The Efficacy of PET Staging for Small-Cell Lung Cancer

A Systematic Review and Cost Analysis in the Australian Setting

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Introduction: This study aimed to establish from the published literature the efficacy of a positron emission tomography (PET)-based strategy for the staging of small-cell lung cancer compared to conventional methods, the potential impact on patient management and outcomes, and cost implications for the Australian health system.

Methods: EMBASE, Current Contents, PubMed, and OVID, databases were searched using relevant search terms. Reference lists of identified studies were examined for additional pertinent papers. Literature review identified 22 relevant studies containing data for 1663 patients. Studies were evaluated regarding the adequacy of pathological or clinical correlation of imaging findings. Efficacy of PET-staging was analyzed. The Medicare benefits schedule was used to compare costs of the two strategies.

Results: Published data confirm that PET staging has a sensitivity approaching 100% and specificity exceeding 90%. Data suggest that compared to conventional staging, PET can alter management (including radiotherapy portal changes) in at least 28% of patients, can result in the addition of life-prolonging radiotherapy in 6%, and avert unnecessary radiotherapy with associated toxicity in 9%. PET-based staging costs 1603 Australian dollars (AUD) and conventional staging 1610 AUD per patient. An additional 540,354 AUD may be saved annually through avoidance of unnecessary radiotherapy.

Conclusions: PET-based staging seems superior to conventional staging, and can significantly alter patient management particularly with regard to the inclusion, omission, and portal design of radiotherapy. The initial costs of the two strategies do not seem significantly different. PET may ultimately reduce healthcare costs through avoidance of inappropriate thoracic radiotherapy. The major advantages of PET-staging may, however, lie in averting unnecessary toxicity and in the appropriate addition of thoracic radiotherapy with potential survival gains.

Key Words: Staging, Positron emission tomography, Small-cell lung cancer.

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Small-cell lung cancer (SCLC) accounts for 15% of all lung cancer presentations. It ranks as the fifth leading cause of cancer deaths in the United States.[1] Although the tumor, node, metastasis staging system is prognostic, clinical management is still guided by the two-tiered staging system first proposed by the Veterans Administration Lung Study Group and later modified by the International Association for the Study of Lung Cancer (IASLC).[2] The IASLC modification provides superior prognostication.[3] This system divides patients into those with limited disease (LD) or extensive disease (ED). LD includes disease limited to one hemithorax including contralateral mediastinal and supraclavicular nodes, and also includes ipsilateral pleural effusion independent of cytological findings.[2] Patients with LD have a median survival of 23 to 27 months,[4,5] compared to 10 to 12 months for those with ED.[6–8] State-of-the-art management for fit patients with LD involves concurrent chemoradiation[5] optimally delivered in twice-daily fractions,[4] although the value of twice-daily irradiation versus high-dose daily radiotherapy is undefined and the subject of ongoing trials (CALGB 30610/RTOG 0538 and CONVERT). Patients with extensive stage SCLC are treated with palliative chemotherapy and do not generally receive thoracic radiotherapy.

Accurate staging is thus paramount to ensure that LD patients are not denied life-prolonging thoracic radiotherapy and conversely, that ED patients are spared the toxicity of concurrent thoracic radiotherapy, which confers them no benefit. The distinction between the limited and extensive stages is also important when considering the merits and dose of prophylactic cranial radiotherapy. Doubling time is 33 days, therefore rapid staging and initiation of treatment is paramount.[9]

Fluorodeoxyglucose (FDG) positron emission tomography (PET) has been widely embraced as part of the routine workup for non–small-cell lung cancer (NSCLC), and is reimbursed by national health funding in Australia and the United Kingdom along with many other countries. In contrast, FDG-PET has not yet been widely incorporated into the staging of SCLC. A literature review was thus undertaken to establish the efficacy of PET in this setting before considering its cost implications compared to a conventional workup.

