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Evidence-Based Series 7-18

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Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer

Y.C. Ung, A. Bezjak, N. Coakley, W.K. Evans, and the Lung Cancer Disease Site Group

Report Date: November 17, 2010

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
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Evidence-Based Series 7-18

Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer: Guideline Recommendations

Y.C. Ung, A. Bezjak, N. Coakley, W.K. Evans, and the Lung Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

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QUESTION

What role should positron emission tomography (PET) play in radiation treatment planning for non-small cell lung cancer (NSCLC)? Specifically, does the combination of PET and computed axial tomography (CT) imaging provide data that is superior to CT imaging data alone for the purposes of radiation treatment (RT) planning?

TARGET POPULATION

Patients with lung cancer for whom thoracic RT is indicated.

INTENDED USERS

Radiation oncologists involved in RT planning.

RECOMMENDATIONS AND KEY EVIDENCE

Combination PET-CT imaging data may be used as part of research protocols in RT planning. Current evidence does not support the routine use of PET-CT imaging data in RT planning at this time outside of a research setting.

- The PET START trial, released in abstract form at the 2009 ASCO Annual Meeting (1), reported on the use of PET-CT compared to CT in treatment planning for patients with stage III non-small cell lung cancer (NSCLC). The primary outcome was the proportion of patients who did not receive combined modality therapy because their tumour was upstaged to stage 4 or their intrathoracic tumour was too extensive for radical RT. The primary outcome was achieved in 15% of the patients randomized to PET, as opposed to 2.7% in the CT arm (p=0.0002). Data on other outcomes, including overall survival, have not yet been reported.

- Twenty-eight non-randomized prospective and retrospective studies provided evidence on the impact of PET imaging data on RT planning (2-29).
- No studies provided data on the effect of PET-based changes in RT planning on patient outcomes such as overall survival, recurrence, or quality of life. Therefore, data on technical measures form the evidence base of this recommendation. These measures include changes in gross treatment volume (GTV) and changes in planning treatment volume (PTV)
- Eighteen studies including a total of 587 patients reported changes in GTV as a result of the inclusion of PET data in RT planning (2-12,20-22,27,29). See Table 3 and its accompanying text in Section 2 of this Evidence-based Series for details of these data.
- Eleven studies including a total of 283 patients reported changes in PTV as a result of the inclusion of PET data in RT planning. (5-7,9,12-17,21). See Table 4 and its accompanying text in Section 2 of this Evidence-based Series for details of these data.
- The limited data available suggest that the addition of PET to RT planning is more likely to decrease the dose to the esophagus rather than increase it. Two of five studies (3,7,8,18,22) providing data on esophageal exposures (V_{50-55}eso), reported statistically significant decreases (-10.4%, $p<0.005$, and -8.7%, $p=0.004$, respectively) (8,18), and one study reported a result with no significance test (22). Changes in total radiation dosages to the esophagus were more variable across the studies, although one study did report a statistically significant ($p=0.004$) decrease of 6.1 Gy (8).
- The available data regarding the effect of PET in RT planning on dose to lung tissue is mixed. While substantial numbers of patients experience a change in V_{20}lung (between 42% and 100% of patients across four studies (3,7,9,22), these changes involve both increases and decreases. However, three studies (8,12,18), did report statistically significant reductions in V_{20} lung. The data do suggest that PET does reduce lung dose, with four studies (8,9,12,18) reporting decreases (range of changes -5.1 to +1.5 Gy), and one of these reported a statistically significant decrease (8).
- Two studies evaluated the impact of PET on the total RT dose administered and treatment control probability: the total RT dose administered to patients increased by approximately 15 Gy because of PET, and the tumour control probability increased by 17.7% and 8.6% ($p=0.026$), respectively (8,18).
- In twelve studies (6,7,9-11,13,14,17,19,21,23,24) with a total of 656 patients, PET detected distant metastases in 8% to 25% of patients and resulted in a change from curative to palliative RT intent in 8% to 41% of patients.

QUALIFYING STATEMENTS

- There is only one randomized trial, the PET-START trial, to inform recommendations on this topic, and this trial has only been reported in abstract form. Should the results of this trial be similar when reported in a peer-reviewed publication with longer follow-up, the recommendation above may warrant review.
- There are no data available that demonstrate an impact of PET-based RT planning on either survival or local recurrence rates.
- The available evidence, besides the PET-START trial, consists of data from small, non-randomized studies that report on changes in treatment volume, changes in treatment intent, and changes in dose delivered to critical organs. These data, taken as a whole, suggest that the addition of PET increases accuracy in RT planning.
- The available data on change in treatment volume and other changes in response to the incorporation of PET into RT planning have not yet been confirmed to be beneficial, for example, through clinicopathological correlation and/or failure analysis patterns.

- Higher quality research, such as randomized trials, should be conducted to better evaluate the utility of PET in RT planning and to determine if the technology provides added value over existing imaging technologies for this purpose. Investigators publishing data related to the use of PET should evaluate and report on a wider range of outcome measures.
- PET may be useful in RT planning under very specific circumstances in the differentiation of malignant from non-malignant tissue, such as lung opacification that may be due to tumour and/or major atelectasis or pneumonitis secondary to airway obstruction. Clinicians should cautiously interpret results in situations where PET is known to produce false-positive results (e.g., presence of inflamed lymph nodes due to pneumonitis).
- When performing RT planning, clinicians should take into consideration the technical specifications of the PET scanner being used, as these may modify the utility of the device for RT planning purposes.

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Evidence-Based Series 7-18: Section 2

Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer: Evidentiary Base

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QUESTION(S)

What role should positron emission tomography (PET) play in radiation treatment planning for non-small cell lung cancer (NSCLC)? Specifically, does the combination of PET and computed axial tomography (CT) imaging provide data that is superior to CT imaging data alone for the purposes of radiation treatment (RT) planning?

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in both men and women in Canada (1). RT is indicated for use in approximately 60% of all patients with lung cancer and is used for a variety of intents, including curative, adjuvant, neoadjuvant, and palliative (2). RT is most commonly applied in stage III non-small cell lung cancer (NSCLC), where it is estimated that it might be indicated for as many as 84% of patients (2).

External beam radiotherapy (RT; also radiation treatment) (i.e., teletherapy) is the most common form of RT and involves the targeting of high-energy photons (i.e., X-rays) at cancerous tissues to promote malignant cell death. Although healthy cells are better able to repair damage from radiation, RT can kill healthy tissues at sufficient dosage, and epithelial tissues are particularly vulnerable. Tissue scarring can result from radiation exposure and lead to reduced elasticity. This is especially relevant in lung cancer, where critical organs such as the heart, spinal cord, esophagus, and the remainder of the normal lung are often in the vicinity of tumour tissues (i.e., organs at risk [OARs]), and damage to these can be detrimental to the patient. Because of the possibility for significant adverse effects from radiation, radiation oncologists are continually seeking methods to target RT more precisely. The use of positron emission tomography with radiolabeled [^{18}F]-2-fluoro-deoxy-D-glucose (^{18}FDG) PET imaging information is being evaluated as a possible means to improve current RT practices.

RT dosage in lung cancer is generally provided to patients in daily fractions, and a typical dose for a solid epithelial tumour ranges from 60 to 70 Gy, with a fractionation

schedule for adults of 1.8 to 2.0 Gy per day. Radiation dosage exposures are commonly described in terms of the percentage of the organ receiving a particular total dose of radiation. For example, V_{20} lung indicates the percentage of the lungs, excluding the planning target volume (PTV), that received a dose of 20 Gy or more over the course of treatment. The extent to which RT has achieved its objective in killing tumour cells is conveyed by the concept of tumour control probability (TCP). Imaging technologies, specifically planning CT, are used in the RT planning process to delineate tumours and adjacent healthy structures. Traditionally, specialized CT scanners are combined with planning software to virtually simulate the tumour and accurately place X-ray beams. Newer approaches, such as 3-dimensional conformal radiotherapy (3DCRT) or intensity-modulated RT are expected to further enhance these efforts.

