Cross-Sectional Diagnostic Imaging in Lung Cancer

A Cancer Care Ontario Recommendations Report

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Cross-Sectional Diagnostic Imaging in Lung Cancer

I. PURPOSE

This recommendations report was developed to provide some initial guidance to Ontario health care providers and planners on the use of cross-sectional diagnostic imaging technology for patients with lung cancer. Topics of interest included the use of imaging equipment to stage disease, assess tumour response to treatment, and detect recurrence following treatment and during follow-up. The recommendations report can serve as a foundational piece and tool from which further discourse around a larger provincial quality agenda and implementation for diagnostic imaging services for cancer can revolve.

II. INTRODUCTION

Diagnostic imaging is essential to determine the staging of disease in patients with an established diagnosis of cancer. Such staging is critical in determining the type and aggressiveness of treatment options offered to patients. Where needed, imaging is also used to assess the response of cancer to therapy and to determine the extent of disease when recurrence is found.

There are concerns with the current state of diagnostic imaging delivery for cancer. There is a perception among Canadians that waiting times for many medical services are excessive and may be causing harm to patients. These concerns about excessive waits apply to diagnostic imaging, particularly cross-sectional imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Of importance, radiologists have identified cross-sectional imaging for cancer as the major determinant for CT and MRI use in the province. As well, some have suggested that many imaging studies ordered during the active treatment of patients with cancer are done for uncertain reasons, with results that will often have no impact on clinical care. Moreover, the significant expansion in the number of CT and MRI machines has not meaningfully influenced wait times for these investigations. For those reasons, Cancer Care Ontario (CCO) established a Diagnostic Imaging Project to develop guidance documents for Ontario health care providers and planners on the use of cross-sectional imaging technologies in cancer.

The recommendations in this document will deal with cross-sectional diagnostic imaging for patients with lung cancer. The recommendations are intended to:

- promote evidence-based practice;

- provide guidance to clinicians about the most appropriate imaging techniques to use in the workup and management of their patients;
- provide useful information to those charged with planning for the number of imaging machines needed for cancer patients in Ontario; and
- be used to monitor the use of imaging modalities in patients with cancer.

III. METHODS

In 2003, CCO established a small working panel, the Diagnostic Imaging Panel, consisting of medical, radiation, and surgical oncologists; diagnostic radiologists; and methodologists, to review guidelines published during the last five years on the use of cross-sectional imaging in oncology. After examining documents from nineteen guideline developers, the panel concluded that the available guidelines did not focus on the particular issues of interest here. Therefore, the panel decided to review the primary research and develop recommendations for Ontario on the use of CT, MRI, and ultrasound for the initial staging, assessment of tumour response during active treatment, and follow-up for patients with six types of cancer: lymphoma, breast cancer, colorectal cancer, prostate cancer, lung cancer, and ovarian cancer.[1] The potential utility of the different imaging technologies may vary across disease sites. The working group developing the recommendations for lung cancer agreed that the use of ultrasound in this type of cancer is limited currently and would not be considered. In contrast, bone scans are commonly used to detect metastatic disease in lung cancer and, although not within the scope of this report, may be a topic for a future report.

A systematic review of the literature identified few randomized studies to provide guidance on the use of cross-sectional imaging in the management of patients with cancer; therefore, it was decided to also include cohort studies and case series reports in the evidence review and incorporate expert opinion in the development of the recommendations. The initial selection and summary of relevant evidence was completed by methodologists at the Program in Evidence-Based Care in consultation with the clinical experts from the Diagnostic Imaging Panel.

The systematic reviews served as the evidentiary foundation to inform the deliberation of clinical experts. Formal and informal consultations with radiologists was facilitated by Dr. Anne Keller, diagnostic imaging representative of the CCO Clinical Council, and undertaken with

[1] The use of positron emission tomography (PET) is being considered in different projects in Ontario, including guidelines under development and clinical trials. Until this work is completed, readers are

members who participated in the provincial MRI and CT Wait Times Strategy Expert Panel and the CCO Diagnostic Imaging Panel. In addition, consultations with oncologists were undertaken, mainly through the relevant disease site groups of CCO's Program in Evidence-Based Care. The recommendations, which are presented in the format developed by the Canadian Association of Radiologists (1), emerged through these consultations.

IV. EVIDENCE REVIEW

A. Literature Search Strategy

An inventory of diagnostic imaging guidelines published in English after 1998 was completed in October 2003 and used to identify existing evidence-based guidelines. English-language evidence published between 1980 and 2004 was searched for through MEDLINE, EMBASE, and the Cochrane Databases of Systematic Reviews and Abstracts of Reviews of Effects. Meta-analyses, systematic reviews, and trials reporting on sensitivity and specificity were sought. Search strategies were modified for each database and disease site (see Appendix 1).

B. Eligibility Criteria

Inclusion

Studies were included if they satisfied all of the following criteria:

1. included patients with confirmed cancer of the lung,
2. evaluated CT, MRI or ultrasonography,
3. described an objective diagnostic standard,
4. reported data for disease recurrence, quality of life, survival, frequency of true- and false-positive tests for extent of disease, or sensitivity, specificity, positive predictive value or negative predictive value to detect distant metastases [2], and
5. were randomized trials, comparative cohort studies, case series (prospective or retrospective) with more than 12 *consecutive* patients, meta-analyses (published in English after 1998) of data from randomized trials, comparative cohort studies or case series, or evidence-based clinical practice guidelines.

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referred to the systematic review completed by the Institute for Clinical Evaluative Sciences (ICES) (http://www.ices.on.ca/file/Pet_jan20041.pdf).