METHODS

Literature Review

EMBASE, Current Contents, MEDLINE, and OVID databases were searched using the Boolean operators "PET," "positron emission tomography," and "small cell lung cancer." The reference lists of identified papers were examined to

identify further studies of relevance. The literature review was confined to English-language papers. Each study was assessed with the inclusion and exclusion criteria below. The results presented are weighted averages across all studies proportional to the patient numbers contributed by each study relative to the total number for each endpoint.

Selection Criteria

Eligible studies were those that included patients with cyto- or histologically confirmed SCLC or mixed SCLC/NSCLC, who underwent PET as part of initial workup for SCLC (in one study, PET was performed 1–11 days after treatment commenced in 33% of the patients).[10] For studies in which PET was performed both for staging and response assessment, only data relating to initial staging were considered. Only data that were explicitly stated or that could unambiguously be calculated from information provided were incorporated into the present results. A single study used both fluorine-18 fluorodeoxyglucose ([^{18}F] FDG), and 3,4-dihydroxy-6-18F-fluorophenylalanine ([^{18}F]FDOPA) as radiotracers;[11] however, only results for FDG-PET are included in the present review.

Cost Analysis

Calculations were based on 1091 new cases of SCLC per annum. This figure was derived from averaged annual Australian SCLC incidence figures for 2001 to 2005 (Mark Short, Australian Institute of Health and Welfare, personal communication). Costs were based on the Australian Medicare Benefits Schedule of July 2010. They thus reflect costs to society from the government perspective. Although these values might not accurately reflect the exact dollar cost of each intervention to society, they do provide a reasonable indication of such costs, and more importantly allow comparisons within a single healthcare system. Costs for investigations are presented in Australian Dollars and are enumerated in Table 1.

The cost of conventional staging included a computed tomography (CT) brain, CT chest, a separately obtained CT abdomen and pelvis, bone scan, liver-function tests, and serum biochemistry.[1] The cost of a CT chest (Table 1. item 56307) was considered separately from a CT abdomen/pelvis (item 56507), rather than a combined CT chest, abdomen, and pelvis as a single investigation (item 56807). This is because almost all patients will have received a CT chest before diagnosis is formally established and staging is undertaken. Thus a CT chest is usually obtained separately from CT abdomen/pelvis, and cost is accrued from two separate attendances and investigations. Identical blood tests are required for both staging approaches. These are therefore cost neutral and were not considered further.

The cost of PET-based staging included a CT brain, CT chest, PET scan, and blood tests. PET appears superior to bone scan for detecting bone metastases even though it does not image below the knees.[10,12–15] PET thus negates the need for bone scan and CT abdomen/pelvis, and thus may possibly be quicker to execute depending on local resources. A brain CT or magnetic resonance imaging (MRI) is still required for staging as PET has only 45% to 50% sensitivity for brain metastases.[12,15] Although MRI is more sensitive than CT for the detection of brain metastases, we chose CT as our staging strategy for cost analysis. This is because CT brain is more widely accessible than MRI for this purpose and is almost exclusively the neuro-imaging modality employed in the presently reviewed literature.

TABLE 1. Cost per Investigation According to Medicare Benefits Schedule (July 2010)

Investigation	Item	Cost (AUD)
PET-CT	61529	953
Bone scan	61421	480
CT chest, abdomen, and pelvis	56807	560
CT chest alone	56307	400
CT abdomen and pelvis	56507	480
CT brain	56007	250

PET, positron emission tomography; CT, computed tomography.

RESULTS

Utility of PET for Initial Staging of SCLC

Twenty-two relevant studies containing data on 1663 patients were identified. Data for 1082 of these patients are from the National Oncologic PET Registry, which provide information on the impact of PET on altering intended management only. These results are tabulated in Table 2.