RT planning requires precise definition of the region of the diseased part of the body that is the target of the radiation dose. In current practice, this region or "volume" is defined three-dimensionally in accordance with principles articulated by the International Commission on Radiation Units and Measurements. The gross tumour volume (GTV) and clinical target volume (CTV) are clinical-anatomical concepts and refer to the physical space occupied by disease. The GTV is "the gross, palpable, visible or clinically demonstrable location and extent of the malignant growth" and is generally defined by all gross disease identified in scans (e.g., CT, PET, fused) and through other clinical information (3). The GTV includes the primary tumour as well as metastatic lymphadenopathy. The CTV contains the GTV and areas where there is a high probability of subclinical malignant disease, and typically includes a volumetric extension of the GTV (e.g., a 0.6 – 0.8 cm margin and/or inclusion of draining lymph node regions) (4-6). Unlike GTV and CTV, the PTV is a geometric definition that is used directly in targeting a radiation beam. The PTV contains the CTV as well as margins to account for variability due to internal motion such as respiration in patient setup ("setup margin") or position of the target for lung tumours ("internal margin") (7). Several algorithms have been proposed to aid in the determination of the PTV, but ultimately it is a clinical judgement that takes into account adjacent topology, specifically the OARs for radiation toxicity.

CT has traditionally been the primary source of anatomic imaging information for target volume selection and delineation in oncology. However, CT is limited by the fact that it has diminished resolution for normal soft tissue structures as well as tumour extent. A number of studies have reported significant variations in the delineations of GTV based on CT data (8,9). There is reason to believe that the tumour metabolic information provided by PET would be valuable in RT planning. Tumour tissues generally exhibit more rapid glycolysis than normal tissues, and the ^{18}fluorodeoxyglucose (^{18}FDG) tracer allows for the metabolic imaging of this tissue. A number of studies have compared the accuracy of PET in comparison to CT for the purposes of diagnosis and staging in lung cancer. This was the topic of a recent systematic review developed by the Lung DSG (10).

One of the conclusions of this systematic review was that PET has greater sensitivity and marginally greater specificity relative to CT in specific instances. This has implications for RT planning in lung cancer. For instance, the systematic review found PET to be superior to CT for mediastinal staging in NSCLC. The greater sensitivity of PET is believed to improve the detection of metastatic lymph nodes that CT would have missed. PET may be better able to detect distant metastases and allow for the exclusion of patients from unnecessary radical RT. Conversely, PET may result in the downstaging of CT-false-positive nodes and the exclusion of non-malignant tissues from the PTV. The benefit of this for patients could be substantial: Graham et al have argued that a reduction of V_{20} lung by 5-17% would reduce the incidence of grade 2 or greater pneumonitis occurring within 24 months of treatment by up to 23% (11).

Despite this strong theoretical rationale for using PET in RT planning, it is not yet clear that the addition of PET imaging data has a clinically significant impact on planning. Furthermore, assuming there is a benefit to including PET data in planning, the optimal approach to using PET data is not yet established. At present, PET tumour contouring remains unsatisfactory, and there is little standardization in its use. For instance, the delineation of tumour volumes based on a metabolic activity threshold in PET has been shown to vary both by tumour size and the background-to-tumour ^{18}FDG uptake ratio (12). Some clinicians include an area of lower uptake, which some term the "anatomic-biologic halo," in the GTV, and one study has shown that including this halo improves coverage of the PTV (13), though, again, the practice is not yet standard.

The Lung DSG initiated this systematic review of evidence on the role of PET in RT planning because of the increasing use and potential importance of PET in this area. This systematic review will provide an evidence-based perspective as to whether planning based on PET-CT imaging data represents an improvement over planning based on CT data alone, and inform guidance on its role in RT planning in the lung cancer setting.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (14). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Lung DSG and two methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on PET in RT planning for lung cancer. The body of evidence in this review is primarily comprised of small sample size retrospective or prospective observational studies. That evidence forms the basis of the recommendations developed by the Lung DSG (see Section 1). The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE (1996 to May 2010), EMBASE (1996 to May 2010), and Cochrane Library (2007, Issue 1) databases were searched for published practice guidelines, technology assessments, systematic reviews, clinical trials and studies. Reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase (http://www.cma.ca/index.cfm/ci_id/54316/la_id/1.htm), the National Guidelines Clearinghouse (http://www.guideline.gov/), and other websites were searched for existing evidence-based practice guidelines. The conference abstracts of The American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO), and the European Society for Therapeutic Radiology and Oncology (ESTRO) (2002-2009) were searched for randomized studies. Search terms indicative of lung cancer, RT planning, and PET technology were used.

Study Selection Criteria

The most useful evidence in determining the value of any intervention is evidence regarding patient outcome. Therefore, studies that reported on any relevant patient outcome, such as survival, recurrence rates, treatment related morbidity, and quality of life, were included.

However, there was an a priori expectation that no such data would be available. Therefore, studies that reported data on more technical measures of RT planning were also

included, as these data would be useful in evaluating improvements, if any, arising from the incorporation of PET-CT imaging. These measures include changes in the target volume definitions (e.g., GTV), radiation exposures to organs at risk, tumour dose and tumour control probability, intent of RT or in the management of patients, and rate of geographical misses, and detection of distant metastases.

Articles were selected for consideration in this systematic review of the evidence if they were published reports of studies of any design that reported on aspects of RT planning for lung cancer patients that incorporated PET imaging data, and that compared the impact of consolidated PET-CT imaging data with RT planning done in the absence of PET data. Retrospective studies for which the RT planning was theoretical (i.e., records were reviewed and investigators determined the RT planning that would have occurred had a PET evaluation been done) were included. Studies including patients with multiple disease types (e.g., lung cancer, head and neck cancer) must have reported data for lung cancer patients specifically, or be comprised of a majority of lung cancer patients in order to be eligible for inclusion. Studies reporting data on the impact of PET on clinical management of patients, including RT management, but also surgical or chemotherapy management, were included if data specific to RT management were reported.

Surveys of clinicians to measure the influence of PET on RT planning were excluded, as were phantom studies. Studies reported in a language other than English were excluded due to a lack of translation resources.

Synthesizing the Evidence

There was considerable inconsistency in the presentation of data across included studies. The nature of the studies and the data they provided did not lend themselves to meta-analysis.

RESULTS

Literature Search Results

Abstracts for 219 studies were retrieved, and of these, 28 journal publications were deemed appropriate for inclusion in this report based on the eligibility criteria outlined above. Four early studies (15-18) and two studies of patients with small cell lung cancer (SCLC) (19,20) that were relevant to the research questions but did not report data appropriate for summary in this report were excluded. Table 1 outlines the quantity and type of studies identified to answer the questions posed in this review (21-42). No practice guidelines, systematic reviews, or meta-analyses were identified, and most studies consisted of small-sample-size observational prospective or retrospective cohort studies. One randomized trial, the PET-START trial, has been reported in abstract form (43).

Table 1. Literature search results: studies included in the evidence summary report.

Question: What role should positron emission tomography (PET) play in radiation treatment planning for lung cancer?	Prospective Cohort (Applied RT plan)	Retrospective (Hypothetical RT plan)	References
Total Included Studies	22	6	(13,21-42,44-48)
Does PET alter target volume definitions: GTV? (Table 3)	13	5	(13,21-33,44,46-48)
PTV? (Table 4)	9	2	(13,24,25,27,30,33,35-39)
Does PET alter the radiation dose and exposure of the lungs or esophagus? (Table 5 & 6)	8	2	(22,25-27,30,33,34,37,39,40)
Does PET alter the total radiation dose applied, and/or the tumour control probability? (Table 7)	1	1	(26,34)
Does PET result in the detection of distant metastases and change the intent of RT? (Table 8)	12	-	(24,25,27-29,32,33,35,36,39,41,42)

Table 2 presents several descriptive characteristics of the included studies. The type of imaging technologies used in the studies varied: nine studies evaluated hybrid PET-CT scanners (13,21-24,31,34,46,48), four studies evaluated gamma camera scanners (25,39,40,42), and the remainder evaluated dedicated PET scanners. The combining (or co-registration) of PET and CT images adds additional measurement error to the development of a target volume definition. Co-registration has traditionally been a manual process involving the visual overlay of images with the help of fixed markers, though more recently it has been automated and improved through the use of computer software and hybrid PET-CT devices. Studies using hybrid scanners will have substantially less measurement error due to co-registration.

Observational studies are inherently more susceptible to bias than are randomized controlled trials. In most of the studies included in this review, insufficient detail on efforts to control bias in the treatment planning process was provided, so it was assumed that planning was done by single or in some cases multiple clinicians. The latter approach would lead to inter-observer variability in results.

A second bias relates to the sequential integration of imaging data, a practice that may not reflect real-world clinical practice. In all studies, RT plans were developed using CT data alone and then subsequently with PET imaging data included. Clinicians typically evaluate PET-CT data simultaneously, and this may become standard practice as PET becomes more integrated in the RT planning process. These potential biases could be controlled for in studies by having independent evaluators conduct planning on CT and PET-CT data separately. Only three studies in this series used independent evaluators of CT and PET-CT data (13,27,37).