[2] Where necessary, true positive, false-positive, sensitivity, specificity, positive predictive value and negative predictive value rates were calculated from data provided in primary reports, using the Predictive Value Calculator available on the web at http://www.azzopardi.freeserve.co.uk/easycalc/Additions/predict.htm.

Exclusion

Letters, editorials, and meeting abstracts were not included. As noted in the Methods section of this report, a post-hoc decision was made to exclude studies of ultrasound in lung cancer.

C. Literature Search Results

Eligible papers for the systematic review on imaging in lung cancer included four evidence-based guidelines (2-5), one report evaluating quality indicators (6), two randomized trials (7,8), two comparative cohort studies (9,10), three pooled analyses of case series reports (11-13), and 15 case series reports (14-28).

D. Outcomes

D.1. Staging of Disease

EVIDENCE-BASED PRACTICE GUIDELINES AND QUALITY INDICATORS

All four evidence-based reports that provided recommendations on the use of CT and MRI for the staging of lung cancer conducted literature searches of key databases, including MEDLINE, for relevant evidence (2-4,6). The range of evidence reviewed by each group varied with little overlap. Three groups graded recommendations based on the quality of the evidence reviewed (2-4,29), and all employed a formal (6) or informal (2-4,29) expert consensus process in the development of the recommendations. One group also included a structured external review process (4). Recommendations relating to the use of cross-sectional imaging are summarized in Table 1, with the complete recommendations detailed in Appendix 2.

The guidelines of the American College of Chest Physicians (ACCP) (2) were primarily based on a pooled analysis reported by Toloza et al (12) and discussed below. They emphasized the potential impact of non-cancer-related factors, such as postobstructive pneumonitis, on measures of diagnostic imaging test specificity in lung cancer (2). Both the ACCP and the British Thoracic Society (BTS) noted the limitations of CT scans for staging the mediastinum (2,3), but the ACCP suggested they are useful for directing further testing (e.g., needle aspiration). The BTS and Royal College of Radiologists (RCR) reported ranges of 60-70% for sensitivity and specificity of CT in the nodal staging of lung cancer (3,4). The BTS did not make recommendations on the use of MRI but did suggest that it is not useful for routine staging and is no better than CT for assessing lymph node enlargement (3). Similarly, the RCR suggested there is no benefit for MRI over CT in the evaluation of chest wall invasion, although MRI may be useful for detecting vascular or mediastinal invasion (4).

The RAND report by Reifel focused on the identification of quality indicators, which are intended to monitor the quality of lung cancer care provided, rather than practice recommendations, which are intended to direct clinical care (6). None of the quality indicators identified by Reifel were specific to the use of cross-sectional imaging; however, the recommendation included in Table 1 was embedded in the text of the report.

Table 1. Summary of existing guideline and quality indicator recommendations on the use of cross-sectional imaging for diagnosis and staging of lung cancer.

Recommendation [a]	Group	Reference
A chest CT scan should be performed on all patients being considered for surgery. The RCR also recommends a CT scan of the upper abdomen.	ACCP BTS RCR	(2-4)
We do not include routine chest imaging with plain films, CT, or MRI as a recommended quality indicator for the staging of non-small cell lung cancer.	RAND	(6)
Patients with enlarged mediastinal lymph nodes on CT scans (*i.e.*, > 1 cm on the short axis) should undergo further evaluation of the mediastinum prior to surgical resection of the primary tumour.	ACCP BTS	(2,3)
A chest MRI should not be performed for staging the mediastinum in patients who are eligible for treatment, but should be performed in patients with NSCLC involving the superior sulcus for evaluation of the brachial plexus or for evaluation of vertebral body invasion.	ACCP	(2)
Diagnostic imaging of bones, liver and brain should be carried out if there is clinical or radiological suspicion of metastatic disease. Site-specific signs or symptoms should be evaluated with the most appropriate study for that site (*e.g.*, head CT scan and abdominal CT scan).	ACCP RCR	(2,4)
Patients with clinical stage I or II lung cancer and a normal clinical evaluation require no further imaging for extrathoracic disease.	ACCP	(2)
Patients with stage IIIA and IIIB disease should have routine imaging for the detection of extrathoracic metastases (*e.g.*, head CT scan and abdominal CT scan). [b]	ACCP	(2)
Patients with abnormal imaging study results should not be excluded from potentially curative surgery without tissue confirmation or overwhelming clinical and radiographic evidence of metastases.	ACCP	(2)

Abbreviations: ACCP – American College of Chest Physicians, BTS – British Thoracic Society, CT – computed tomography, MRI – magnetic resonance imaging, NSCLC – non-small cell lung cancer, RCR – Royal College of Radiologists, SCLC – small cell lung cancer.

[a] Unless indicated otherwise, recommendations for the ACCP, BTS, and RCR are graded A or B, indicating at least a moderate to high level of evidentiary support.

[b] Based primarily on clinical consensus; limited evidence.

Randomized Trials

Both randomized trials of CT were conducted by the Canadian Lung Oncology Group in patients with apparently operable lung cancer, primarily non-small cell type (NSCLC) (7,8). Since early identification of metastases may avoid the performance of unnecessary surgery for patients with lung cancer, the primary outcome of interest in both studies was the performance of thoracotomy without cure, defined as unresectable disease at the time of the thoracotomy, incomplete resections, or recurrence of disease (within three years for the 1995 trial). Both trials randomized patients centrally, performed intent-to-treat analyses, followed 99-100% of patients for one year (8) or three years (7), and included an adjudication committee to confirm results. The randomized groups were similar on all reported patient and disease characteristics, and both trials reported unadjusted analyses because analyses adjusted for baseline characteristics provided similar results. The trial results are reported in Table 2.

