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Overview

Effectiveness of Respiratory-gated Positron Emission Tomography/Computed Tomography for Radiotherapy Planning in Patients with Lung Carcinoma — A Systematic Review

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Abstract

Aims: A systematic review of the literature evaluating the clinical use of respiratory-gated (four-dimensional; 4D) fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) compared with non-gated (three-dimensional; 3D) PET/CT for radiotherapy planning in lung cancer.
Materials and methods: A search of MEDLINE, Cochrane, Web of Science, SCOPUS and clinicaltrials.gov databases was undertaken for articles comparing 3D and 4D PET/CT tumour volume or 4D PET/CT for radiotherapy planning. PRISMA guidelines were followed.
Results: Thirteen studies compared tumour volumes at 3D and 4D PET/CT; eight reported significantly smaller volumes (6.9–44.5%), three reported significantly larger volumes at 4D PET/CT (16–50%), one reported no significant difference and one reported mixed findings. Six studies, including two that reported differences in tumour volumes, compared target volumes or studied geographic misses. 4D PET/CT target volumes were significantly larger (19–40%) when compared with 3D PET/CT in all but one study, where they were smaller (3.8%). One study reported no significance in 4D PET/CT target volumes when compared with 4D CT, whereas another study reported significantly larger volumes (38.7%).
Conclusion: The use of 4D PET/CT leads to differences in target volume delineation compared with 3D PET/CT. These differences vary depending upon technique and the clinical impact currently remains uncertain. Correlation of pretreatment target volumes generated at 3D and 4D PET/CT with postsurgical histology would be ideal but technically challenging. Evaluation of patient outcomes based on 3D versus 4D PET/CT derived treatment volumes warrants further investigation.

Key words: FDG PET/CT; lung cancer; radiation therapy; respiratory gating; systematic review

Statement of Search Strategies Used and Sources of Information

A literature search of MEDLINE/PubMed, Cochrane, Web of Science, Scopus and clinicaltrials.gov databases was carried out, searching for articles on the use of 4D PET/CT in lung carcinoma. The search strategy included three major operator criteria, which were linked with the 'AND' function. The first criteria consisted of 'respiratory-gated' or '4D', the second criteria consisted of 'PET/CT' or 'positron emission tomography' and the third criteria consisted of 'lung', 'thorax' or 'radiotherapy'. Case studies, studies not comparing tumour or planning volumes between 4D and 3D PET/CT or 4D PET/CT and 4D CT, articles not published in English, phantom studies and studies with fewer than five subjects were excluded (to minimise publication bias). After duplications were excluded, studies were screened for eligibility based on title, abstract and subsequently on full text by two authors independently (RF, AS). The results were stored in a bibliographic management software. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were adhered.

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Introduction

^{18}Fluorine-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) provides key functional and anatomical information for the staging and management of patients with lung carcinoma, with its role in radiotherapy planning becoming more widely accepted [1–3]. One of the main limitations of thoracic PET/CT is the susceptibility to movement artefact from respiration as, unlike conventional CT imaging, it cannot be acquired in a single breath hold. This can cause blurring of the apparent tumour edge and inaccuracies in the measurement of standardised uptake values (SUV) [4]. This may then lead to geographical misalignment of the contoured radiotherapy target volume with the actual tumour position, with the potential for excess normal tissue to be unintentionally irradiated or for geographical misses of the tumour. There is also the theoretical risk that if the patient's breathing patterns are different between follow-up scans, the measured change in SUV may be inaccurate and adversely influence the interpretation of the treatment response.

Four-dimensional (4D) CT is currently the standard-of-care for radiotherapy planning of lung malignancy [5]. Similar methodology has more recently been applied to the use of PET/CT, with several methods for gating and contouring of tumours being presented [6]. Studies can be gated by dividing the patient's respiratory cycle and reconstructing the data for either specified amplitude ranges (amplitude-based gating) or specific phase ranges of the respiratory cycle (phase-based gating) [7]. One of the issues currently faced is defining the percentage of the raw data that is included in the reconstruction. Too small a percentage of the data will lead to insufficient counts, whereas too great a percentage of the data included predisposes the study to more movement artefact, which would nullify the purpose of respiratory gating. This becomes increasingly more difficult when trying to accommodate for irregular breathing patterns [8]. Also, the misalignment of the gated PET and CT data has the potential for inaccuracies in SUV measurement [4,9]. The use of 4D CT for attenuation correction aids in minimising this artefact. However, this does increase the radiation dose to the patient [10]. Another method to aid in the registration of respiratory-gated PET and CT is to use a deformation matrix to register all the PET data with respiration, such as a motion freeze technique [11].

The rationale for these methods is to negate respiratory motion, improving accuracy of tumour volume delineation and quantification of lesional tracer activity, potentially enabling more precise metabolic active tumour targeting [12]. The aim of this overview is to systematically appraise the literature and determine whether 4D PET/CT is an effective tool for radiotherapy treatment planning of lung tumours.

Materials and Methods

A literature search of MEDLINE/PubMed, Cochrane, Web of Science, Scopus and clinicaltrials.gov databases was carried out, searching for articles on the use of 4D PET/CT in lung carcinoma. The search strategy included three major operator criteria, which were linked with the 'AND' function. The first criteria consisted of 'respiratory-gated' or '4D', the second criteria consisted of 'PET/CT' or 'positron emission tomography' and the third criteria consisted of 'lung, 'thorax' or 'radiotherapy'. Case studies, articles not published in English, phantom studies and studies with fewer than five subjects were excluded (to minimise publication bias). After duplications were excluded, studies were screened for eligibility based on title, abstract and subsequently on full text by two authors independently (RF, AS). The results were stored in a bibliographic management software. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria were adhered to [13]. P values < 0.05 were considered statistically significant.

Results

Results are current to January 2017. The MEDLINE/PubMed, Cochrane, Web of Science, Scopus and clinicaltrials.gov database search strings yielded a total of 1583 results (Figure 1). After selection based on a review of the abstracts, the remaining studies underwent full-text assessment. This resulted in 17 articles meeting the inclusion criteria. The study characteristics are shown in Table 1.

Target Volumes: 3D PET/CT versus 4D PET/CT

Traditionally when planning radiotherapy, a clinical target volume (CTV) is generated to encompass the gross tumour volume (GTV) and potential areas of adjacent microscopic disease extension. An internal target volume (ITV) can then be created to account for movement of the GTV/CTV within the patient (e.g. due to breathing). In stereotactic ablative radiotherapy, a CTV is not defined, but a composite GTV is drawn on a maximum intensity projection (MIP), then expanded to an ITV directly. A further margin is added to the ITV to account for set-up variability and uncertainties in treatment delivery to create a planning target volume (PTV) [30]. By looking at the differences in volumes reported, when using non-gated (3D) PET/CT and 4D PET/CT, it may be possible to determine if, first, there is a significant difference in the reported tumour volumes between the two methods and, second, if the difference affects the PTV used.

Impact on Gross Tumour Volume

Thirteen studies of the 17 included within the literature review assessed the effect of respiratory-gated PET/CT on the GTV when compared with non-gated PET/CT, with mixed results being reported (Table 2). Most studies indicated that there is a decrease in measured tumour volume when respiratory gating is used, but not all of them demonstrated this difference to be significant.

Of the studies that reported a significant decrease in tumour volume, Grootjans *et al.* [20] studied 83 lesions in

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