Systematic review

Positron emission tomography and computed tomographic imaging (PET/CT) for dose planning purposes of thoracic radiation with curative intent in lung cancer patients: A systematic review and meta-analysis

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ABSTRACT

Background and purpose: PET/CT is a proposed management to improve the accuracy of high dose radiochemotherapy in lung cancer patients. This systematic review was performed to investigate the possible impact on clinical outcome and to quantify the effect on patient selection and target definition.
Material and methods: Systematic literature searches were conducted, eligible full-text articles were assessed for quality and data were extracted.
Results: Thirty-five cross-sectional studies and one observational study fulfilled the inclusion criteria. No randomized trials or data with regard to clinical endpoints were found. The summary estimates of a change in target definition were 36% in patients with a former staging PET, and 43% and 26% in patients without a staging PET, for non small- and small cell lung cancer respectively. The corresponding summary estimates of a change in treatment intent from curative to palliative treatment were 20% and 22% and 9% respectively.
Conclusion: PET/CT for dose planning improves target definition and patient selection. Approximately two in five patients had a significant change in target definition and one in five received palliative treatment instead. The proportions seem to be similar regardless of the availability of a previous staging-PET.
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Rationale: 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 at a stage of their disease that is too advanced for surgery but without distant metastatic spread (i.e. with mediastinal metastases or advanced growth of the primary tumour) and are categorised as locally advanced or stage III tumours. These patients may be treated with curative intent with high dose irradiation and concurrent 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 for dose planning purposes in the radiotherapy work-up is to use the combination of Positron Emission Tomography (PET) and CT, i.e. PET/CT. The use of PET/CT could better select suitable patients to high dose radiation therapy as patients with previously unknown metastatic disease would be managed with a palliative approach instead. PET/CT may also increase the likelihood of correctly delineating 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, will likely decrease [1]. During recent years, numerous retrospective and prospective series and non-systematic reviews have been published that support the use of PET/CT over CT alone for dose planning. Most of the studies have analysed a change in target definition or the proportion of patients that could be diagnosed with stage IV disease, and therefore no longer are suitable for radiochemotherapy. Very few have reported outcome on the clinical endpoints survival or health related quality of life (HRQL). Furthermore, the majority of the studies of PET/CT for dose planning purposes were performed before PET/CT was introduced in a standardized manner with regard to staging of

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potentially curable lung cancer. The value of an additional PET/CT for dose planning with a previously performed staging PET is less studied.

The purpose of this health technological assessment (HTA) was to evaluate whether the use of PET/CT for dose planning purposes improves radiotherapy for patients suitable for curative treatment with high dose radiochemotherapy, and to quantify the effect on patient selection and target definition.

Material and methods

Literature search

In March 2015 two librarians performed a systematic literature search from year 2000 and onwards in Medline, Embase, the Cochrane Library and Centre for Reviews and Dissemination, using the terms "lung neoplasms", "positron emission tomography", and "radiotherapy" with relevant synonyms. The search was limited to English, Danish, Norwegian or Swedish language and studies in humans. Up-dated searches were performed in November 2015 and June 2016 (Supplementary appendix 1). The lists of published HTA reports at the websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service, the Norwegian Knowledge Centre for the Health Services and the Danish Health Authority were also checked. In order to identify on-going or completed, but still not published studies, a search in www.clinicaltrials.gov was performed. Finally, the reference lists of relevant articles for any additional studies were scrutinised.

Study selection

Two of the authors (AH, PA), independently of one another, assessed the obtained abstracts with regard to fulfilment of the study inclusion criteria, 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 three of the other authors (CM, AS, OS). After reading the articles, independently of one another, it was decided in a consensus meeting which articles finally should be included in the systematic review.

Data extraction

Data were extracted by one of the authors (AH). For each article the year of publication, country, number of patients, age, gender, tumour stage and outcome variables (survival, proportion of patients with a change in target definition or treatment intention and interobserver variability) were recorded.

The studies were divided into two groups with regard to the access of a staging PET/CT. The first group included studies in which the dose planning based on 18FDG-PET/CT was compared to CT alone with access to a previous staging PET/CT (PICO 1, see Supplementary Table 1). The other group included studies in which the dose planning based on 18FDG-PET/CT was compared to CT alone without access to a staging PET/CT (PICO 2, see Supplementary Table 1). The proportions were recalculated to have a uniform calculation method in all the studies (i.e. number of patients with findings divided by the entire study population treated with curatively intended radiochemotherapy). The extracted data were subsequently scrutinised by another author (CM) and discussed among authors.