Detection of mediastinal metastases

In the 1995 trial, patients were randomized to mediastinoscopy or CT to detect the presence of mediastinal disease (7). Patients in the CT group with a positive test, defined as the presence of nodes >1cm on the shortest transverse axis, also underwent mediastinoscopy (136 patients). All patients with negative diagnostic tests underwent a thoracotomy. With positive mediastinoscopy or the presence of N2 disease at thoracotomy as the gold standard, CT sensitivity for the detection of mediastinal metastases was 78% and specificity was 69%. No statistically significant differences were detected between the CT and mediastinoscopy groups on the primary outcome, thoracotomy without cure (Table 2).

Detection of extrathoracic metastases

The 2001 trial compared limited and full investigation strategies for identifying extrathoracic metastases in asymptomatic patients (8). A conservative approach for identifying signs and symptoms of metastatic disease was agreed upon before the study began. All patients underwent a mediastinoscopy and chest CT. In the limited investigation group, if no extrathoracic metastases were detected, an immediate thoracotomy was performed. In the full investigation group, additional imaging including bone scintigraphy; CT of the liver, adrenal glands and head; ultrasound for hepatic lesions; and other tests as indicated, were performed before the decision to perform a thoracotomy was made. No statistically significant differences were detected between limited and full investigation strategies.

Table 2. Results of Canadian Lung Oncology Group randomized trials of CT scan.

Outcome	1995 trial (7)			2001 trial (8)		
	Investigation type		Relative risk [a] (95% CI)	Investigation type		Relative risk [a] (95% CI)
	Med (N=342)	CT (N=343)		Full (N=318)	Limited (N=316)	
Primary outcome: 'Thoracotomy without cure'	109 (32%)	103 (30%)	0.95 (0.75 to 1.19) p=0.34	58 (18%)	73 (23%)	0.80 (0.56 to 1.13) p=0.20
Thoracotomy performed	248 (73%)	235 (69%)	NR	221 (69%)	235 (74%)	0.94 (0.78 to 1.14)
Thoracotomy (in patients with benign disease)	12 (of 25)	4 (of 20)	0.42 (0.12 to 1.13)	19	22	NR
Thoracotomy without cure or in patients with benign disease	121 (35%)	107 (31%)	0.88 (0.71 to 1.10)	77 (24%)	95 (30%)	0.81 (0.60 to 1.10)
Thoracotomy with subsequent recurrence	NR	NR	NR	43 (14%)	61 (19%)	0.70 (0.47 to 1.03)
Death	177 (52%)	186 (54%)	1.05 (0.91 to 1.22)	74 (23%)	87 (28%)	0.84 (0.61 to 1.14)

Abbreviations: CI – confidence interval, CT – computed tomography, Med – mediastinoscopy, N – number of patients, NR – not reported.

[a] Relative risk <1.0 favours the CT group (7) or full investigation group (8).

POOLED ANALYSES

Detection of mediastinal metastases

Three articles reported pooled analyses of case series studies examining the use of CT for mediastinal staging of lung cancer (11-13) (Tables 3 and 4). All analyses were well conducted, describing their purpose and search strategy, including independent selection of studies according to defined eligibility criteria, and describing the analytic process. Two of the analyses aimed to compare CT with positron emission tomography (PET) (11,13). Patient level data were reported separately in two analyses (11,12) and combined with nodal level data in the third analysis (13). Fewer than 30% of studies were included in more than one analysis because of different eligibility criteria. In two analyses, 85-100% of studies defined the criterion for a positive CT as nodes ≥1cm on the short axis diameter (12,13) and, in two analyses, <50% of the included studies required that independent interpretation of the imaging test and reference test be conducted (11,13).

Pooled sensitivity and specificity for CT in the detection of mediastinal involvement were similar in all analyses and accuracy rates were modest (70-75%), with an overall prevalence rate of 28-32% for mediastinal metastases (11,12). However, Toloza et al reported marked heterogeneity in the studies included in their analysis, with sensitivities ranging from 0.20 to 0.86 and specificities from 0.57 to 0.93 (12). Similar variation was evident in the other two analyses.

Table 3. Characteristics of pooled analyses of imaging tests for staging the mediastinum.

1st author, Year	Literature search	Cancer type	Imaging test	Number of studies included	Gold standard
Gould, 2003 (11)	Medline, Embase, Biosis, CancerLit Up to Mar 2003 Any language	NSCLC	CT for mediastinal staging	23 studies with >10 patients (≥5 with mediastinal metastases)	Histologic confirmation
Toloza, 2003 (12)	Medline, HealthStar, Cochrane 1991-2001, July English	NSCLC and SCLC	CT for mediastinal staging	20 studies with >50 patients	Histologic confirmation or ≥1 year of follow-up
Dwamena, 1999 (13)	Medline 1990-1998, Jan English	NSCLC	CT for mediastinal staging	29 studies	Histologic confirmation

Abbreviations: CT – computed tomography, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer

Table 4. Results of pooled analyses of imaging tests for staging the mediastinum.

1st author, Year	Number of patients	Accuracy %	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (range)	NPV % (range)	Prevalence of mediastinal metastases
Gould, 2003 (11)	1,119	70 [a]	59 (52-66)	78 (72-83)	--	--	32%
Toloza, 2003 (12)	3,438	--	57 (49-66)	82 (77-86)	56 (26-84)	83 (63-93)	28%
Dwamena, 1999 (13)	2,226	75	60 (58-62)	77 (75-79)	50	85	Range, 12%-62%

Abbreviations: CI – confidence interval, CT – computed tomography, NPV – negative predictive value, PPV – positive predictive value.