Eleven of 22 studies clearly employed adequate clinical or pathological correlation to confirm or refute their imaging findings.[10,12,15–23] Three studies had incomplete clinicopathological correlation of their imaging findings (43%, 83%, and 87%, respectively).[14,24,25] The adequacy of clinicopathological correlation could not be definitively assessed in six more studies, mainly because of the unspecified length of clinical follow-up.[13,26–30] Two studies were inadequate in terms of clinicopathological verification of imaging findings.[11,31] Eight studies were prospective, and [12,13,18,20,23,27,31] 14 were retrospective.[10,14–17,19,21,22,24–26,28–30]

Published data confirm that PET-based staging has a sensitivity approaching 100% and specificity exceeding 90%. CT-PET improved specificity compared to PET alone (100% versus 83%) in the only (prospective) study reporting on this outcome.[23] Data suggest that compared to conventional staging, PET can alter management (including radiotherapy portal changes) in 28% of the patients. If studies omitting data on radiotherapy portal changes are included, PET alters management in 38% of patients. This is because of the large impact of the National Oncologic PET Registry study with 1082 patients.[31] PET can result in the addition of potentially life-prolonging radiotherapy in 6%, and can avert unnecessary radiotherapy with associated toxicity in 9%. For patients with LD, PET can alter radiotherapy portals in 23%. Seven studies specifically analyzed individual discordant sites as determined by PET versus conventional staging (Table 3).

Cost Analysis

A PET-based staging strategy costs 1603 AUD per patient (CT brain + CT chest + PET scan). Conventional

TABLE 2. Utility of FDG-PET in SCLC Staging

RT Portal Change % (LD patients)	Required RT (%)	Averted RT (%)	% True Upstaged	% True Downstaged	Falsely Upstaged (%)	Falsely Downstaged (%)	Specificity	Sensitivity	PET or PET-CT	Adequate Follow Up (F/U) Correlation	Pt No	Reference
12[a]	—	4	8	8	3	0	1[b]	92–98	100	PET	Yes	120	Brink et al.[12]
16[a]	—	12	4	4	12	2	4[bc]	—	100	PET	Yes	51	Vinjamuri et al.[15]
41[a]	—	—	—	—	—	—	—	—	—	Unspecified	no	1082	(Hillner et al.[31]
47	25	0	33	33	0	0	0	—	100	PET	Yes	15	Blum et al.[22]
22[d]	14	Only LD	8	8	Only LD	2	Only LD	—	—	PET and PET-CT	Yes	63	Niho et al.[10]
26[e]	12	13	7[e]	9	17	—	—	—	—	PET and PET-CT	Yes	46	Azad et al.[16]
37	33	4 (surgery)	13	13	4	0	0	—	—	PET and PET-CT	Equivocal	24	Kamel et al.[26]
—	29	Only LD	4	8	Only LD	4	Only LD	96	100	PET	Equivocal ? length F/U	24	Bradley et al.[27]
—	30[f]	Only LD	—	—	Only LD	—	Only LD	—	—	PET-CT	Yes	60	van Loon et al.[20]
—	24[f]	Only LD	—	—	Only LD	—	Only LD	—	—	PET-CT	Unable to assess	21	van Loon et al.[29]
—	—	—	—	10	3 equivocal	0	3 PET CT[c], 13 PET	100 PET-CT 83 PET	93 PET 93 PET	PET-CT	Yes	29	Fischer et al.[23]
—	—	0	0	0	0	0	0	—	100	PET	Equivocal ? length F/U	18	Kut et al.[13]
—	—	—	—	42	8	0	0	—	100	PET	Equivocal F/U in only 83%	12	Arslan et al.[24]
—	—	0	27	19[g]	0	0	0	—	—	PET	Equivocal Only in 43%	26	Schumacher B et al.[14]
—	—	—	—	—	—	—	—	100	100	PET	Equivocal Histo in ≥86% ? length F/U in others	7	Hauber et al.[25]
—	—	0	0	0	0	0	0	—	100	PET	Yes	8	Pandit et al.[17]
—	—	—	—	11	5	0	0	—	—	PET	Yes	18	Chin et al.[18]
—	—	4	4	4	4	0	0	—	100	PET	Yes	25	Shen et al.[19]
—	—	—	—	—	—	—	—	—	100	PET	Unable to assess	3	Zhao et al.[28]
—	—	—	—	—	—	—	—	—	100	PET	Unable to assess	5	Sazon et al.[30]
—	—	—	—	—	—	—	—	—	100	PET	Yes	2	Saunders et al.[21]
—	—	—	—	0	0	0	0	—	—	PET	No	4	Jacob et al.[11]
Weighted average												
28	23	6	9	9	6							

