range 8–176 days)	+	?	-
Lin 2011 Australia	Retrospective cross-sectional	26	3/26 (12 %)	Scan interval 40 ±12 days	+	?	?
McManus 2013 Australia	Prospective cross-sectional	30	11/30 (37 %)	30 is a subset of study population with a staging PET	+	?	?
Pommier 2010 France	Prospective cross-sectional	25	1/25 (4 %)	25 is a subset of study population with a staging PET	+	+	-
		Summary ratio:	21/102				
		Summary estimate of ratios from individual articles:	20% (95% CI 9-39%)	Meta-analysis conducted in the software R, applying a random effects model.			

NSCLC = non small cell lung cancer

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.3b PICO 2 (without staging PET/CT)
Outcome variable: Change in treatment intent (change from curative to palliative treatment)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results: Change in treatment intention	Comments	Directness *	Study limitations*	Precision *
NSCLC							
Ung 2011b Canada	Randomised controlled trial	310	PET group: 22/152 (14 %) CT group: 4/158 (3 %) RR 5.7 95% CI 2.0-16 Absolute risk reduction (ARR) 11%, 95% CI 5.6-18.6	Abstract	?	-	?+
Socha 2013 Poland	Retrospective cross-sectional	100	24/100 (24 %)		?	-	?
Abramyuk 2012 Germany	Retrospective cross-sectional	104	26/104 (25 %)	Median interval between CT and PET/CT 19 days	+	?	?
Bradley a 2004 USA	Prospective cross-sectional	26	2/26 (8 %)		?	?	?
Ceresoli 2007 Italy	Retrospective cross-sectional	21	3/21 (14 %)		-	?	-
Davis 2015 Canada	Prospective cross-sectional	36	4/36 (11 %)*	* 5 patients missing	+	?	?
Kalff 2001 Australia	Prospective cross-sectional	105	27/105 (26 %)		?	?	+?
Kolodziejczyk 2011 Poland	Prospective cross-sectional	100	25/100 (25 %)	PET/CT performed within 2 weeks from CT	+	+	+

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer,

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.3b PICO 2 (without staging PET/CT)
Outcome variable: Change in treatment intent (change from curative to palliative treatment)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results: Change in treatment intention	Comments	Directness *	Study limitations*	Precision *
McManus 2001 Australia	Prospective cross-sectional	153	46/153 (30 %)		+	?	+
McManus 2013 Australia	Prospective cross-sectional	46	15/46 (33 %)		+	?	+
Mah 2002 Canada	Prospective cross-sectional	30	7/30 (23 %)		?	?	-
Pommier 2010 France	Prospective cross-sectional	109	14/109 (13 %)		+	+	+
Spratt 2010 USA	Retrospective cross-sectional	11	3/11 (27 %)		+	?	-
Vojtisek 2014 Chech Republic	Retrospective cross-sectional	31	3/31 (10 %)		?	?	-
Zheng 2014 China	Retrospective cross-sectional	23	3/23 (13 %)		+	-	-
	Summary ratio:		202/895				
	Summary estimate of ratios from individual articles:		22% (95% CI 18-26%)	Meta-analysis conducted in the software R, applying a random effects model.			

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer,

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.3b PICO 2 (without staging PET/CT)
Outcome variable: Change in treatment intent (change from curative to palliative treatment)

* + No or minor problems
? Some problems
- Major problems

Author, year, country	Study design	Number of patients n=	Results: Change in treatment intention	Comments	Directness *	Study limitations*	Precision *
SCLC							
Azad 2010 Australia	Retrospective cross-sectional	46	4/46 (9 %)		?	?	?
Bradley 2004b USA	Prospective cross-sectional	24	2/24 (8 %)		?	+	?
	Summary ratio:		6/70				
	Summary estimate of ratios from individual articles:		9% (95% CI 4-18%)	Meta-analysis conducted in the software R, applying a random effects model.			