[a] Represented by point on receiver operating curve at which sensitivity and specificity are equal.

COHORT AND CASE SERIES REPORTS

Staging of potentially resectable disease

Four case series, including two retrospective reports (14,17), evaluated the use of CT for staging of potentially resectable NSCLC (14-17). Three of the studies clearly identified the criteria for a positive CT (>1cm node in short axis diameter) (14,16,17), and none of the studies reported blind assessment of CT scan. The gold standard in all four studies was surgical or pathological staging. The results, shown in Table 5, suggest a low level of accuracy for CT, with consistent and moderate rates of understaging and variable rates of overstaging. In three of the studies, CT did not accurately identify any of the pathologic stage II tumours (15-17).

Detection of mediastinal metastases

Seven case series not included in the pooled analyses also evaluated CT or MRI for the detection of mediastinal metastases (14,18-23). Four reports were based on retrospective data (14,21-23). All studies involved patients with potentially resectable disease, used postoperative pathological staging as the gold standard, and, with one exception, defined a positive CT as one in which mediastinal nodes >1cm in diameter were identified. Kiernan et al employed a broader definition of positive CT, which included clinical evaluation as well as lymph node size (18), and Takenaka et al specified a lymph node-saline ratio >0.6 as the criteria for a positive test with respiratory-triggered short inversion time inversion recovery (STIR) MRI (19). Blinding of assessors was not specified in any of the studies.

Table 5. Case series reports of CT for staging potentially resectable NSCLC.

Study	N	Imaging test	Accuracy %	Under-staged, %	Over-staged, %
Cetinkaya, 2002 (14)	180	CT of chest & upper abdomen + other tests as required	48	26	26
Roberts, 1999 (15)	50 (negative mediastinoscopy)	CT of chest & abdomen + other tests as required	42	30	28
Gdeedo, 1997 (16)	74 (negative mediastinoscopy)	CT of chest	35	22	43
Lahde, 1995 (17)	151	CT of chest, upper abdomen & head	48 [a]	21	7

Abbreviations: CT – computed tomography, N – number of patients, NSCLC – non-small cell lung cancer

[a] 22% of tumours were indeterminate on CT staging.

The accuracy of CT in identifying mediastinal malignancy was variable (range, 60-86%, Table 6) and consistent with the results obtained in the pooled analyses (11-13). The study by Kiernan et al reported the highest level of accuracy; however, non-imaging data were also considered in the identification of metastases and the contribution of CT to the diagnosis is unclear (18). Similarly modest results were obtained for MRI (19). In evaluating MRI, Takenaka used novel criteria for specifying a positive test; however, the lymph node-saline ratio was significantly correlated with the standard criteria based on the short-axis diameter of lymph nodes (r^2, 0.25; $p<0.001$), and the results of that small study require further confirmation (19).

Detection of brain metastases

One comparative cohort study (9) and two case series reports, one prospective (25) and one retrospective (24), evaluated CT or MRI for the detection of brain metastases. In the comparative study, Yokoi et al used MRI to detect asymptomatic brain metastases in a group of 177 pre-surgical patients with NSCLC and compared the results to those obtained with a historical control group of 155 patients examined with CT (9). Baseline patient characteristics were not significantly different between groups. The number of brain metastases detected within 12 months of surgery was similar in both groups (7%), with 3.4% and 0.6% identified pre-operatively by MRI and CT, respectively (p=0.069). Tumours detected by MRI were significantly smaller than those detected by CT (mean, 12.8 mm versus 20.3 mm, p=0.041); however, no significant survival differences were detected between the groups (median time from start of treatment, 20 months versus 11 months; two-year survival, 33% versus 27%, for MRI and CT, respectively, p=0.344).

Table 6. Case series reports of CT, MRI, or EUS for detection of mediastinal metastases.

Study	Patients	N	Imaging test	Accuracy % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	Prev %
Cetinkaya, 2002 (14)	NSCLC	180	CT	63	30	81	46	68	35
Kiernan, 2002 (18)	NSCLC	92 [a]	CT	86	64	94	80	88	27
Takenaka, 2002 (19)	NSCLC	25	CT	60	46	75	67	56	52
			MRI [b]	60	46	75	67	56	
			MRI [c]	88	100	75	81	100	
Laudanski, 2001 (20)	NSCLC	92	EUS	77 (67-85)	70 (51-85)	81 (69-90)	64	85	33
			CT	68 (58-78)	60 (41-77)	73 (60-83)	51	79	
			EUS + CT	70 (59-79)	73 (54-88)	68 (55-79)	52	84	
Kristensen, 1995 (21)	NSCLC	64	CT	80	72 (51-88)	85 (70-94)	75	82	39
Mori, 1992 (22)	Lung cancer [d]	133	CT	74	61	82	60	80	32
Wittens, 1991 (23)	Lung cancer [d]	144	CT	74	38	85	45	82	24

Abbreviations: CI – confidence interval, CT – computed tomography, EUS – endoscopic ultrasound, MRI – magnetic resonance imaging, N – number of patients, NPV – negative predictive value, NSCLC – non-small cell lung cancer, PPV – positive predictive value, Prev - prevalence.

[a] Stage could not be determined by CT for an additional 2 patients.

[b] Electrocardiograph-triggered T1-weighted MRI.

[c] Respiratory-triggered short inversion time inversion recovery MRI.

[d] Patient population included 6% small cell lung cancer (22) and 3% other carcinoma (23).