[a]Excluding radiation portal alterations.
[b]Reflecting known insensitivity for brain metastases.
[c]Missed liver metastases.
[d]Does not include potential for downstaging.
[e]Would be 33% but some staged patients were unfit for, or refused treatment. If all staged patients were fit for treatment, 9% would avoid RT.
[f]Study specifically designed to answer this question.
[g]Further 8% unconfirmed.
PET, positron emission tomography; FDG, Fluorodeoxyglucose; SCLC, Small-cell lung cancer; RT; radiation therapy; CT, computed tomography; LD, limited disease.

TABLE 3. Evaluation of Discordant Sites

% PET Correct	% Conventional Correct	% Indeterminate	Reference
67	7	26	Azad et al.[16]
33	0	66	Chin et al.[18]
94	0	6	Niho et al.[10]
79	14	7	Blum et al.[22]
60	20[a]	20	Kut et al.[13]
65	18	18	Schumacher et al.[14]
72	15[b]	12	Brink et al.[12]

[a]Detection of pericardial effusion accounts for all these cases of CT superiority.
[b]Detection of brain metastases accounts for 70% of these cases of CT superiority.
CT, computed tomography.

staging costs 1610 AUD (CT chest + CT brain + CT abdomen and pelvis + bone scan).

Based on 1091 new cases per annum, if 6% of patients are downstaged by PET, and are all assumed fit enough to receive concurrent thoracic radiotherapy, which improves survival by 12 months on average and costs 5503 AUD per patient, an extra 360,226 AUD would be incurred per annum. However, this could be offset by the 540,354 AUD saved annually through the avoidance of unnecessary radiotherapy in the 9% of patients who are upstaged to ED. Overall, this represents a modest cost saving of 2752 AUD per life-year gained.

DISCUSSION

As yet there are no randomized data for PET in the staging of SCLC, and less data exist overall than for NSCLC. However, data does exist from prospective studies with good clinicopathological correlation of PET findings in 227 patients.[12,18,20,23] In addition, retrospective data with good clinicopathological confirmation are also available from seven studies comprising 210 patients.[10,15–17,19,21,22] The data appear consistent across the literature, suggesting that SCLC is highly PET avid. PET staging appears superior to conventional methods in terms of demonstrating the primary tumor and undetected secondaries (because of improved sensitivity). PET also appears able to better distinguish false metastatic findings compared to CT (improved specificity). It should be noted that PET specificity depends on the prevalence of other PET-avid disease in the population being staged (e.g., tuberculosis, sarcoidosis, and histoplasmosis), and may differ in some populations from the 90-plus percent reported in the literature. However, PET specificity in the context of SCLC would be similar to that for NSCLC in the same population. PET also seems superior in detecting involved mediastinal and supraclavicular lymph nodes. This has important implications for radiotherapy portal design, efficacy, and toxicity.[20] Apart from a minority of studies showing no difference between staging strategies,[11,17,28] the literature consistently demonstrates PET staging as more accurate than conventional methods. Importantly, no study showed conventional imaging to be superior to PET in the initial workup of SCLC. Studies evaluating discrepancies between PET-based staging and conventional methods on a site-by-site basis similarly found PET consistently more accurate.

However, PET does have limitations that are important to appreciate. Although superior to bone scans for detecting bone metastases,[10,12–15] PET is inferior to CT and MRI in detecting brain metastases from SCLC, with a sensitivity of just 46% to 50%.[12,15] PET is also limited in sensitivity for mucosal and urogenital-tract lesions, and care should be taken in its interpretation in these areas. Pericardial and pleural effusions are inadequately assessed by PET,[13] but accurately assessed by PET-CT. PET infrequently missed liver secondaries in 0.9% of patients. Many of the reported inaccuracies of PET in the articles reviewed relate to the known insensitivity of PET for brain metastases, mucosal lesions, and effusions. Some of these inaccuracies may have been averted by the coregistration of PET images with CT,[23] and would thus be overcome by modern scanners that almost universally incorporate a co-mounted CT scanner for image coregistration and attenuation correction. Such technology maximizes the synergism and cross sensitivity/specificity of both PET and CT. Insensitivity of FDG-PET staging for brain metastases, however, can only be overcome through the concomitant use of contrasted CT brain or MRI.