Quality assessment

The quality of the included studies were independently assessed by five of the authors (AH, PA, CM, AS, OS) using a slightly modified checklist for case series [2]. The appraisal addressed directness (external validity), risk of bias (internal validity) and precision and was presented in three levels. The certainty of evidence across studies was assessed by all authors and rated for all outcomes separately using the GRADE system [3]. The grading of the cross-sectional studies started at the GRADE ⊕⊕⊕⊕ level, similarly to cross-sectional studies of diagnostic accuracy.

Statistical analyses

Statistical analyses were performed with R (R Core Team, 2015) and the meta-package (Guido Schwarzer, 2016), pooling estimated proportions across studies using a random effects model. Exact confidence intervals for individual study proportions were calculated using the Clopper-Pearson method.

Results

The literature search identified a total of 1311 articles. Thirty-six fulfilled the inclusion criteria for the systematic review [4–39]. The selection process of articles is summarised in Fig. 1, and the search strategy in the Supplementary appendix 1.

The included studies, their design and patient characteristics are presented in Supplementary Tables 2a and 2b. The excluded studies with reason for exclusion are presented in Supplementary Table 3. Of the 36 studies one study was an observational study with historical controls, and the remaining 35 were cross-sectional prospective or retrospective studies. In general the directness (external validity) was high, but a number of studies have enrolled varying proportions of stage I disease which was not the scope of our intended population. The studies have been performed during a rather large time period during which the PET-technique has developed, interpretation and study set-up have varied and a majority of the studies are of a relatively low quality individually. There were study limitations where outcomes were assessed in various ways. The cut-off levels for a significant change of the target definitions (GTV, CTV and PTV) were not always reported, and the blinding procedure differed between trials. Several studies were rather small in size with low precision. For studies of SCLC in the second group (PICO 2) the overall precision was low due to the limited number of studies. With regard to PICO 1 (dose planning with PET/CT compared with CT alone for patients with access to a staging PET) there were no studies that reported data on survival or health related quality of life. All of the studies included only patients with NSCLC. A change of the target definition was reported in four cross-sectional trials with a total of 93 patients (Supplementary Table 4). The proportion of patients with a change target definition varied between 16% and 71% with a summary estimate of 36% (95% confidence interval (CI): 16–62), Fig. 2. The certainty of evidence was assessed as moderate (GRADE ⊕⊕⊕○). A change of the treatment intent from curative to palliative treatment was reported in four cross-sectional studies with a total of 102 patients (Supplementary Table 5). The proportion of patients with a change of the treatment intent varied between 4% and 37% with a summary estimate of 20% (95% CI: 9–39), Fig. 3. The certainty of evidence was assessed as moderate (GRADE ⊕⊕⊕○). With regard to PICO 2 (dose planning with PET/CT compared with CT alone for patients without access to a staging PET) overall survival was reported in the observational study, but it had major limitations. The patients in the study group had more severe disease at baseline than the patients in the comparison group, which only consisted of historical controls, and survival could not be properly assessed.