A third bias may be present in studies for which the study design was a retrospective case review. The six retrospective studies in this series established a hypothetical PET-based RT plan using PET data obtained for other purposes (e.g., staging) (23,26,30,31,45,48). These studies may be biased relative to prospective studies in that investigators may have been less conservative in their planning definitions knowing the definitions would not be applied in real patients. One prospective study was also vulnerable to the same bias in that a non-treating physician conducted the PET-based RT planning (27). Details on the clinicians involved in

planning (e.g., whether they were treating physicians or not) were not provided in most studies, and others might be subject to the same threats to validity.

All studies evaluated patients with NSCLC (and in two studies, patients with SCLC, and with 'lung cancer' without further specification were also included) for whom radical RT was deemed appropriate on the basis of conventional imaging data. Two studies reported including patients with recurrent NSCLC (25,28), and one indicated that all patients were at high risk for tumour recurrence (36). One study only included patients with positive lymph nodes (30). Only limited details on specific pathological features were included in the remainder of the studies in this series.

The studies included in this systematic review reported data on a total of 1054 patients. Samples ranged in size from 5 to 153 patients, with a mean of 38 patients and a median of 59 patients. Most studies provided basic summary statistics only (e.g., means, proportions, ranges), and did not report results from statistical testing (e.g., p-values, confidence intervals).

Table 2. Characteristics of included non-randomized studies.

Study	PET Equipment	PET/CT Image Co-Registration	Prospective or Retrospective?	Sample Size (n)	Population
Hanna 2010 (46)	Discovery LS (GE Medical)	Hybrid PET/CT	Prospective	28	NCSLC
Spratt 2010 (48)	Discovery LS (GE Medical)	Hybrid PET/CT	Retrospective	11	NCSLC
Vinod 2010 (45)	Gemini GLX-6 (Philips Medical)	Software	Retrospective	5	NCSLC
Feng 2009 (44)	-	Software	Prospective	14	NCSLC
Kruser 2009 (47)	Discovery LS (GE Medical)	Hybrid PET/CT	Prospective	38	34=NCSLC 4=SCLC
Ceresoli 2007 (32)	GE Advance	No	Prospective	18	NSCLC
Gondi 2007 (21)	Discovery LS (GE Medical)	No	Prospective	14	NSCLC
Grills 2007 (22)	-	Hybrid PET/CT	Prospective	21	NSCLC
Hong 2007 (31)	Phillips Allegro	Hybrid PET/CT	Retrospective	19	NSCLC
MacManus 2007 (33)	GE Quest 300-H	No	Prospective	10	NSCLC
Lewandowska 2006 (23)	Biograph SL (Siemens)	Hybrid PET/CT	Retrospective	20	NSCLC
Ashamalla 2005 (13)	GE-LSO-based Discovery ST	Hybrid PET/CT	Prospective	19	NSCLC
Brianzoni 2005 (24)	Biograph Duo LSO (Siemens)	Hybrid PET/CT	Prospective	22	NSCLC, SCLC [a]
De Ruysscher 2005 (34)	Biograph SOMATOM Sensation 16 (Siemens)	Hybrid PET/CT	Prospective	21	NSCLC
Deniaud-Alexandre 2005 (25)	Picker Triple-Head Coincidence GC	Software	Prospective	101	NSCLC[b]
Messa 2005 (35)	GE Advance	Software	Prospective	21	NSCLC
Roberts 2005(36)	PENN-PET 300-H	No	Prospective	17[c]	NSCLC

Study	PET Equipment	PET/CT Image Co-Registration	Prospective or Retrospective?	Sample Size (n)	Population
van der Wel 2005 (26)	ECAT Exact 922	Visual	Retrospective	21	NSCLC
Bradley 2004 (27)	CTI ECAT HR+ (Siemens)	Software	Prospective	24	NSCLC
Schmucking 2003 (37)	-	Software	Prospective	27	NSCLC
Erdi 2002 (38)	GE Advance	Visual + Software	Prospective	11	NSCLC
Mah 2002 (39)	Irix *y*-PET[3] (Marconi)	Software	Prospective	30	NSCLC
Giraud 2001 (40)	Picker Dual Head CDET GC	Software	Prospective	12	NSCLC
Hicks 2001 (41)	PENN-PET 300-H (UMG Medical Systems)	No	Prospective	153	NSCLC
Kalff 2001 (28)	GE Quest 300-H	No	Prospective	59	NSCLC[d]
Mac Manus 2001 (29)	GE Quest 300-H	No	Prospective	153	NSCLC
Roman 2001 (42)	Picker Axis Dual-Head GC (Marconi)	No	Prospective	60	Lung Cancer
Vanuytsel 2000 (30)	CTI-Siemans 931/08/12	No	Retrospective	105[e]	NSCLC

Notes: - = not reported, GC = gamma camera.
[a] Approximately two thirds of patients had NSCLC.
[b] Of 101 patients, 22 had recurrent NSCLC.
[c] All patients had NSCLC, prior pneumonectomy, and were deemed at high risk for residual tumour recurrence.
[d] Primary and recurrent NSCLC.
[e] 73 patients had positive lymph nodes; only these were included in volumetric analyses.

Measures and Outcomes

The PET-START Trial

The PET START trial (NCT00136864) randomized patients to either standard combined modality therapy for stage III NSCLC or to PET imaging prior to combined modality therapy with curative intent. Data from this trial were reported in abstract form at the 2009 ASCO Annual Meeting (43). The primary outcome was the proportion of patients who did not receive combined modality therapy because their tumour was upstaged to stage IV or their intrathoracic tumour was too extensive for radical radiation treatment. The abstract provides insufficient detail to assess the methodological quality and potential for bias in the trial with respect to randomization method, blinding, and the balance of prognostic factors between the arms. The trial was originally designed to enrol 400 patients who had undergone conventional staging for lung cancer and were found to have stage III NSCLC. However, it was reported that the trial was stopped after a planned interim analysis in November 2008 because of superior efficacy on the PET arm; it is not clear whether this early termination was based on an a priori stopping rule. In the abstract, data were available for 289 patients; 15% of patients in the PET-CT arm achieved the primary outcome compared with 2.7% in the CT arm (p=0.0002). No data were reported on other outcomes in the abstract.

The Impact of PET on Target Volume Definitions

As expected, no studies were identified that reported on patient outcomes such as survival, recurrence, treatment related morbidity, or quality of life. Therefore, this review will concentrate on the technical data reported by the included studies.

The key technical measures (e.g., changes in GTV or PTV) considered in this review were not reported consistently across the studies; only one study reported on all the measures considered relevant in this review (27). For most measures, the data reported were also inconsistent across studies: for example, some reported the number of patients experiencing a change in GTV and not the mean change in GTV. The following results are comprehensive and have included any data reported in the studies, and, if possible, summary values calculated from raw data provided in tables.

Changes in target volume definitions presented in this section represent net changes: in some cases, it is likely that PET data resulted in volume decreases due to a better differentiation of benign masses, as well as increases due to the identification of involved mediastinal nodes missed by CT. One study reported simultaneous GTV increases and decreases in six of 20 patients, though this study was an exception as most reported only net changes (23).

Gross Tumour Volume - GTV

Eighteen studies including a total of 587 patients reported changes in GTV as a result of the inclusion of PET data in RT planning (Table 3) (13,21-33,44,46-48). The magnitude of GTV changes was reported in eleven out of 18 of these studies (21,23-27,32,33,44,47,48); one other study reported the proportion of patients experiencing a change over 25% (13). In the nine studies (21,23,24,25,27,32,44,47,48) that reported the magnitude of the increase in GTV, the mean increase per patient in patients with an increase ranged from 10.6% to 153% (median study increase 49%); the greatest increase reported for any single patient was 735%. In the eleven studies (21,23,24-27,32,44,46-48) that reported the magnitude of the GTV decrease in affected patients, the mean decrease per patient across those studies ranged from 13.9% to 71% (median study decrease 40.5%); the greatest decrease reported for a single patient was 143%.

Table 3. Patients who experienced changes in gross tumour volume (GTV) due to PET in radiotherapy planning.