The reviewed literature suggests that more than a quarter of patients could have their management altered through the use of PET staging. A significant minority of patients could be spared the toxicity of unnecessary thoracic radiotherapy; whereas a further minority who would otherwise have missed out on concurrent radiotherapy could be correctly identified as benefiting from this life-prolonging treatment. Furthermore, PET could alter radiotherapy portals in about a quarter of LD patients. Surgical series confirm that CT tends to underestimate lymph-node involvement in the mediastinum and supraclavicular areas in SCLC.[32,33] PET appears superior to CT in this regard,[20] and its use might therefore improve the efficacy of radiotherapy and/or reduce its toxicity. When performed in addition to standard investigations, PET frequently detects metastatic foci not detected by other imaging modalities.[11–14,17,22,23,25–27] This does not often change patient management, however, because in the majority of such cases, ED has already been diagnosed.

The literature on PET-staging for SCLC reviewed here is subject to substantial limitations. Although complete histological confirmation of all PET findings would be the gold standard, this is neither practical nor is it ethically clear. Consequently, most studies rely on a combination of histological confirmation together with clinical follow-up of suspected sites of disease, interpreting their natural course or response to treatment as proof of their true nature. This problem is shared by NSCLC PET studies. A further limitation is the lack of randomized data. However, as previously noted, a significant volume of good quality nonrandomized data, both prospective and retrospective, have now been accumulated. The available data seem consistent. Not every study reported data for each endpoint of interest. Thus, many findings of this review are based on the results of only a few studies.

It is acknowledged that the present cost analysis is also subject to limitations. The cost analysis is by no means meant to be exhaustively detailed; rather, it is illustrative of the relative costs of the two staging strategies. Micro-costings of the investigations and treatment were not performed. Rather, Medicare reimbursement amounts were used for calculations. These Medicare figures are, however, used by government healthcare funding committees for cost-effectiveness calculations (Dale Brooker, Department of Health and Ageing, personal communication), and may therefore be regarded as reflecting true costs with a high degree of accuracy. Conventional cost-effectiveness methodology often employs a decision tree analysis. However, for the current study, a decision tree incorporating the proportion of patients categorized as ED after each successive conventional staging procedure was felt not to be reflective of clinical reality where staging investigations are often ordered together. Furthermore, reliable data about such staging endpoints is not available to populate the tree. Hence we adopted a more straightforward method of costing each approach and limiting the analysis to staging and initial treatment only. In any case, second-line treatment and its associated costs are likely to be similar for progressive disease regardless of initial staging and treatment strategy.

In a Danish study, the costs of staging and primary treatment were compared using PET/CT versus standard staging. Patients were admitted for all staging investigations—the duration of which was shorter with PET/CT. No significant cost difference was found.[23]

CONCLUSIONS

The true improvement offered by PET in staging SCLC is difficult to define because of variations in and limitations of study designs, the lack of randomized data, and the lack of complete histological corroboration in most studies. However, it is fair to note that the majority of studies have reported adequate correlation of PET findings with clinical or pathological outcomes, that results appear consistent across studies and patient populations, that where discrepancies between CT and PET have been investigated, PET has consistently proved to be more accurate, and that substantial data are accumulating in favor of PET. A successful randomized trial is unlikely given the prohibitive numbers of patients required to demonstrate differences in clinically meaningful endpoints. Within such context and limitations, the current literature suggests that PET-based staging appears superior to conventional staging and can significantly alter patient management, particularly with regard to the inclusion, omission, and portal design of radiotherapy. Initial costs of the two strategies do not seem significantly different, provided no doubling up of investigations occurs. The main advantages of PET-staging may however lie in averting unnecessary toxicity and in the appropriate addition of thoracic radiotherapy with potential survival gains.

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