In both case series reports, most patients received radiotherapy or chemotherapy for treatment of the primary tumour, blind assessment of the imaging data was conducted, and the definition of a positive or negative test was referenced (24) or based primarily on clinical judgement (25). The gold standard used for assessment of the diagnostic test was clearly defined in one study (24), and follow-up appeared complete in both studies. Overall, cranial CT was associated with a high level of accuracy in detecting brain metastases in NSCLC (98%) (Table 7), and a positive test result was much more likely in a patient with brain metastases than without (likelihood ratio for a positive CT test, 146). Among the 25 NSCLC patients identified with brain metastases, 16 showed no neurological symptoms (24). Among the 112 SCLC patients asymptomatic for brain metastases in the Hochstenbag et al study, 17 were identified with brain metastases by MRI during initial staging (15%), and 16 of those patients subsequently developed symptoms or died with brain metastases (25). Six patients were also up-staged by MRI from limited disease to extensive disease.

Table 7. Case series report of CT for detection of brain metastases.

Study	Patients	N	Imaging test	Gold standard	Sens %	Spec %	PPV %	NPV %	Prev %
Ferrigno, 1994 (24)	non-small cell lung cancer (stage I-II, 20%)	184	cranial CT	follow-up [a], current symptoms & physical evidence	92	99	96	99	14

Abbreviations: CT – computed tomography, N – number of patients, NPV – negative predictive value, PPV – positive predictive value, Prev – prevalence, Sens – sensitivity, Spec – specificity.

[a] CT defined as true positive if neurological symptoms developed with 6 months of CT and true negative if no signs or symptoms of cerebral involvement within 12 months of diagnosis.

Detection of bone metastases

One small prospective case series reported data for MRI in the detection of bone involvement (26) (Table 8). MRI interpretation was conducted by two radiologists blinded to other metastatic staging results and the criteria for a positive MRI were defined. The accuracy of MRI against a gold standard of bone marrow biopsy was good (84%).

Table 8. Case series report of MRI for detection of bone metastases.

Study	Patients	N	Gold standard	Imaging test	Sensitivity %	Specificity %	PPV %	NPV %	Prevalence (% with bone-marrow involvement)
Milleron, 1994 (26)	SCLC	32	Bone marrow biopsy	MRI of dorsal & lumbar spine	86	84	60	95	22

Abbreviations: MRI – magnetic resonance imaging, N – number of patients, NPV – negative predictive value, PPV – positive predictive value, SCLC – small cell lung cancer.

D.2. Assessment of Tumour Response to Treatment

In a prospective case series report, Pujol et al compared CT with fibreoptic bronchoscopy in evaluating response to chemotherapy for 83 patients with advanced NSCLC (stage IIIA-IV) and 50 SCLC patients (20 with limited disease) (27). Of the 133 eligible patients, 106 received both tests. The level of response was assessed independently for both tests, using the World Health Organization criteria for CT and standardized criteria for bronchoscopy. The performance of CT relative to bronchoscopy for the detection of complete tumour response is summarized in Table 9. Overall concordance between the two tests across all levels of response (complete response, partial response, no change, and disease progression) was statistically significant (kappa, 0.271; $p<0.001$); however, a multivariate analysis found that tumour response status as determined by CT, but not bronchoscopy, was a significant predictor for survival ($p=0.004$).

Table 9. Case series report of CT for assessment of tumour response to treatment.

Study	Patients	N	Gold standard	Imaging test	Accuracy %	Sens %	Spec %	PPV %	NPV %	Prev %
Pujol, 1996 (27)	lung cancer treated with chemotherapy	106	complete response on fibreoptic bronchoscopy	CT	80	68	85	66	86	29

Abbreviations: CT – computed tomography, N – number of patients, NPV – negative predictive value, PPV – positive predictive value, Prev – prevalence, Sens – sensitivity, Spec – specificity.

D.3 Follow-up and Detection of Recurrent Disease

Evidence-Based Practice Guidelines And Quality Indicators

One ACCP evidence-based guideline (5) and the RAND quality indicator report (6) provided recommendations on the follow-up and surveillance of lung cancer. Key features of the process employed by the ACCP and the RAND groups in the development of recommendations were summarized in a previous section of this report.

Among the recommendations made by the ACCP for follow-up after curative treatment of lung cancer, only one related to the use of imaging other than PET and it was based on limited evidence (5). For patients treated with curative intent, the ACCP recommended surveillance with a chest CT or chest radiograph, along with a medical history, and physical examination, every 6 months for the first two years and then annually. They also recommended that patients be counselled on symptom recognition and encouraged to contact their physician if symptoms occur. The RAND report commented on the lack of evidence on appropriate follow-up strategies for lung cancer and did not recommend any quality indicators for this purpose (6).

COHORT AND CASE SERIES REPORTS

Younes et al retrospectively evaluated data from 130 consecutive patients followed for two years after complete resection of NSCLC (10). Patients received either a strict, routine follow-up, involving scheduled physical exams, chest X-rays, CT scans, and liver function tests (67 patients) or symptomatic follow-up (63 patients). The characteristics of the two groups were comparable. No significant differences were detected with respect to recurrences (14 with strict follow-up versus 18 with symptom-initiated follow-up) or median survival after recurrence (7.9 months versus 6.6. months, respectively, p=0.219).

Results of a small retrospective case series report of CT are summarized in Table 10 (28). The intent of the study was to evaluate PET; however, CT was also performed on all patients. Criteria for a positive CT test were not reported. Radiotherapy was part of the treatment approach for most patients in the palliative intent group, which may have affected the accuracy rate for CT since radiotherapy-related changes can sometimes be difficult to differentiate from tumour-related changes.

Table 10. Case series report of CT for detection of recurrent lung cancer.