Study	n	Gross Tumour Volume (GTV)				
		Change Δ	Increase ▲		Decrease ▼	
		n_{Δ} (%)	n_{Δ} ($\overline{\%}$)	Range	n_{Δ} ($\overline{\%}$)	Range
Hanna 2010 (46)	28	5(18%)	-	-	-	-
Spratt 2010 (48)	11	8 (72%)	3 (27%)	-	4 (36%)	-
Feng 2009 (44)	14	14(100%)	4(28)	-	10(71%)	-
Kruser 2009 (47)	38	25(65%)	17(44%)	-	19(50%)	-
Ceresoli 2007 (32)	18	7 (39%)	5 (114%)	40-235%	2 (61.5%)	39-84%
Gondi 2007 (21)	14	14 (100%)	2 (66%)	57-76%	12 (39%)	0.7-88%
Grills 2007 (22)	21	17(81%)	12/20 (-)	-	5/20 (-)	-
Lewandowska 2006 (23)	20	20 (100%)	4 (32%)	10-80%	16 (45%)	3-82%
Hong 2007 (31)	19	18 (95%)		-	18 (95%)[h]	-
MacManus 2007 (33)	10	4(40%)	0 (-)	-	4 (-)	-
Ashamalla 2005 (13)	19	10[a] (53%)	5 (-)	-	5 (-)	-

Study	n	Gross Tumour Volume (GTV)				
		Change Δ	Increase ▲		Decrease ▼	
		n_{Δ} (%)	n_{Δ} ($\overline{\%}$)	Range	n_{Δ} ($\overline{\%}$)	Range
Brianzoni 2005 (24)	22[b]	11 (50%)	6 (10.6%)	1.7-26%	5 (13.9%)	2.2-26%
Deniaud-Alexandre 2005 (25)	92[c]	45 (49%)	24 (27%)	2-78%	21 (42%)	3-143%
van der Wel 2005 (26)	21	12 (57%)	0 (-)	-	12[d] (28%)[d]	-
Bradley 2004 (27)	24	24 (100%)	15 (153%)	5-735%	9 (22%)	1-78%
Kalff 2001 (28)	41	12 (29%)	5 (-)	-	7 (-)	-
Mac Manus 2001 (29)	102[e]	38 (37%)	22 (-)	-	16 (-)	-
Vanuytsel 2000 (30)	73[f]	45 (62%)[g]	16 (-)	-	29 (-)	-

Note: Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change.
[a] Only changes greater than or equal to 25% of GTV via CT reported.
[b] Approximately two-thirds of patients had NSCLC.
[c] Of the 101 patients in this study, 92 were eligible for RT planning.
[d] Change in nodal volume only. No change in primary tumour volume.
[e] 102/153 patients received radical RT.
[f] Number of patients with positive lymph nodes (73/105).
[g] Change was insufficient or incorrect in 9 patients when compared with surgery information.
h Change in GTV was based on using the 40% maximum intensity threshold

Planning Target Volume - PTV

Eleven studies including a total of 283 patients reported changes in PTV as a result of the inclusion of PET data in RT planning (Table 4) (13,24,25,27,30,33,35-39). The magnitude of PTV changes was reported in 10 of these studies (13,24,25,27,30,33,35,37,38,39). In the four studies (24,25,27,42) that reported the magnitude of the PTV increase, the mean increase per patient across those studies ranged from 7% to 159% (median increase 27%); the greatest increase for any single patient was reported as 381%. Four other studies (13,33,35,37) reported increases of PTV per patient of 10% or more in patients with an increase. In the six studies (13,24,25,27,30,38) that reported the magnitude of PTV decrease , the mean decrease per patient was less than 29% across all studies; the greatest decrease for any single patient was 70%. Four other studies (33,35,37,39) reported decreases of PTV per patient of 3% or more in affected patients.

Table 4. Changes in planning target volumes due to PET in radiotherapy planning.

Study	n	Planning Target Volume (PTV)				
		Change Δ	Increase ▲		Decrease ▼	
		n_{Δ} (%)	$n_{\blacktriangle}$ ($\overline{\%}$)	Range	$n_{\blacktriangledown}$ ($\overline{\%}$)	Range
MacManus 2007 (33)	10	9 (90%)	3(-)	≥10%	6 (-)	≥10%
Ashamalla 2005 (13)	19	8 (42%)	4 (-)	≥ 20%	4 (≥ 20%)	-
Brianzoni 2005 (24)	25[a]	11(44%)	6 (5.4%)	1-22%	5 (4.5%)	0.8-28%
Deniaud-Alexandre 2005 (25)	92[b]	43 (47%)	23 (35%)	2-97%	20 (27%)	7-67%
Messa 2005 (35)	21[c]	10 (48%)	7 (-)	≥ 25%	3 (-)	≥ 25%
Roberts 2005 (36)	17	10 (58%)[d]	- (-)	-	- (-)	-
Bradley 2004 (27)	24[e]	24 (100%)	15 (159%)	2-381%	9 (9%)	2-49%

Study	n	Planning Target Volume (PTV)				
		Change Δ	Increase ▲		Decrease ▼	
		n_{Δ} (%)	$n_{\blacktriangle}(\overline{\%})$	Range	$n_{\blacktriangledown}(\overline{\%})$	Range
Schmucking 2003 (37)	27	27 (100%)	2 (0.7%)	-	25 (92%)	3-21%
Erdi 2002 (38)	11	11 (100%)	7 (19%)	5-46%	4 (18%)	2-48%
Mah 2002 (39)	30	-	- (-)	30-76%	- (-)	24-70%
Vanuytsel 2000 (30)	10[f]	-	- (-)	-	- (29%)	-

Note: Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change.
[a] Approximately two thirds of patients had NSCLC. The data here refer to CTV.
[b] Of the 101 patients in this study, 92 were eligible for RT planning.
[c] Changes it CTV, not PTV, reported.
[d] Change in target volume, dosage, or concurrent chemotherapy.
[e] Raw data provided in table.
[f] Data provided for only first 10/73 consecutive patients.

Geographic Misses

Few studies provided specific details on the inclusion of PET-positive tissue that had been missed in CT-based planning; most reported aggregate data on GTV expansions (reported above). However, specific instances of such geographic misses were reported in three studies. Mah et al 2002 reported that, in five of 23 (22%) patients suitable for radical RT, FDG-avid nodes were detected within 5 cm of the primary tumour; these nodes had not been included in the CT-based GTV (39). Similarly, in a study by Lewandowska et al 2006, PET identified CT-occult mediastinal nodal metastases in 9/20 cases which were not included in the CT-based GTV (23). In both of these studies the GTVs were expanded to incorporate these nodes. MacManus et al 2007 reported that in 3/10 (30%) cases regions were located entirely outside the CT PTV. These areas would not have been contained within the target volume if the treatment was delivered using the CT plan alone (33).

The Impact of PET on Organs at Risk Radiation Exposure and Dose

Esophageal Exposure and Dose

Five studies reported on changes in esophageal radiation exposure due to PET in a total of 166 patients (Table 5) (22,25,26,34,40). The mean percentage of the esophageal volume exposed to a radiation dose of 50-55 Gy (V_{50}eso, V_{55}eso) per patient decreased in 3 studies (22,26,34) and increased in two studies (25,40); the range of changes in the studies was from -10.4% to 4.5%. Two of the three studies reporting a decrease in esophageal exposure indicated that the mean decrease was statistically significant with p-values <0.005 (26,34).

Six studies including a total of 179 patients reported on the impact of PET on the maximal esophageal radiation dose (Table 6). The mean dose per patient received by the esophagus decreased in four studies (22,26,34,45), and increased in two studies (25,27); the range of changes in the studies was from -8.8 Gy to +6.1 Gy. In one study, a decrease of 6.1 Gy was reported to be statistically significant (26).

Lung Exposure and Dose

Ten studies including a total of 267 patients reported data on changes in lung radiation exposure due to PET (22,25-27,30,33,34,37,39,40), and seven of these provided data on the number of patients experiencing a change, or the mean value of the change (Table 5) (22,24-27,30,34,40). The greatest reported increase in V_{20} lung for any single patient was 2000%; the greatest decrease was 100%. Four of these studies (25,27,30,40) reported a change in V_{20} lung in between 46% and 100% of the studied patients. Three studies (26,30,34) reported a

statistically significant decrease in V_{20} lung across the studied patients. Two studies (33,39) reported that changes in V_{20} lung were not statistically significant but did not provide data

Four studies including a total of 154 patients reported on the impact of PET on the maximal lung radiation dose (Table 6). The mean dose received by the lungs decreased in three studies (22,26,34) and increased in one study (27); the range of changes in the studies was from -5.1 Gy to +1.6 Gy. One study reported a statistically significant decrease in dose (26).