A change of the target definition was reported in 29 cross-sectional trials (26 NSCLC, 3 SCLC) with a total of 1243 patients (Supplementary Table 6). The proportion of patients with a change varied between 9% and 75%, with a summary estimate of 43% (95%
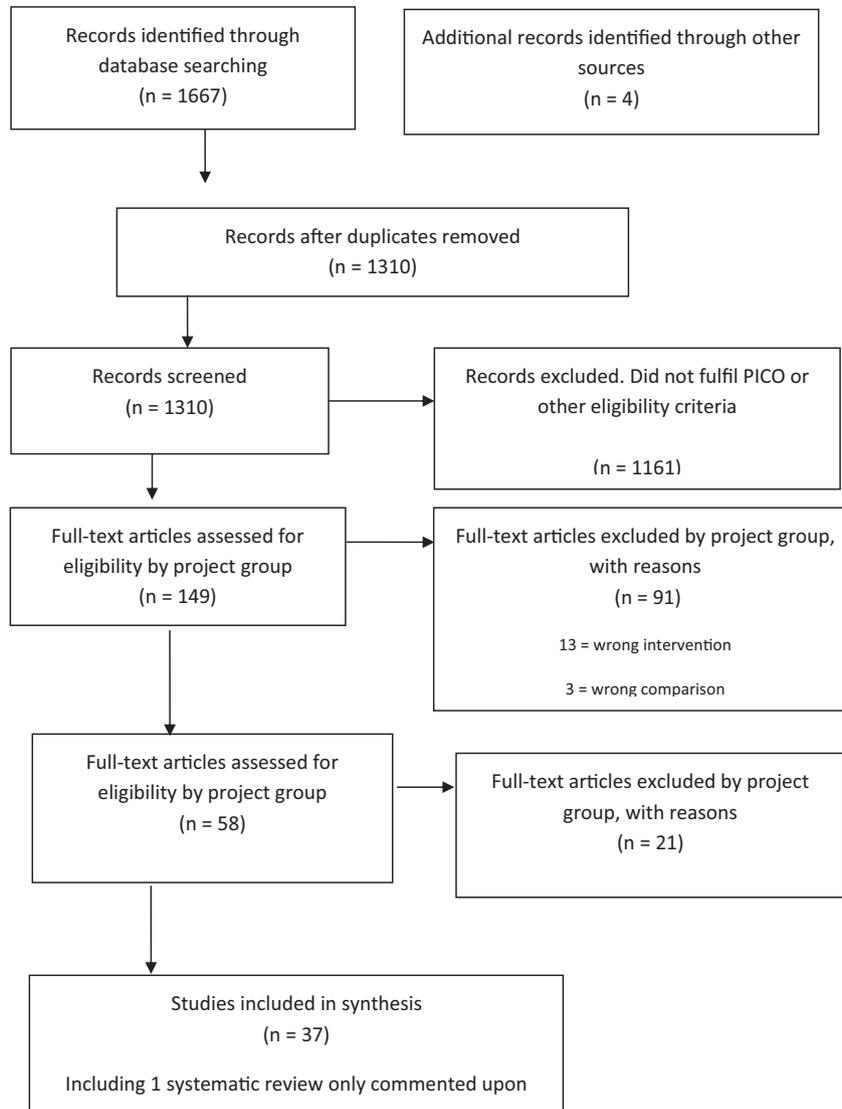
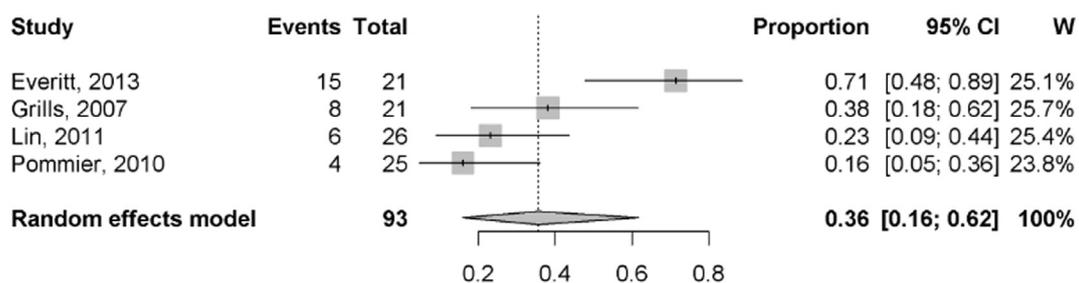Fig. 1. Flow chart with selection process of included articles.

Fig. 2. Proportion of patients with a change of the target definition (=event) in patients with a staging PET, w = weight.

CI 35–51) for NSCLC (Fig. 4) and 26% (95% CI: 14–44) for SCLC (Supplementary Fig. 1). The certainty of evidence was assessed as moderate (GRADE ⊕⊕⊕○). A change of the treatment intent was reported in 16 cross-sectional trials (14 NSCLC, 2 SCLC, n = 895 Supplementary Table 7). The change of the treatment intention varied between 8% and 33% with a summary estimate of 22% (95% CI: 18–26) for NSCLC (Fig. 5) and 9% (95% CI: 4–18) for SCLC (Supplementary Fig. 2). The certainty of evidence was assessed as moderate (GRADE ⊕⊕⊕○). A change in interobserver variability was reported in total in four cross-sectional trials (Supplement

Table 8). All studies used different measures to study interobserver variability. They report decreased standard deviation, increased concordance index and decreased volume discrepancy with PET/CT. The certainty of evidence was assessed as low (GRADE ⊕⊕○○).