Summary estimate NSCLC and SCLC: 20% (95% CI 16-25%)

NSCLC= non small cell lung cancer, SCLC= small cell lung cancer,

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 4.4 PICO 1 + 2 (with staging PET and without staging PET)
Outcome variable: Interobserver variability

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Number of patients n=	Results interobserver variability		Comments	Directness *	Study limitations	Precision *
			PET/CT	CT				
NSCLC								
Ashamalla 2005 USA	Prospective cross-sectional	19	16/19 (84 %) had a ≤ 10% volume discrepancy relative to the mean treatment volume p=0.0035	7/19 (37%) had a ≤ 10% volume discrepancy relative to the mean treatment volume		?	+	?
Fitton 2008 Netherlands	Retrospective cross-sectional	22	Standard deviation 0.4 cm p=0.0003	Standard deviation 1.3 cm	True for tumors in the hilar region, heart, great vessels, pericardium, mediastinum, and/or the region associated with atelectasis	-	?	-
Hanna 2010 Ireland	Retrospective cross-sectional	28	Concordance index 0.64 p=0.03	Concordance index 0.57	With staging PET (PICO C1)	?	?	?
Zheng 2014 China	Retrospective cross-sectional	23	GTV mean ratio volume difference 1.5 cm^3	GTV mean ratio volume difference 2.3 cm^3		+	-	-

GTV= gross tumor volume

Appendix 5

ETHICAL ANALYSIS OF

Question	Answer/ comment
1. From the patient's perspective, how does this method/technology affect the patient's quality of life and life expectancy?	On a group level the QoL will possibly be improved as some patients will not receive burdensome high dose treatment in vain, and life expectancy will possibly increase.
2. How severe is the patient's need that the method/technology must meet?	Very severe with a high risk of premature death
3. Does method/technology have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	No
4. Can method/technology affect the patient's ability and possibility to be independent?	Independence due to side effects will possibly occur to a smaller population due to improved accuracy in patient selection. Independence due to tumour progression may also occur to fewer patients due to increased tumour control because of more accurate target definition and subsequent tumour control.
5. If implemented, does this method/technology require any special steps to not compromise the patient's autonomy?	No
6. How does this method/technology affect the patient's physical, moral and personal integrity?	No impact
7. Is method/technology cost-effective?	Possibly so, due to improved patient selection where resources will not be spent in vain on patients with distant spread.
8. How does this method/technology affect resources?	For the time being there is a risk of crowding out of other patient groups as the PET-availability is limited in VGR. However two additional PET-scans are planned during 2016-2017.
9. Is this method/technology in conflict with professional values?	No
10. Does this method/technology change the role of the professional in relation to the patient?	No

11. Does this method/technology affect, or does it put any new demands on, a third party?	No
12. Is there any legislation of relevance with regard to this method/technology?	No
13. Is there any risk of conflict between the procedure of this method/technology and values of the society, or values of different groups?	No
14. Is there a risk that an introduction of this method/technology will cause a conflict with particular interests?	No
15. Can an introduction of the method/technology influence the trust of the health care system?	No
CONCLUSIONS	There are no obvious ethical concerns with implementing PET/CT in the work-up for radiotherapy of lung cancer.

Project: PET/CT prior to radiotherapy for lung cancer
Appendix 6 Related trials in www.clinicaltrials.gov