Table 5. Impact of PET on lung and esophageal radiation dose.

Study	n	V_{55}eso[a]	V_{20}lung						
		Change Δ	Change Δ	Increase ▲			Decrease ▼		
		V_{55}eso	N_{Δ} (%)	$n_{\blacktriangle}$	V_{20}lung	Range	$n_{\blacktriangledown}$	V_{20}lung	Range
MacManus 2007 (33)	10	-	-	-	NS	-	-	NS	-
Grills 2007 (22)	20	-1%[b]	-	-	2%	-	-	-	-
De Ruysscher 2005 (34)	21	-10.4% p<.005	-	-	-	-	-	7.8% p<.001	-
Deniaud-Alexandre 2005 (25)	92[c]	0.8%[b]	37/81 (46%)	15	154%	3-2000%	22	19%	3-100%
van der Wel 2005 (26)	21	-8.7% p=.004	-	-	-	-	-	2.6% p=.012	-
Bradley 2004 (27)	24	-	20 (83%)	15	7.3%	1-31%	5	6.2%	2-9%
Schmucking 2003 (37)	27	-	-	-	-	-	-	-	5-17%
Mah 2002 (39)	30	-	-	-	NS	-	-	NS	-
Giraud 2001 (40)	12	4.5%	5 (42%)	1	5.5%	-	4	22.8%	7-49%
Vanuytsel 2000 (30)	10[d]	-	10 (100%)	-	-	-	10	27% p=.001	8-59%

Notes: NS = no statistically significant change observed. Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change.
[a] Percentage of the lung volume receiving 20 Gy (V_{20}lung).
[b] Voeso50.
[c] Of the 101 patients in this study, 92 were eligible for RT planning. For V_{20}lung, data were available only for 81 patients.
[d] Data provided for only first 10/73 consecutive patients.

Table 6. Impact of PET on mean lung and esophageal radiation dose (TCP).

Study	n	Δ RT Dose (Gy)	
		Esophagus	Lung
Vinod 2010 (45)	1	-2.5	-
Grills 2007 (22)	20	-1.5	-1.2
De Ruysscher 2005 (34)	21	-8.8	-5.1
Deniaud-Alexandre 2005 (25)	92[a]	+1.8	-
van der Wel 2005 (26)	21	-6.1 p=.004	-1.1 p=.004
Bradley 2004 (27)	24	+6.1	+1.6

Note: Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change.
[a] Of the 101 patients in this study, 92 were eligible for RT planning.

Impact of PET on Total Radiation Dosage and Tumour Control Probability (TCP)

Modifications of the total radiation dose to the tumour taking account of the need to limit the radiation dose to the lung, esophagus, and spinal cord were reported to show an increase in two studies by a mean of 13.7 Gy (from 55.2±2.0 Gy to 68.9±3.3 Gy with PET,

p=0.002) across 21 patients (including 15 stage III), and a mean of 15 Gy (from 56.0±5.4 Gy to 71.0±13.7 Gy, p=0.038) across 21 stage III patients (Table 7). In both studies, patient-specific details (e.g., the number of patients for whom the dose increased) were not reported.

TCP increased in the two studies reporting on this measure (Table 7). In one study, the TCP increased 17.7% (from 6.3±1.5% to 24.0±5.6%, p=0.01) among 21 patients (34), and in the other it increased 8.6% (from 14.2±5.6% to 22.8±7.1%, p=0.026) among 21 patients (26). In this latter study, the change was reported as being statistically significant (p=0.026).

Table 7. Impact of PET on radiation dosage and tumour control probability (TCP).

Study	n	Total RT Dose			Tumour Control Probability (TCP)		
		CT-based	PET-based	Change Δ	CT-based	PET-based	Δ TCP(%)
De Ruysscher 2005 (34)	21	55.2±2.0	68.9±3.3	+13.7 p=.002	6.3±1.5%	24.0±5.6%	+17.7% p=.01
van der Wel 2005 (26)	21	56.0±5.4	71.0±13.7	+15 p =.038	14.2±5.6%	22.8±7.1%	+8.6% p =.026

Note: Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change. Values following the "±" refer to the standard error of the mean.

Impact of PET on Clinical Management and Patient Outcomes

Changes in RT Intent

Six studies reported that the inclusion of PET imaging information in RT planning resulted in the detection of distant metastases (Table 8) (25,27,29,33,39,42). The proportion of patients for which distant metastases were identified ranged from 8% to 25% (median study identification rate 17.5%) across these six studies.

Eleven studies reported on whether PET information, such as the identification of distant metastases, resulted in a change from curative to palliative RT intent (24,25,27-29,32,35,36,39,41,42). The percent of patients for whom the intent of RT was changed ranged from 8% to 41% of patients across the 11 studies. Specific reasons for the change in patient management were not consistently provided in studies, though several cited more "extensive disease" or distant metastases.

Table 8. Impact of PET on the detection of distant metastases and treatment intent.

Study	n	PET detected distant metastases n (%)	Δ Curative to palliative RT n (%)	Reasons for Change
Ceresoli 2007 (32)	21	3 (14%)	3 (14%)	Bone metastases (n=2) Large tumour not amenable to high-dose radiotherapy (n=1)
MacManus 2007 (33)	10	1	-	Not reported
Brianzoni 2005 (24)	25	-	3 (12%)	Not reported
Deniaud-Alexandre 2005 (25)	101	8 (8%)	9 (9%)	Unexpected metastasis (n=8)[a] Extensive intrathoracic disease (n=1)
Messa 2005 (35)	21	-	3 (14%)	Distant metastases or Extensive intrathoracic disease (n=3)
Roberts 2005 (36)	17	-	3 (18%)	Multiple metastases (n=1) Lung nodule and hilar adenopathy (n=1) Regional recurrence and bone metastases (n=1)
Bradley 2004 (27)	24	2 (8%)	2 (8%)	Intrapulmonary metastases (n=1) Liver metastases (n=1)
Mah 2002 (39)	30	7 (23%)	7 (23%)[b]	Distant paratracheal node (n=1) Distant contralateral hilar nodes (n=1)

Study	n	PET detected distant metastases n (%)	Δ Curative to palliative RT n (%)	Reasons for Change
				Distant contralateral node (n=1) Contralateral lower lobe lesion (n=1) Left rib metastasis (n=1) Bilateral kidney metastases (n=1) Remote diaphragmatic mass (n=1)
Hicks 2001 (41)	153	-	34 (22%)	"More extensive disease" (n=34)
Kalff 2001 (28)	59	-	17 (41%)[c]	"More extensive disease" (n=17)
Mac Manus 2001 (29)	153	32 (21%)	46[d] (30%)	Not reported
Roman 2001 (42)	60	15[e] (25%)	6 (10%)	Mediastinal disease (n=4) Distant metastases (n=2)

Note: Δ is an upper case letter Delta from the Greek alphabet, and is used to indicate change.
[a] 1/8 patients was false-PET-positive for intrapulmonary FDG uptake; some false-positive FDG-avid regions corresponded to concomitant pulmonary tuberculosis.
[b] This study also reported patients changed from palliative to curative intent because of PET identified less extensive disease (n=6), and patients for whom the modality of treatment was changed (n=14).
[c] This study also reported patients changed from palliative to curative treatment (e.g., radical RT, brachytherapy, surgery) intent (n=5).
[d] PET "strongly influenced" change in 10/46, and was "principal reason" in 36/46.
[e] 8/15 were true positive, 7/15 false positive (determined by CT): 5/7 were false-positive cerebral lesions.

ONGOING TRIALS

The National Cancer Institute's clinical trials database was searched (http://www.cancer.gov/clinicaltrials/search) for reports of new or ongoing trials. Information was supplement by data available in the U.S. National Institutes of Health clinical trials registry (http://www.clinicaltrials.gov/). Trials are reported below.

Protocol ID and NLM Identifier	Trial Sponsor	Estimated Enrolment	Patients' Age	Purpose
20328 E-20328, NCT00385164	Alberta Cancer Board Calgary Health Region	20	18+	Patients planned for radical radiation for NSCLC will undergo conventional CT stimulation and also PET/CT scans for definition of radiation target volumes
AG NUK/RT 2006-1 NCT00697333	Arbeitsgemeinschaft Nuklearmedizin und Strahlentherapie der DEGRO und DGN	394	18+	Simultaneous radio-chemotherapy in advanced non-small cell lung cancer. The study focuses on a randomised comparison of conventional radiotherapy planning with irradiation of macroscopic tumour and lymph nodes together with prophylactic target volumes vs. irradiation only of FDG-positive lesions. Primary endpoint is the local disease control in the chest.
20060021 NCT00380666	University of Aarhus The Danish Medical Research Council	30	18+	The trial evaluates the utility of 18FDG-PET/CT scan in the target definition process when SBRT is planned for stage I NSCLC.