Study	Patients	N	Imaging test	Accuracy % (95% CI)	Sens %	Spec %	PPV %	NPV %	Prev %
Bury, 1999 (28)	stage I, II or IIIa NSCLC treated with apparent curative result	58	CT [a]	91 (81-97)	69	98	90	92	22
	Stage IIIa or IIIb NSCLC treated with palliative intent	68		78 (66-87)	72	90	94	59	69
	Total	126		84	72	95	93	79	48

Abbreviations: CI – confidence interval, CT – computed tomography, N – number of patients, NPV – negative predictive value, NSCLC – non-small cell lung cancer, Prev – prevalence, PPV – positive predictive value, Sens – sensitivity, Spec – specificity.

[a] Confirmed by biopsy or clinical course, with follow-up between 8 and 40 months.

V. EXPERT CONSULTATION

The draft report, with recommendations developed by a small panel of experts in oncology and radiology, was distributed with a 4-item survey in February and March 2006 to a broader group of Ontario radiologists and oncologists for review as part of an external consultation process. The external consultation included the 34 members of the provincial Lung Cancer Disease Site Group and 25 other Ontario health care providers. Among the 16 respondents (27%), which included one radiologist, one respirologist, four surgeons, five radiation oncologists, and five medical oncologists, 15 completed the report survey and 12 provided written comments. Fourteen respondents agreed that the methods used in the report

development were appropriate; one neither agreed nor disagreed. Thirteen respondents agreed with the draft recommendations as stated, that the recommendations should be approved as guidelines for practice, and that they would follow the recommendations of the report. One respondent neither agreed nor disagreed with the latter three points and one disagreed, recommending that full staging be used for all patients. The report was also reviewed by the PEBC Report Approval Panel, who acknowledged the limited evidence base for the report and agreed the recommendations were clear.

Radiology Perspective

One radiologist who reviewed the draft report suggested that the inclusion of PET scanning is critical and should be incorporated into the recommendations as soon as possible. This point was also made by several oncology representatives. In addition, it was noted that the use of intravenous contrast was not mentioned nor the potential use of MRI if a contrast agent for CT scanning is contraindicated.

The evaluation of PET scanning is being considered in different projects in Ontario, including guidelines under development and clinical trials, and was not within the scope of the current report. However, until the current projects are completed, readers are referred to the systematic review completed by the Institute for Clinical Evaluative Sciences (ICES) (http://www.ices.on.ca/file/Pet_jan20041.pdf).

The panel acknowledged that chest CT scans may be used with or without intravenous contrast; however, if intravenous contrast is contraindicated then a non-contrast CT would be appropriate.

Oncology Perspective

Among the 12 respondents providing written comments, two indicated that they already follow the report recommendations, two commented on the absence of PET recommendations (as indicated above) and the comments of the remainder are summarized below, along with the actions taken in response.

1. Why were the American Society of Clinical Oncology (ASCO) guidelines ignored?

Before the current report was developed, the Diagnostic Imaging Panel searched for existing practice guidelines to consider for potential endorsement in October 2003. The 2003 ASCO guidelines (30) were published after that search was completed and this has been clarified in the *Literature Search Strategy* section of this report. Similar to the other guidelines reviewed in this report, the ASCO guidelines included a search of MEDLINE for evidence,

provided literature search criteria, and involved an expert consensus process in evaluating evidence and developing recommendations.

The ASCO recommendations relevant to lung cancer staging with CT and MRI are summarized in Appendix 2 and are consistent with the recommendations in the current report. The main differences relate to:

- The ASCO recommendation for staging locoregional disease, which suggests that a contrast agent be used with the CT scan. Use of intravenous contrast with chest CT has become accepted practice but is not mandatory. Ideally, the radiologist will determine whether intravenous contrast is required for a CT scan based on the information provided by the referring physician, including any potential contraindications. For many lesions (peripheral tumours for example) it is not an absolute necessity but is useful for more central lesions if there is suspected mediastinal contact or lung collapse. Whether or not intravenous contrast can be used, a CT scan is preferred over MRI for initial staging of lung cancer. MRI should be reserved for clarifying a specific concern.
- The ASCO recommendation for brain imaging in asymptomatic patients is limited to those with stage III disease being considered for aggressive local treatment. The limited value of brain imaging in patients with advanced disease that will be treated palliatively is acknowledged and the recommendation for asymptomatic patients with advanced disease was therefore revised and limited to those patients appropriate for aggressive treatment.

The ASCO recommendations on follow-up are also consistent with the current report, indicating that routine follow-up studies do not have a role for most asymptomatic patients and those not undergoing therapy.

2. *Prevalence statements whenever PPV or NPV are reported would be helpful.*

   Data on prevalence were added to the report where available.

3. *We have seen early stage NSCLC patients with positive results for extrathoracic disease on bone scans etc and would recommend full staging for all patients.*

   Although some asymptomatic patients with early-stage NSCLC may benefit from full staging, the routine use of CT or MRI in screening for metastatic disease is currently unproven. The use of other imaging modalities (e.g. bone scanning, PET scanning) is not addressed in this report.

4. *Should a cranial CT scan be done for patients with stage I or II disease? Although the initial yield may be small, the treatment plan would change.*

Although the treatment plan may change, there is currently no data to indicate that patient outcomes would also change; therefore, the recommendation indicating that the benefit of cranial CT is unclear in this patient population was retained.