NCT number	Title	Design	Objectives	Status	N	Completion date
NCT01507428	Study of Positron Emission Tomography and Computed Tomography in Guiding Radiation Therapy in Patients With Stage III Non-small Cell Lung Cancer	Interventional randomised open label phase II	Local-regional, progression-free (LRPF) rate (time frame two years)	Recruiting	138	Nov 2016
NCT00221169	Role of PET CT in Determining Target Volumes in Radiation Therapy for Lung Cancer	Interventional single group phase 0	Clinical pathological correlation of PET CT with surgically resected NSCLC	Completed	31	Jan 2009
NCT00123747	Study of 18F-Fluorodeoxyglucose in Patients Receiving a Treatment Planning Study of 3 Dimensional Conformal Radiation Therapy Guided by Breath Held CT and PET Imaging for Patients With Non-Small Cell Lung Cancer	Interventional single group open label phase II	To define the effect of respiratory-gating upon PET based radiotherapeutic treatment planning parameters relative to the free-breathing condition for patients with NSCLC To define the relationship between PET based treatment planning volumes and CT based treatment planning volumes within the realm of respiratory-gating for patients with NSCLC	Completed	23	Oct 2008
NCT00310219	Positron Emission Tomography Scan and CT Scan in Planning Radiation Therapy for Patients With Stage II or Stage III Non-Small Cell Lung Cancer	Interventional single group open label	The impact of positron emission tomography (PET)/CT fusion planning on GTV (cm^3) vs. planning with CT scan alone The impact of positron emission tomography (PET)/CT fusion planning on number of contoured lymph nodes vs. planning with CT scan alone The impact of positron emission tomography (PET)/CT fusion planning on location of involved lymph nodes vs planning with CT scan alone	Completed	52	Nov 2013
NCT01888692	To Evaluate the Impact of PET/CT on Radiation Treatment Planning in Relation to Changes in GTV in Stage 3 NSCLC	Observational	Impact of PET/CT fusion on gross tumor volume for primary and nodal disease for each patient by comparing GTV contours using three separate data sets.	Terminated (slow accrual)	29	Dec 2010

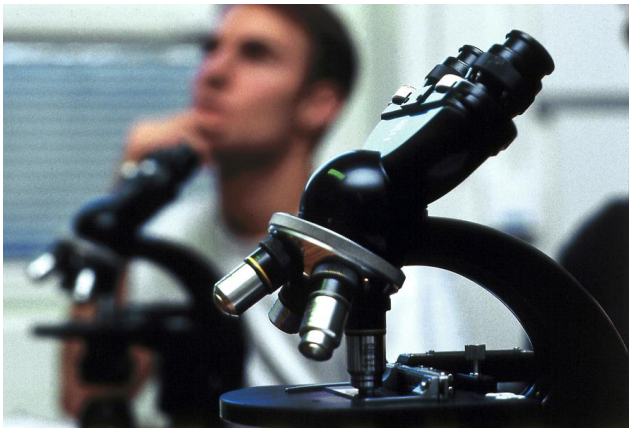
Project: PET/CT prior to radiotherapy for lung cancer
Appendix 6 Related trials in www.clinicaltrials.gov

NCT number	Title	Design	Objectives	Status	N	Completion date
NCT00697333	Radiotherapy Planning Based on Positron Emission Tomography With Fluoro-deoxyglucose For Advanced NSCLC	Interventional randomised open label phase II	Time to local progression Overall survival Normal tissue toxicity In and out field progression	Recruiting	200	May 2017
NCT00958321	Positron Emission Tomography and Computed Tomography in Planning Treatment for Patients Undergoing 3-Dimensional Conformal Radiation Therapy for Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery. ICORG 06-35	Interventional single group open label phase II	Rate of successful delivery of PET-CT scan based 3-D conformal radiotherapy (Pilot) Rate of loco-regional recurrence outside the PET-CT planning target volume (PTV) but within conventional 3-D PTV (Phase II) Acute and long-term radiation-induced toxicity Comparison of dose delivery to organs at risk, according to planning method	Terminated (slow accrual)	?	Dec 2016
NCT02247713	An International Study on the Use of PET/CT in Radiotherapy Planning in Low and Middle Income Countries	Observational cohort study	2-year overall survival Observer agreement with expert contours as a measure of the effect of a training intervention on tumor volume delineation Baseline PET/CT characteristics as a measure for PET/CT scanner performance	Not yet recruiting	520	Dec 2017
NCT00572923	Concurrent Chemo-Radiotherapy for Limited Disease Small Cell Lung Cancer (LD-SCLC) on Basis of FDG-PET-Scans	Observational cohort study	Isolated Nodal Recurrences Overall survival Progression-free interval	Completed	52	Feb 2009