Protocol ID and NLM Identifier	Trial Sponsor	Estimated Enrolment	Patients' Age	Purpose
LU-11-0044 NCT00123747	Alberta Cancer Board	30	18+	Study of 18F-Fluorodeoxyglucose (FluGlucoScan) 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

DISCUSSION

Proponents of PET have claimed that PET has value in the clinical management of lung cancer by producing more accurate diagnosis and staging, lower rates of futile thoracotomies, and better clinical management decisions leading to improved patient outcomes. This optimism for PET extends to its role in RT planning for lung cancer. Many clinicians feel that PET contributes to the identification of CT-occult disease, particularly mediastinal lymph nodes, and leads to the beneficial expansion of target volumes. However, the resolution of PET is not sensitive enough to detect microscopic disease. The high sensitivity of PET has been demonstrated to appropriately exclude patients from radical therapy when distant metastases are present. There is growing consensus that PET has a greater specificity to exclude non-malignant areas, for example, in differentiating atelectasis, and that this can appropriately reduce target volumes and radiation exposure to patients. The intention of this review was to systematically evaluate the available evidence related to these and related issues and to determine what role, if any, PET should play in RT planning for lung cancer patients.

The PET START Trial (43) is the only randomized trial reported to date that addresses PET CT for treatment planning in NSCLC. Unfortunately, this trial has only been reported in abstract, with insufficient detail to fully assess its quality and potential for bias. However, once this trial has been published in a peer-reviewed publication, it will likely report significant data that may address at least some of the issues described in detail below.

The review of the available literature showed that a large proportion of patients experienced changes in target and planning volumes through the use of PET imaging data (see Tables 3 and 4 and accompanying text). Two studies reported on the PET-based detection of geographic misses that resulted in increases in target volumes. While in some cases the changes in volume are minor and would not be considered clinically relevant, on the whole they are substantial. Increases and decreases of greater than 10% in both GTV and PTV were commonly reported across all studies. What is not clear from these studies is whether the PET-based changes in volumes were truly appropriate and led to better outcomes. Very few studies have confirmed through surgical biopsy whether the changes were appropriate, although in lung cancer this biopsy correlation is often difficult to achieve. However, assuming that the majority of measured change was beneficial, these values suggest that PET is contributing to both the exclusion of non-malignant tissue and the inclusion of CT-occult tissue in RT planning.

Changes in volume size have the potential to produce corresponding changes in organ radiation exposure if tissue is included in or excluded from the PTV. The limited data available suggest that the addition of PET to RT planning is more likely to decrease the dose to the esophagus than to increase it. Two of five studies (22,25,26,34,40) reporting esophageal exposures ($V_{50\text{-}55}$eso), reported statistically significant decreases (-10.4%, $p<0.005$, and -8.7%, $p=0.004$, respectively) (26,34). Changes in total radiation dosages to the esophagus were variable across the studies, although one study did report a statically significant ($p=0.004$) decrease of 6.1 Gy (26,34).

The available data regarding the effect of PET in RT planning on dose to lung tissue is mixed. While substantial numbers of patients experience a change in V_{20} lung (between 42% and 100% of patients across four studies (26,27,30,34), these changes involve both increases and decreases. However, three studies (26,30,34), did report statistically significant reductions in V_{20} lung. The data do suggest that PET does reduce lung dose, with three of four studies (26,27,30,34) reporting decreases (range of changes -5.1 to +1.5 Gy), and one of these reporting a statistically significant decrease (26).

Changes in the total administered radiation dosage and tumour control probability were reported in two studies only (26,34). In both studies the effect of PET was to increase the total radiation dosage administered to patients (+14,15 Gy), and to increase the tumour control probability of RT (+18%,9%); in both studies the changes were statistically significant ($p<.04$, both studies). On the assumption that PET allows for more accurate administration of radiation to malignant structures, the reported net increases in radiation dosage suggest that PET may contribute to more effective RT.

There are data that suggest that the incorporation of PET into RT planning has an impact on the management of patients. In ten studies (24,25,27-29,32,35,36,39,42), PET was reported to detect distant metastases in 8% to 25% of patients, and change the intent of RT from curative to palliative in 8% to 41% of patients. If confirmed in more rigorously conducted trials, these results would support the use of ^{18}FDG PET in the evaluation of distant metastases in patients with stage III NSCLC for whom RT is indicated.

There are no data available to date that show an impact of PET-based RT planning on patient outcomes such as survival or local recurrence rates. If PET is used in the determination of disease extent, it is important to confirm that areas of ^{18}FDG uptake in mediastinal nodes or in distant, particularly isolated, sites are confirmed histologically or cytologically so that patients are not inappropriately denied potentially curative therapy.

This systematic review highlights the limitations of the available evidence. There is rather poor consistency in reporting among the studies evaluating PET in RT planning. The measures and outcomes described in studies vary considerably, and the corresponding results are reported in inconsistent manners. This heterogeneity in analysis and presentation is a detriment to clinicians seeking to use this literature to inform treatment planning. In the individual studies, there is rarely independent evaluation of the CT and PET-CT imaging data to preclude bias. Investigators conducting research in this area should evaluate, at a minimum, all of the measures and outcomes considered in this systematic review, and present their own results in a fulsome and consistent fashion. Such practices will allow for the optimal use of research findings.

There are a number of issues regarding the use of PET in RT planning for which there is little or no evidence to inform clinical practice. Atelectasis is known to contribute to inter-observer variability in treatment planning in NSCLC (40). However, it is not known whether PET contributes to or diminishes the inter-observer variability seen in the delineation of target volumes in this situation. The exclusion of atelectatic tissue by PET is a reason to believe that PET may reduce variability, but this supposition has not been widely evaluated in empirical studies. Two studies incorporated inter-observer comparisons in their study designs: one found that PET produced greater concordance between observers in volumes (13), and the other found that the effect of PET varied by observer (39).

The optimal PET intensity measure for defining the tumour's edge remains unclear. Some studies report using regressive threshold functions (22), but the majority report using a fixed threshold (percentage of the maximal SUV intensity [e.g., 40-50%]), or do not report the intensity measure used at all. Some argue that regressive or lower fixed-threshold values (10-20%) are preferred (49,50). As well, some authors advocate contouring the distinct "halo" seen around the area of maximal intensity of PET because of the clinical ease of this approach and the lesser inter-planner variability it generates (13). There has been no rigorous

evaluation to determine an optimal threshold to date. As well, there are technical aspects of PET that impede the use of the technology. The evaluation of the lungs by PET is affected by respiratory motion, which generates a degree of measurement error thereby complicating co-registration. Hybrid PET/CT technologies help to reduce these errors but do not remove them altogether. No studies in this series compared hybrid PET/CT to dedicated PET devices.

Clearly, higher quality evidence is needed to guide clinical and policy decision making regarding the use of PET in RT planning. This evidence should be generated by well-designed studies, which typically require large numbers of patients and appropriate technological resources, including high-quality PET scanners. A major study in lung cancer patients is currently underway in Ontario (43) that will address at least some of the questions covered by this review.

CONCLUSIONS

Data from a number of small, non-randomized studies suggest that the inclusion of PET imaging in the planning process produces modifications in RT planning that may be beneficial. These changes include changing the intent of treatment from curative to palliative in a substantial proportion of patients and changes in target and planning volumes. In many cases, these changes are substantial and clinically significant, although it is not certain that these changes result in better clinical outcomes. Data from these studies also suggest that PET has a small but consistent protective effect on the lungs and esophagus, and a few studies confirm a benefit for PET in terms of increasing the total dose and tumour control probability. PET may be most useful in those cases where there is a large area of lung opacification that may be due to tumour and/or atelectasis/pneumonitis secondary to airway obstruction.

These data, taken as a whole, are highly suggestive of a benefit of PET in RT planning in lung cancer, and further evaluation of PET for this purpose is warranted. PET should continue to be used cautiously as part of research protocols, bearing in mind current uncertainties and evolving knowledge. Clinicians should be particularly mindful of situations in which PET is known to produce false-positive results (e.g., presence of inflamed lymph nodes due to pneumonitis). When performing RT planning, clinicians should take into consideration the technical specifications of the PET scanner being used as these may modify the utility of the device for RT planning purposes.