Discussion

To our knowledge, this is the largest systematic review of the impact of PET/CT for dose planning purposes prior to radiation of lung tumours including 36 original trials from year 2000 and
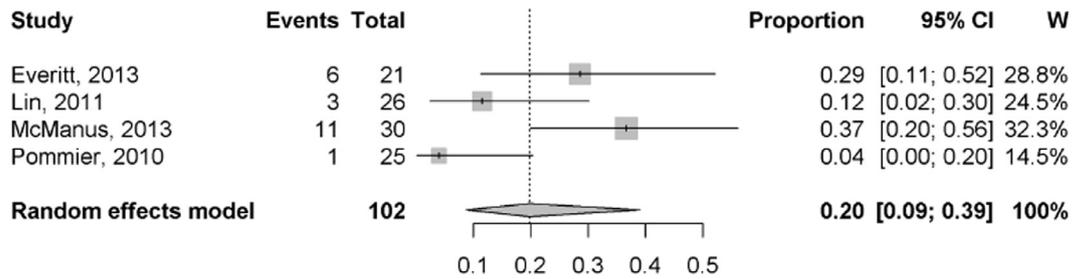
Fig. 3. Proportion of patients with a change of the treatment intent (=event) in patients with a staging PET, w = weight.
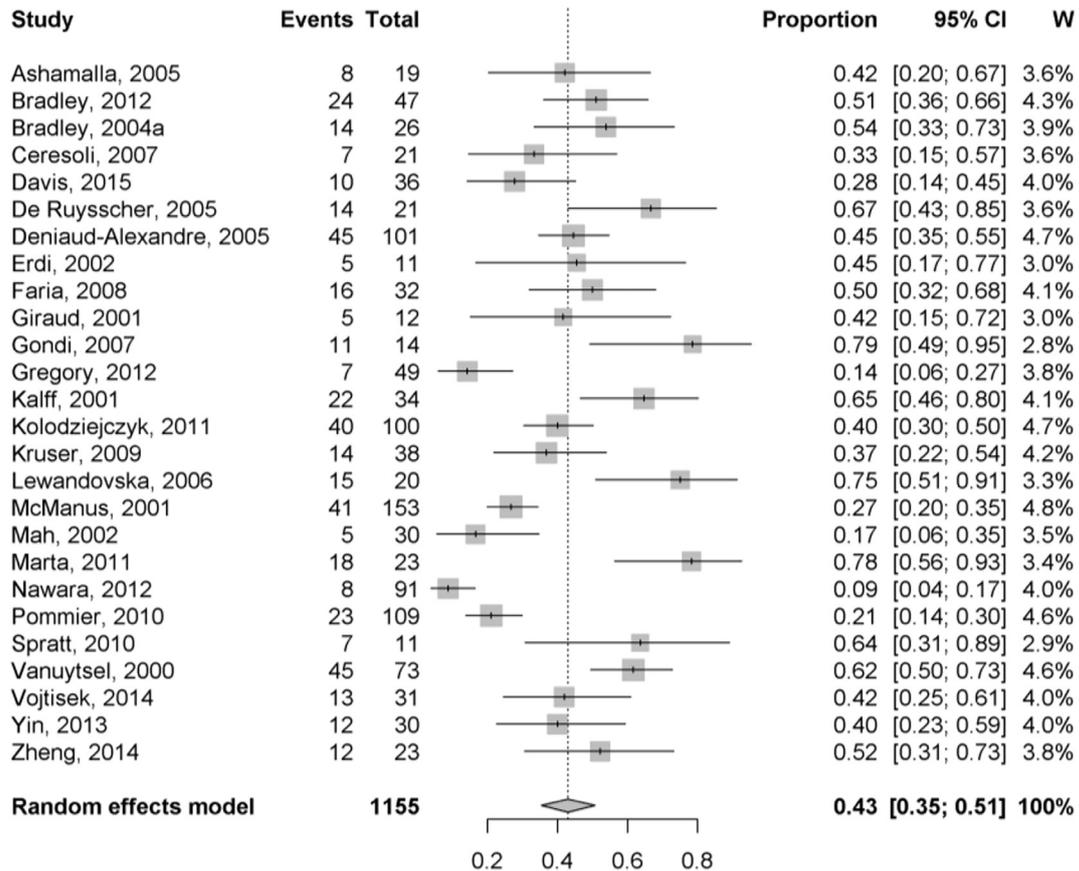