5. *Much of the evidence relates to surgical patients, not those with locally advanced unresectable disease where distant staging is more important (higher yield).*

The limited data on the use of imaging to evaluate unresectable disease is acknowledged with only three studies in this report focusing on patients with stage III or IV NSCLC (24,27,28)

6. *Chest radiologist input on the following would be helpful:*
    a. *Under what circumstances should contrast be used with a CT scan?*
    b. *When should contrast be considered in ordering an MRI?*
    c. *In reading a CT scan, what are the benefits of lung vs. mediastinal windows?*

The radiologist decision to use a contrast agent in imaging is based on information provided by the referring physician, including patient clinical history and any potential contraindications for the use of contrast. The use of contrast with CT is addressed in point 2 above. Gadolinium is not routinely required in thoracic MRI as the mediastinum / chest wall has well demarcated fascial planes due to the higher inherent contrast of the technique. It is used when an MR angiogram is performed but this is rarely needed with modern MR imaging techniques. On a thoracic CT scan, three sets of data are evaluated; the mediastinal windows (vascular, soft tissue structures and lymph nodes), lung windows (tracheobronchial tree, fissural demarcations and lung nodules / metastases) and bone windows (metastases).

7. *Under assessment of response:*
    a. *Suggest that interval imaging should not be more frequent than every three months unless clinical circumstances suggest the patient is not responding. Allowing CT scans after every chemotherapy would be excessive.*
    b. *To optimize resource utilization, suggest "Assessment of tumour response with imaging may not be undertaken if it would not change management."*

In the absence of evidence for or against a specific schedule of interval imaging to assess response, it is felt that this may still be appropriate although limiting the frequency to 3

months or more may be reasonable unless lack of response to treatment is clinically suggested. The recommendation on interval imaging was therefore changed from "subject to the discretion of the treating physician" to "at a frequency of no more than every 3 months".

8. *Are cost-benefit data available?*

Economic analyses are important aspects of technology assessment; however, they are not within the scope of the current report.

9. *A follow-up evaluation on the impact of the report recommendations on wait times for diagnostic imaging is suggested.*

An evaluation of the impact of the report recommendations may be valuable, particularly in conjunction with a periodic reassessment of the evidence and recommendations, and may be considered by Cancer Care Ontario.

VI. RECOMMENDATIONS

These recommendations were developed by radiology and oncology experts in Ontario and are informed by research evidence and clinical expertise.

Lung Cancer			
Clinical/ Diagnostic Problem	*Investigation* [1]	*Recommendation*	*Comment*
Staging (with the exception of cerebral metastases)	CT	Indicated (primary)	• Chest and upper abdomen imaging for all patients prior to the institution of a definitive treatment plan. • In asymptomatic patients with stage I or II NSCLC, the utility of extensive screening for metastatic disease is unproven, however, in practical terms, addition of upper abdominal CT to the initial CT thorax in investigation of possible lung masses probably represents optimal utilization of resources.
	MRI	Indicated (supplementary)	• Chest and upper abdomen imaging for specific patients as indicated in the ACCP guidelines (i.e., for evaluation of the brachial plexus or vertebral column in patients with NSCLC involving the superior sulcus) and when cardiac or mediastinal involvement is suspected. • Not indicated as the primary screening tool for the detection of other chest or abdominal metastases. • Abdominal MRI may be useful for clarification of potential metastases to liver or abdomen identified by CT.
Detection of cerebral metastases	Cranial MRI	Indicated (limited, primary)	• Unless contraindicated (e.g., patient has a pacemaker), strongly recommended in symptomatic patients or asymptomatic patients with advanced NSCLC, SCLC, and superior sulcus tumours for whom aggressive treatment may be appropriate. • Benefit for neurologically asymptomatic patients with early-stage NSCLC is unclear.
	Cranial CT	Indicated (limited, secondary)	Use when MRI is contraindicated.

Lung Cancer			
Clinical/ Diagnostic Problem	*Investigation* [1]	*Recommendation*	*Comment*
Assessment of tumour response	CT	Indicated (primary)	In the absence of evidence, interval imaging with chest CT is reasonable with intervals likely based on the treatment schedule but at a frequency of no more than every 3 months.
	MRI	Indicated (supplementary)	Cranial MRI may be considered in follow-up of cranial metastases.
Follow-up and Recurrence	CT	Indicated (limited)	• Utility is dubious for post-treatment staging or routine screening of asymptomatic patients. • Conduct of imaging tests should be guided by: * the potential for recurrence according to the initial disease stage and treatment; and * the implications of a positive test for subsequent treatment (including palliation). • The use of a single imaging test should be considered unless multiple modalities will contribute to the treatment plan.
	MRI	Indicated (limited)	

Abbreviations: ACCP – American College of Chest Physicians, CT – computed tomography, MRI – magnetic resonance imaging, NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer.

[1] CT scans may be used with or without intravenous contrast.

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Appendix 1. Search strategies used for literature searches.

MEDLINE	EMBASE
exp lung neoplasms/ lung neoplasms/sc [secondary] liver neoplasms/sc brain neoplasms/sc bone neoplasms/sc exp abdominal neoplasms/sc exp neoplasms/sc neoplasm staging/ staging.mp. exp neoplasm metastasis/ neoplasm recurrence, local/ neoplasm, residual/	exp lung cancer/ exp metastasis/di cancer staging/ cancer recurrence/
ultrasonography/ ultrasonography, doppler/ exp ultrasonography, doppler, duplex/ endosonography/ exp tomography, x-ray/ exp tomography, x-ray computed/ exp magnetic resonance imaging/ neoplasm metastasis/di, ra, ri, sc, us	diagnostic imaging/ echography/ exp computer assisted tomography/ nuclear magnetic resonance imaging/
randomized.mp. randomized controlled trials/ randomized controlled trial.pt. clinical trial.pt. exp case-control studies/ exp cohort studies/ cross-sectional studies/ exp clinical trials/ control groups/ double-blind method/ matched-pair analysis/ random allocation/ single-blind method/ exp "sensitivity and specificity"/ sensitivity.mp. follow-up studies/ follow-up.mp. surveillance.mp. guidelines/ practice guidelines/ guideline.pt. practice guideline.pt. (Medline.mp. or systematic.mp.) and (review.mp. or review.pt.) meta-analysis.pt. meta-analysis/	"sensitivity and specificity"/ case control study/ prospective study/ retrospective study/ clinical trial/ multicenter study/ randomized controlled trial/ systematic review.mp. systematic review/ meta-analysis/

Appendix 2. Evidence-based guideline recommendations on imaging in staging lung cancer.