CONFLICT OF INTEREST

The members of the Lung DSG disclosed potential conflict of interest relating to this practice guideline. One of the guideline lead authors (Dr. Yee C. Ung), is a primary investigator for the OCOG PET START Trials. Only the publicly available details and data from the PET START Trial abstract have been reported in this systematic review.

JOURNAL REFERENCE

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For a complete list of the Lung Cancer Disease Site Group members,
please visit the CCO Web site at http://www.cancercare.on.ca/

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Evidence-Based Series 7-18: Section 3

Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer: EBS Development Methods and External Review Process

Y.C. Ung, A. Bezjak, N. Coakley, W.K. Evans, and the Lung Cancer Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: November 17, 2010

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung Cancer DSG of the CCO PEBC. The series is a convenient and up-to-date source of the best available evidence on positron emission tomography in radiation treatment planning for lung cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

On the initial RAP review, the most important issue raised was that the authors had not appropriately justified their recommendations, given the evidence that was identified. Moreover, the recommendations themselves were unclear. On reviewing the RAP feedback, it was clear that the draft recommendations were conveying an impression of a stronger recommendation for PET in RT planning than the authors actually wished to make, and this misunderstanding seemed to have generated the majority of the RAP feedback.

Given this issue, the authors reorganized and greatly clarified the recommendations, making it clear that they were only recommending PET for RT planning in the context of research protocols, and not more generally. Other changes were made in the text of the document to address additional and more minor concerns the RAP had raised, and the document was resubmitted to RAP. The document was reviewed and accepted by RAP in December 2009.

External Review by Ontario Clinicians

The PEBC external review process consists of two approaches, an external targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review, and the approval of the report by the PEBC Report Approval Panel, the Lung DSG circulated Sections 1 and 2 to external review participants for review and feedback. Box 1 summarizes the draft recommendations and supporting evidence developed by the Lung DSG.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review February 3, 20109)

QUESTION
What role should positron emission tomography (PET) play in radiation treatment planning for non-small cell lung cancer (NSCLC)? Specifically, does the combination of PET and computed axial tomography (CT) imaging provide data that is superior to CT imaging data alone for the purposes of radiation treatment (RT) planning?

RECOMMENDATIONS AND KEY EVIDENCE
Combination PET-CT imaging data may be used as part of research protocols in RT planning. Current evidence does not support the routine use of PET-CT imaging data in RT planning at this time outside of a research setting.

- The PET START trial, released in abstract form at the 2009 ASCO Annual Meeting (1), reported on the use of PET-CT compared to CT in treatment planning for patients with stage III non-small cell lung cancer (NSCLC). The primary outcome was the proportion of patients who did not receive combined modality therapy because their tumour was upstaged to stage 4 or their intrathoracic tumour was too extensive for radical RT. The primary outcome was achieved in 15% of the patients randomized to PET, as opposed to 2.7% in the CT arm (p=0.0002). Data on other outcomes, including overall survival, have not yet been reported.
- Twenty-three non-randomized prospective and retrospective studies provided evidence on the impact of PET imaging data on RT planning (2-24).
- No studies provided data on the effect of PET-based changes in RT planning on patient outcomes such as overall survival, recurrence, or quality of life. Therefore, data on technical measures form the evidence base of this recommendation. These measures include changes in gross treatment volume (GTV) and changes in planning treatment volume (PTV)
- Fourteen studies including a total of 496 patients reported changes in GTV as a result of the inclusion of PET data in RT planning (2-12,20-22). See Table 3 and its accompanying text in Section 2 of this Evidence-based Series for details of these data.
- Eleven studies including a total of 283 patients reported changes in PTV as a result of the inclusion of PET data in RT planning. (5-7,9,12-17,21). See Table 4 and its accompanying text in Section 2 of this Evidence-based Series for details of these data.
- The limited data available suggest that the addition of PET to RT planning is more likely to decrease the dose to the esophagus rather than increase it. Two of five studies (3,7,8,18,22) providing data on esophageal exposures ($V_{50\text{-}55}$eso), reported statistically significant decreases (-10.4%, p<0.005, and -8.7%, p=0.004, respectively) (8,18), and one study reported a result with no significance test (22). Changes in total radiation dosages to the esophagus were more variable across the studies, although one study did report a statistically significant (p=0.004) decrease of 6.1 Gy (8).
- The available data regarding the effect of PET in RT planning on dose to lung tissue is mixed. While substantial numbers of patients experience a change in V_{20}lung (between 42% and 100% of patients across four studies (3,7,9,22), these changes involve both increases and decreases. However, three studies (8,12,18), did report statistically significant reductions in V_{20} lung. The data do suggest that PET does reduce lung dose, with four studies (8,9,12,18) reporting decreases

(range of changes -5.1 to +1.5 Gy), and one of these reported a statistically significant decrease (8).
- Two studies evaluated the impact of PET on the total RT dose administered and treatment control probability: the total RT dose administered to patients increased by approximately 15 Gy because of PET, and the tumour control probability increased by 17.7% and 8.6% (p=0.026), respectively (8,18).
- In twelve studies (6,7,9-11,13,14,17,19,21,23,24) with a total of 656 patients, PET detected distant metastases in 8% to 25% of patients and resulted in a change from curative to palliative RT intent in 8% to 41% of patients.

QUALIFYING STATEMENTS
- There is only one randomized trial, the PET-START trial, to inform recommendations on this topic, and this trial has only been reported in abstract form. Should the results of this trial be similar when reported in a peer-reviewed publication with longer follow-up, the recommendation above may warrant review.
- There are no data available that demonstrate an impact of PET-based RT planning on either survival or local recurrence rates.
- The available evidence, besides the PET-START trial, consists of data from small, non-randomized studies that report on changes in treatment volume, changes in treatment intent, and changes in dose delivered to critical organs. These data, taken as a whole, suggest that the addition of PET increases accuracy in RT planning.
- The available data on change in treatment volume and other changes in response to the incorporation of PET into RT planning have not yet been confirmed to be beneficial, for example, through clinicopathological correlation and/or failure analysis patterns.
- Higher quality research, such as randomized trials, should be conducted to better evaluate the utility of PET in RT planning and to determine if the technology provides added value over existing imaging technologies for this purpose. Investigators publishing data related to the use of PET should evaluate and report on a wider range of outcome measures.
- PET may be useful in RT planning under very specific circumstances in the differentiation of malignant from non-malignant tissue, such as lung opacification that may be due to tumour and/or major atelectasis or pneumonitis secondary to airway obstruction. Clinicians should cautiously interpret results in situations where PET is known to produce false-positive results (e.g., presence of inflamed lymph nodes due to pneumonitis).
- When performing RT planning, clinicians should take into consideration the technical specifications of the PET scanner being used, as these may modify the utility of the device for RT planning purposes.

Methods

Targeted Peer Review: During the guideline development process, four targeted peer reviewers from Ontario, Alberta, and British Columbia, considered to be clinical and/or methodological experts on the topic, were identified by the Lung DSG. Several weeks prior to the completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. The three reviewers agreed, and each was sent the draft report and a questionnaire via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 24, 2010. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Lung DSG reviewed the results of the survey.

Professional Consultation: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All Ontario radiation oncologists in the PEBC database who treat lung cancer were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on March 8, 2010. The consultation period ended on April 23, 2010. The Lung DSG reviewed the results of the survey.

Results

Targeted Peer Review: Three responses were received from four reviewers. Key results of the feedback survey are summarized in Table 1.

Table 1. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1		2
2. Rate the guideline presentation.					3
3. Rate the guideline recommendations.			1	1	1
4. Rate the completeness of reporting.					3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
7. Rate the overall quality of the guideline				3	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
8. I would make use of this guideline in my professional decisions.				1	2
9. I would recommend this guideline for use in practice.				1	2

6. What are the barriers or enablers to the implementation of this guideline report?

1. PET has already been incorporated in the work-up of lung cancer. Should the guideline mention the differences in table (flat or curve) and position o the arms, etc..? One suggestion is ask the Nuclear colleagues always do the PET/CT with flat table and arms up to help the fusion for RT planning. Having a written statement will facilitate them to do the change as a routine.
   Response: This is more of a technical issue. Some centres routinely do this, but not all diagnostic nuclear medicine departments have the capability. In addition, not only the flat bed or pallet, but also placing the patient in the correct radiation therapy treatment position are of concern. Changes were made to the document.