Fig. 4. Proportion of NSCLC patients with a change of the target definition (=event) in patients without a staging PET, w = weight.

onwards. It supports the view that the number of patients who will have a meaningful change in the tumour target volume or a change of treatment intent from curative to palliative are substantial and the analysis gives a pooled estimate of the magnitude of these changes.

Approximately two in five patients with NSCLC had a significant change of the target definition and one in five received palliative treatment instead of high dose radiation. It is somewhat less with regard to SCLC (one in five and one in ten respectively), however data is based on fewer studies. It is of great interest to note that the proportions of NSCLC patients with changes in target volumes and treatment intention seem to be similar regardless of the availability of a previous staging-PET or not. The results of the proportions of changes of both target definition and treatment intent are unquestionably influenced by the time interval between the staging PET and the subsequent dose planning PET. Everitt et al. [15] reported a median time interval of 23 days (range 8–176 days) and McManus et al. [28] reported results for a staging-PET older

than 3 weeks. In a study by Lin et al. [27] the median scan interval for the entire group was 33 days (range 7–56 days). When patients were divided according to progression, i.e. with or without progression between the staging PET and dose planning PET, the scan interval was 40 days (range 21–56 days) and 22 days (range 7–37), respectively. In addition they found that progressive disease was detected in 76%, 86% and 100% of the patients if the scan interval was 4, 5 or 6 weeks, respectively. In comparison a scan interval of less than 4 weeks resulted in 33% of patients identified with progressive disease. The patient number in the study by Lin et al. is rather small ($n = 25$). However, based on these studies data indicate that a new PET/CT for dose planning has an significant impact on target definition and treatment intent even after a narrow interval such as three to four weeks.

The interobserver variability was assessed with different endpoints and the studies could not be analysed together but individually report less divergence with the introduction of PET/CT. It has been shown that further improvement in delineation accuracy
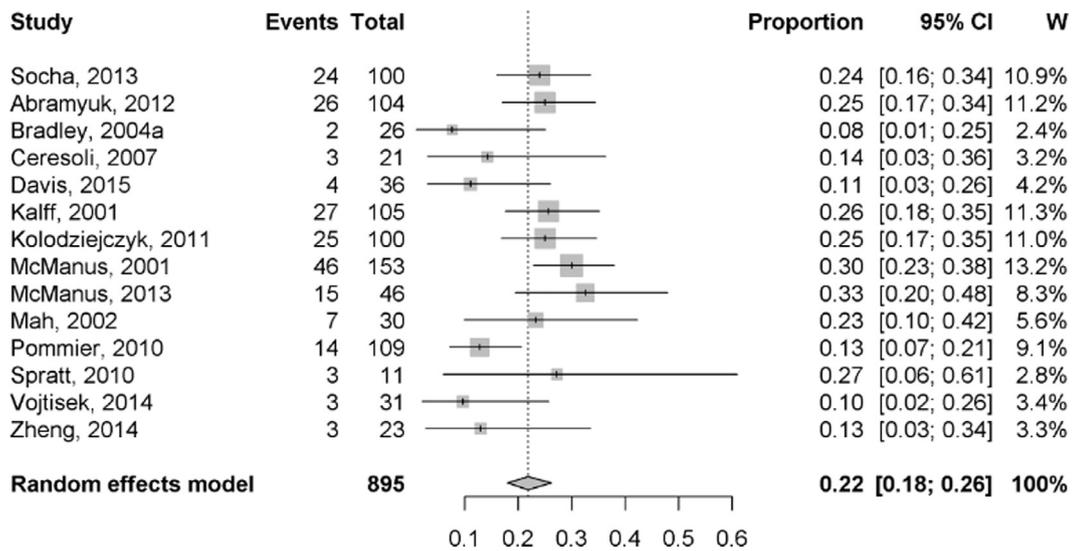
Study	Events	Total		Proportion	95% CI	W
Socha, 2013	24	100		0.24	[0.16; 0.34]	10.9%
Abramyuk, 2012	26	104		0.25	[0.17; 0.34]	11.2%
Bradley, 2004a	2	26		0.08	[0.01; 0.25]	2.4%
Ceresoli, 2007	3	21		0.14	[0.03; 0.36]	3.2%
Davis, 2015	4	36		0.11	[0.03; 0.26]	4.2%
Kalff, 2001	27	105		0.26	[0.18; 0.35]	11.3%
Kolodziejczyk, 2011	25	100		0.25	[0.17; 0.35]	11.0%
McManus, 2001	46	153		0.30	[0.23; 0.38]	13.2%
McManus, 2013	15	46		0.33	[0.20; 0.48]	8.3%
Mah, 2002	7	30		0.23	[0.10; 0.42]	5.6%
Pommier, 2010	14	109		0.13	[0.07; 0.21]	9.1%
Spratt, 2010	3	11		0.27	[0.06; 0.61]	2.8%
Vojtisek, 2014	3	31		0.10	[0.02; 0.26]	3.4%
Zheng, 2014	3	23		0.13	[0.03; 0.34]	3.3%
Random effects model		**895**		**0.22**	**[0.18; 0.26]**	**100%**