Author, Year (Reference)	Recommendations
American College of Chest Physicians, 2003 (2)	• For patients with either a known or suspected lung cancer who are eligible for treatment, a CT scan of the chest should be performed. • In patients with enlarged mediastinal lymph nodes on CT scans (*i.e.*, > 1 cm on the short axis), further evaluation of the mediastinum should be performed prior to surgical resection of the primary tumour. • For patients who are operative candidates, where available, a whole-body FDG-PET scan is recommended to evaluate the mediastinum. • In patients with abnormal results of FDG-PET scanning, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumour. • For patients with either a known or suspected lung cancer who are eligible for treatment, an MRI of the chest should not be performed for staging the mediastinum but should be performed in patients with NSCLC involving the superior sulcus for evaluation of the brachial plexus or for evaluation of vertebral body invasion. • Patients with abnormal clinical evaluations should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant directed evaluation of that site with the most appropriate study (*e.g.*, head CT scan, bone scan, and abdominal CT scan). • Patients with clinical stage I or II lung cancer and a normal clinical evaluation require no further imaging for extrathoracic disease. • Patients with stage IIIA and IIIB disease should have routine imaging for the detection of extrathoracic metastases (*e.g.*, head CT scan, bone scan, and abdominal CT scan). • Patients with abnormal imaging study results should not be excluded from potentially curative surgery without tissue confirmation or overwhelming clinical and radiographic evidence of metastases.
British Thoracic Society, 2001 (3)	• All patients being considered for surgery should have a plain chest radiograph and a CT scan of the thorax including the liver and adrenal glands. • Confirmatory diagnostic percutaneous needle biopsy in patients presenting with peripheral lesions is not mandatory in patients who are otherwise fit, particularly if there are previous chest radiographs showing no evidence of a lesion. • Patients with mediastinal nodes greater than 1 cm in short axis diameter on the CT scan should undergo biopsy by staging mediastinoscopy, anterior mediastinotomy, or needle biopsy as appropriate. **Small Cell Lung Cancer (SCLC)** • The incidence of subclinical metastatic disease is much higher in SCLC than NSCLC and all patients being considered for surgery should be staged by CT scanning and mediastinoscopy and screened by scanning of bones and brain and iliac crest bone marrow sampling.
Royal College of Radiologists' Clinical Oncology Information Network, 1999 (4)	• All patients with a working diagnosis of lung cancer should have a full history, physical examination, assessment of performance status, chest x-ray, full blood count and serum biochemistry (to include urea and electrolytes, liver function tests and calcium). • Patients who appear on initial examination and investigation to have potentially curable disease should have a CT scan of thorax and upper abdomen with contrast enhancement if necessary. • Diagnostic imaging of bones, liver and brain should not be part of routine staging

	and should only be carried out if there is clinical or radiological suspicion of metastatic disease. • If patients have signs or symptoms suggestive of metastases or abnormal serum biochemistry, they should be investigated further with appropriate organ scans. **Small Cell Lung Cancer (SCLC)** • All patients with SCLC should have a history (including recording of Performance Status), examination, chest x-ray, full blood count, serum biochemistry (including urea and electrolytes, liver function tests and LDH) and imaging of upper abdomen.
American Society of Clinical Oncology, 2004 (30)	• A chest X-ray and chest (CT) scan with infusion of contrast material are recommended to stage locoregional disease. The CT should extend inferiorly to include the liver and adrenal glands. Assuming there is no evidence of distant metastatic disease on CT scan, FDG-PET scanning complements CT scan and is recommended. • For patients with clinically operable NSCLC, biopsy is recommended of mediastinal lymph nodes found on chest CT scan to be greater than 1.0 cm in shortest transverse axis, or positive on FDG-PET scanning. Negative FDG-PET scanning does not preclude biopsy of radiographically enlarged mediastinal lymph nodes. • For the staging of distant metastatic disease, an FDG-PET scan is recommended when there is no evidence of distant metastatic disease on CT scan of the chest. • A bone scan is optional in patients who have evidence of bone metastases on FDG-PET scanning, unless there are suspicious symptoms in regions not imaged by FDG-PET. In patients with a surgically resectable primary lung lesion, bone lesions discovered on bone scan or FDG-PET require histologic confirmation or corroboration by additional radiologic testing (x-ray, CT, and/or MRI). • Head CT or MRI brain imaging with and without infusion of contrast material is recommended in patients who have signs or symptoms of CNS disease, as well as asymptomatic patients with stage III disease who are being considered for aggressive local therapy (chest surgery or radiation). • The finding of an isolated adrenal or liver mass on ultrasonography, CT scan, or FDG-PET scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.

Abbreviations: CNS – central nervous system, CT – computed tomography, FDG-PET – fluorodeoxyglucose positron emission tomography, LDH – lactate dehydrogenase, MRI – magnetic resonance imaging, NSCLC – non-small cell lung cancer, SCLC – small cell lung cancer.

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