2. The report is identifying the need for additional data to be collected regarding the impact of FDG PET/CT on patient outcomes. This will be difficult as this indication is now clinically funded in Ontario, unless the collection of additional data is made to be a condition of funding.
   Response: Even when funded, the idea is that patient outcomes will need to be evaluated for Quality Assurance purposes. Each centre will need to review their own results.

Summary of Written Comments and Modifications/Actions

The main points contained in the written comments (original style unchanged) are detailed below, followed by the DSG response in italics.

- Appropriate evidentiary base. Not all recommendations are appropriate to the evidence. No cost analysis undertaken.
  Response: While no cost analysis data is available at present, this data might be available at a later date, with the data from the PET START Trial.

- My suggestion is to divide the initial question in two questions: 1) What role should PET play in radiation treatment planning for lung cancer? 2) Does the combination of PET and CT imaging provide data that is superior to CT imaging data alone for the purposes of RT planning?
  Response: This has been discussed in our in our consultations, However, we believe they are the same questions, worded differently, and the wording of the second statement is more specific. No changes were made in the document.

- The absence of evidence of an impact on "clinical outcomes" is not evidence of absence. While the authors state "no studies were identified that reported on patient outcomes such as survival, recurrence, treatment related morbidity, or quality of life, "they do find evidence of "substantial and clinically significant' changes in treatment intent, staging, target volumes, volumes of organs at risk, and tumour control probability. Yet these changes are judged insufficient to support the use of PET CT for RT planning. Technical advancements in diagnostic technologies are not usually held to the standard of improved survival, recurrence, morbidity or QoL. Instead they are adopted when improved accuracy or efficiency can be reliably demonstrated.
  Response: Substantial and clinically significant changes do not imply that the correct change was made (3). In addition, there is the debate in the nuclear medical literature about linking health technological assessments to outcomes (4). No changes were made in the document.

- I'm uncertain as to what the last qualifying statement regarding "technical specifications of the PET scanner" means. The data presented uses instrumentation ranging from modified gamma cameras through to PET/CT Instrumentation but does not stratify results according to imaging equipment/technique utilized. In Ontario, only CareImaging continues to use a PET scanner. Modified gamma cameras are not used in any jurisdiction.
  Response: The data still include gamma cameras, which is why they are included. We refer to the technical specification of the PET scanner to include issues such as the resolution capabilities of the machine. No changes were made in the document.

- I think it is useful to mention that CT is acquired in seconds and PET in 30-40 minutes and this has to do with movements during breathing.
  Response: CT is usually acquired in seconds with a breath hold, while the PET is done with the patient free breathing over 20-30 minutes. In addition to organ motion, there is diffusion of the FDG at the edge of the image, which makes precise measurement difficult with PET. While these technical issues factor into the change in the size of the GTV, the reported change in GTV volume is much larger that what the breathing motion or diffusion of FDG would contribute.

- Table 2 of the Evidentiary Base needs to be modified. The Heading "PET Scanner" is misleading as several of the papers utilized modified Gamma Cameras; I would use "Instrumentation". The Gondi paper utilized PET/CT image co-registration. For consistency, in the Gondi paper, I would refer to "GE Discovery LS". In the Erdi paper, the instrument is "GE Advance"; the Mah paper, "Marconi Irix γ-PET3 GC",; the Roman paper, "Marconi Axis Dual-Head GC"; finally, for consistency in both the Roberts and Hicks paper, "UMG PENN-PET 300-H". It is particularly Important to consistently identify where modified gamma cameras have been used.
  Response: However, not everyone recognizes dedicated PET, PET CT or GCCI by their company names. Changes were made for clarity in Table 2.

- PET START: The authors rightly note the conflict of interest posed by Dr. Ung's primary status with PET START. However, this leads to awkward formulations in the guideline. On EB p7, the trial description is too restricted. While I agree a discussion of outcomes should be limited to published data, issues of study design should be fulsomely reported here. On EB p13 and R p2, the authors should refrain from anticipating the impact of the future PETSTART report, in particular striking the statement that "it will likely report significant data."
- *Response: The authors are only commenting on the significant upstaging data as contained in the abstract. No changes were made in the document.*

- Very well done. Was this RTOG reviewed? A Phase II Comparative Study of Gross Tumor Volume Definition With or Without PET/CT Fusion in Dosimetric Planning for Non-Small Cell Lung Cancer (NSCLC): Primary Analysis of Radiation Therapy Oncology Group (RTOG) 0515. Jeffrey Bradley, Kyounghwa Ba, Noah Choi, Ken Forster, Barry Siegel, Jacqueline Brunetti, James Purdy, Sergio Faria, Toni Vu, and Hak Choy. Presented at the ASTRO meeting 1-5 November 2009, USA
  Response: Abstracts were not searched. The manuscript has just been submitted. No changes were made in the document

- To facilitate reading the CONCLUSIONS (many people only read the Conclusions), I would suggest the following, without changing the content:
  CONCLUSIONS
  Data from a number of small, non-randomized studies suggest that the inclusion of PET imaging in the planning process produces modifications up to 50% of the cases in RT planning;
  These changes include changing the intent of treatment from curative to palliative in 8-25% of patients, and change in target and planning volumes;
  These changes may be substantial and clinically significant, but it is not known if these changes result in better clinical outcomes.
  These studies also suggest that PET has a small but consistent protective effect on the lungs and esophagus, and few studies confirm a benefit for PET in terms of increasing the total dose and tumour control probability.
  PET may be useful in those cases where there is a large area of lung opacification that may be due to tumour and/or atelectasis/pneumonitis secondary to airway obstruction
  The data, taken…….
  Response: PET does produce a lot of modifications and in small, nonrandomized trials there is a high degree of patient selection, making it difficult to present a firm statement about 50% modification (the range was from 18% to 100%). The same issue arises for the change in intent from curative to palliative. In addition, with newer radiation therapy techniques such as intensity modulated radiation therapy, patients previously deemed unsuitable for radical radiation therapy may now be suitable for aggressive treatment. Hopefully, the reader will be encouraged to review the data more critically by reading the full document rather than just the conclusions.

- The report is identifying the need for additional data to be collected regarding the impact of FDG PET/CT on patient outcomes. This will be difficult as this indication is now clinically funded in Ontario, unless the collection of additional data is made to be a condition of funding.
  Response: Every institution should have quality control measures and quality assurance (QA) reviews of their clinical practice. This is especially important for clinical experience to ensure the PET data are interpreted accurately and that the clinical outcome is consistent with the imaging findings. Because the use of PET combined with CT planning will be new to some clinicians, they should have close interactions with the oncologist and the radiologist. The more rigorous data collection will be from well-designed clinical trials, but, at an institutional level, there are QA rounds and multidisciplinary case conferences to help evaluate the impact on clinical outcomes.

- Minor typographical errors
  Response: All have been addressed and corrected

Professional Consultation: Seven responses were received. One practitioner did not fill out the survey because they were no longer treating lung. Two practitioners submitted only additional comments and did not complete the form. The complete form was filled out by 4 of the 23 reviewers. Key results of the feedback survey are summarized in Table 2.

Table 2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.		1		2	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.		1	1	1	1
3. I would recommend this guideline for use in practice.		1	1	2	

4. What are the barriers or enablers to the implementation of this guideline report?

- Guideline basically says more information is required – I agree, however it is far from clear whether or not such research is likely to be funded. Currently a moot point since PET for this indication is not covered by OHIP.
- Guideline report reports conflicting results and paucity of randomized trials. Therefore it is hard to know what to do.

Summary of Written Comments and Modifications / Actions

The main points contained in the written comments (original style unchanged) are detailed below, followed by the DSG response in italics.

- Good report, poor data (not their fault)

- Is this for all lung cancers or for non small cell variety only? Title does not reflect it.
  Response: Yes it is only for NSCLC. The document has been changed.

- Why was the JCO 2009 pet start trial abstract only in the conclusion, and not included in the recommendations?
  Response: Abstracts were not routinely searched for this guideline.

  Recommendations for practice
- Paper by macmanus report of international atomic energy agency on use of
  Pet published in june 2009,91,85-94 green journal should be referenced And quoted
  Response: This can be referenced; however, it is not part of the literature review. No changes were made in the document.

- Completed trial of rtog 0515 should be mentioned.
  Response: The manuscript was just submitted. No changes were made in the document.

Literature Search Update

The literature search was updated prior to the release of the guideline. Five additional studies were found, but these did not change the recommendations.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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