0.1 0.2 0.3 0.4 0.5 0.6

Fig. 5. Proportion of NSCLC patients with a change of the treatment intent (=event) in patients without a staging PET, w = weight.

and reduced interobserver variability can be achieved with multiple training interventions [40].

The certainty of evidence with regard to the outcome variables was assessed as moderate. The grading does not assess the magnitude or importance of the clinical outcome but the methodology of the studies involved. Throughout the last decades the technical development with regards to PET/CT imaging and interpretation has been extensive which impacts on the results of the included studies. In addition the design of a majority of the studies do not enable high level evidence conclusions but have rather low study quality which has to be kept in mind when assessing the results. Many of the studies are small with vague definitions of the cut-off levels for important changes, different and indistinct blinding, and their retrospective design further decrease the level of evidence. This high-light the need for well-defined PET-protocols to increase decrease the variability in interpretation [41]. The precision is however improved since the data could be pooled and the results in all studies were consistent with one another.

Our findings are in line with a previously reported systematic review by Ung et al. in which they concluded that PET/CT leads to substantial modifications of target volumes and changes in treatment intention [42]. They pointed out that it was uncertain whether these changes also would result in a better clinical outcome. To what extent the changes in delineation of target structures will influence survival, side effects of treatment, and quality of life still remains to be definitely clarified, and dose plan data still need to be linked to clinical outcome [43]. Ung et al. have performed the only RCT that have addressed this issue and have reported a significantly improved overall survival [44], but the trial is only reported in abstract form so far and therefore not included in this analysis. A survival benefit would however seem 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 [45,46].

In spite of the superiority of PET/CT to detect distant metastases there is still a risk to incorrectly refer patients to palliative treatment due to false positive PET findings when PET/CT is implemented before dose planning. If there are any uncertainties whether there is a distant spread the PET-positive lesions should always be verified as malignant with a histopathological examination [47].

On-going studies of pre-radiotherapeutic PET/CT, listed in clinicaltrials.gov, will probably add more knowledge on the impact on loco-regional progression rate, time to progression, and survival when PET/CT is used. However, we have not identified any on-going or planned phase III trials. It is not likely that another large randomised, controlled trial will be performed, even if a confirmatory prospective trial of Ung's unpublished data would be warranted. The hitherto accumulated data accounted for in this review have however been considered robust and convincing enough for clinical societies to recommend PET/CT based dose planning for lung cancer (EORTC, NCCN, IAEA) [40,48,49]. In addition PET/CT for dose planning permits further development with dose painting of areas more prone for relapse [50,51] and motion adapted treatment with 4DPET [52].

In conclusion, the studies published so far indicate that approximately two out of five patients will have a significant change in target definition and one out of five patients will no longer be suitable for radiochemotherapy due to metastatic disease, supporting the view that PET/CT should be performed prior to dose planning. This seems to be valid even if a staging PET/CT is done more than 3–4 weeks before radiotherapy planning, and would also probably be beneficial for patients with SCLC.

Conflict of interest statement

None of the authors has any conflicts of interest to declare.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.02.011.

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