GTV= gross tumor volume

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

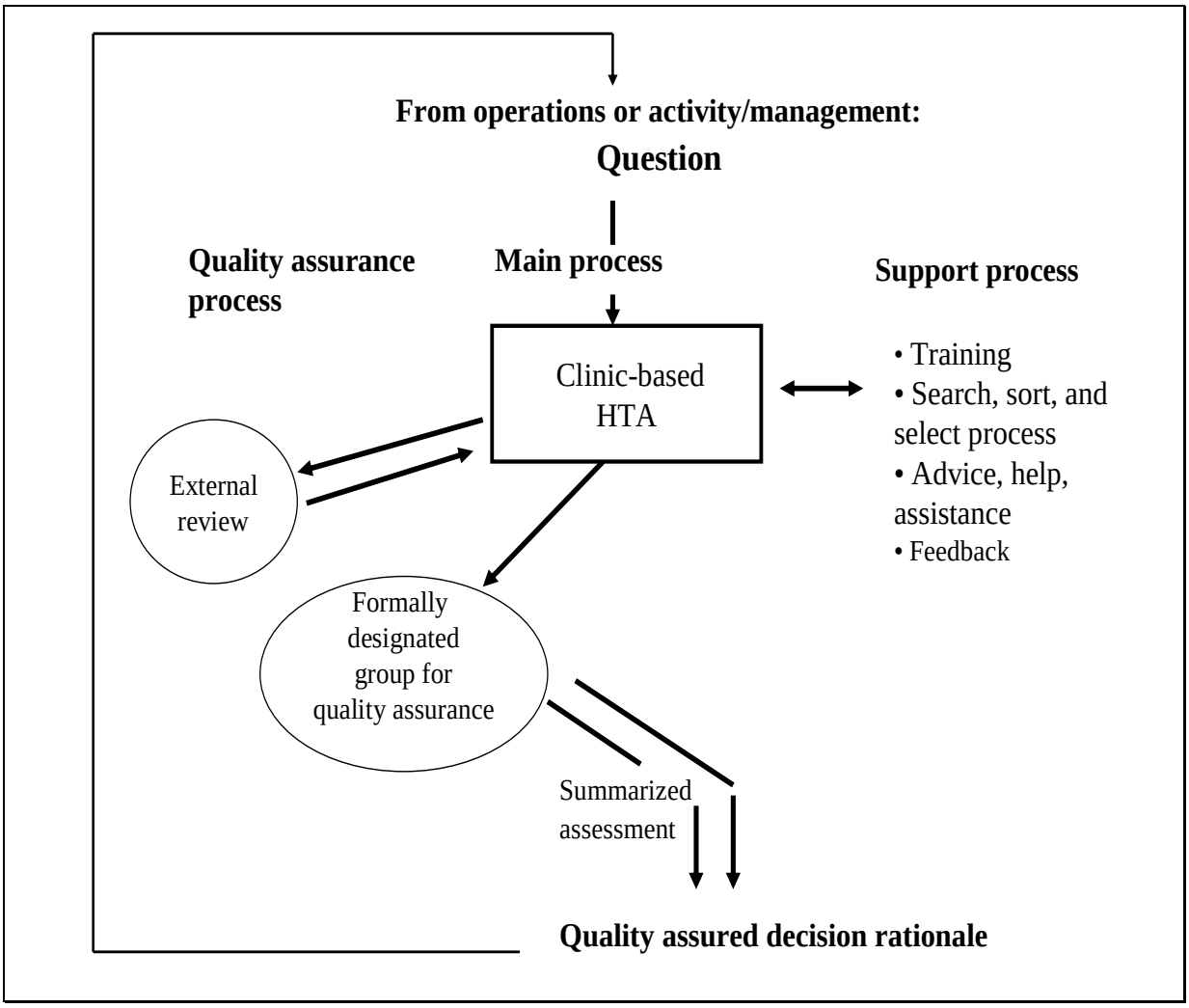
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕O)
Low quality of evidence	= (GRADE ⊕⊕OO)
Very low quality of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh, Professor, MD.
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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