

Diagnostic Imaging in Lymphoma

A Cancer Care Ontario Recommendations Report

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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 lymphoma. 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, nature, and aggressiveness of treatment options to be offered to patients, as well as predicting prognosis. Where needed, imaging is also used to assess the response of cancer to therapy and to determine the extent of the 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 active treatment among patients with cancer are done so for uncertain reasons and that, in some cases, results may have little or no impact on clinical care. Moreover, significant expansion in the number of CT and MRI machines has not meaningfully influenced wait times for these investigations. For these 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 diagnostic imaging for patients with lymphoma and are intended to promote evidence-based practice, provide guidance to clinicians about which imaging techniques are the most appropriate to use in the workup and management of their patients, provide information that is useful to those charged with planning

for the number of imaging machines needed for patients with cancer 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 meet the inclusion criteria or did not focus on the particular issues of interest to be endorsed. Therefore, the Panel decided to review the primary research and develop recommendations for Ontario on the use of CT, MRI, and ultrasound (US) 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 Although regularly used in patients with lymphoma, gallium-67-citrate (Ga-67) scans and PET scans are not reported on here because they were not a part of the original project scope. These modalities will be addressed in a separate document.

Because 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, cohort studies and case series reports were also included in the evidence review, and expert opinion was incorporated 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 (PEBC) in consultation with the clinical experts from the Diagnostic Imaging Panel.

The 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 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 (DSGs) of CCO's Program in Evidence-Based Care.

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

The recommendations that emerged through these consultations are presented in the format developed by the Canadian Association of Radiologists (1).

IV. EVIDENCE REVIEW

A. Literature Search Strategy

English language evidence published between 1980 and 2004 was searched through MEDLINE, EMBASE, and the Cochrane Databases of Systematic Reviews and Abstracts of Reviews of Effects. Clinical practice guidelines, meta-analyses, systematic reviews, and trials reporting on sensitivity and specificity were also sought. Search strategies were modified for each database and disease site (see Appendix A).

B. Eligibility Criteria

Inclusion

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

1. Included patients with confirmed lymphoma,
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.

Exclusion

Letters, editorials, and meeting abstracts were not included.

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.freemove.co.uk/easycalc/Additions/predict.htm>, and the Critical Appraisal Diagnostic test available on the Web at <http://www.hutchon.net/diagnostic-test.htm>.

C. Literature Search Results

No evidence-based practice guidelines or randomized controlled trials that met the inclusion criteria were available for review. One comparative study, nine consecutive case series, and two retrospective studies were found. Three papers used either CT or MRI for the staging of disease (2-4). Five papers studied the ability of CT, MRI, or mediastinal sonography to detect tumour response to treatment (5-9). Two papers compared CT with other modalities, one to mediastinal sonography (6) and the other to MRI (7). Four consensus-based guidelines were from established groups that provided standard clinical practice recommendations concerning the use of CT in the follow-up of patients with lymphoma (1, 10-12). Four papers investigated the follow-up of patients with lymphoma by identifying the methods that were successful in the detection of relapses (13-16).

D. Outcomes

Staging

Staging of lymphoma involves the determination of the localization of the disease, detected by physical examination combined with clinical and imaging procedures. Staging guides the selection of treatment and predicts prognosis. The publications identified relate to the use of imaging in staging (2-4). Detection rates for CT and MRI in staging patients with Hodgkin's Disease (HD) and Non-Hodgkin's Lymphoma (NHL) are presented in Table 1.

Chang et al (2) used CT to determine the proportion of patients who would be suitable candidates for anti-*Helicobacter pylori* eradication. All records from between the years 1992-1996 were retrospectively reviewed, and 53 patients with NH gastric lymphoma of B-cell phenotype were identified. The accuracy of CT staging of abdominal lymph nodes compared with postoperative clinical stage was 75%, which may be low for patients with gastric mucosa-associated lymphoid tumour (MALT). The failure to detect lymph node involvement could be fatal because the patient would receive incomplete treatment.

With 52 consecutive patients at two centres, Buchmann et al (3) calculated the following accuracy of CT using Receiver Operating Characteristic curves: lymph nodes, 92%; extranodal, 92%; supradiaphragmatic, 90%; and infradiaphragmatic, 95%. The CT findings were compared to positive emission tomography (PET) results, and, where they disagreed, a combination of bone marrow biopsy (BMB), MRI, and follow-up was used to determine the correct stage. For bone marrow involvement, the CT accuracy rate was found to be 90%, but the sensitivity rate was extremely low at 38%.

Tesoro-Tess et al (4) studied the role of MRI in staging patients with lymphoma. They evaluated 72 previously untreated patients with chest, abdominal, and pelvic MRI. The overall sensitivity of MRI for all lymph nodes was consistent at 87%, with the majority of understaged nodes located in the para-aortic area (75%). When considering only inter-thoracic disease, MRI found 12% more mediastinal adenopathies than did chest radiograph (CXR). Overall, MRI influenced the staging (upgraded) in 11 of 74 patients (15%) and demonstrated the presence of unsuspected disease in nine of 42 patients (21%). The accuracy of MRI detection of bone marrow involvement was 83%.

Table 1. Detecting abdominal nodal and bone marrow involvement.

Study	Patients	N	Imaging test	Gold standard	Acc (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Detection of nodal disease									
Chang, 1999 (2)	untreated NH gastric lymphoma (MALT)	53	CT	pathological staging	75	63	88	86	68
Tesoro-Tess, 1991 (4)	untreated HD or NHL	70	MRI	lymphography	97	91	100	100	96
Detection of bone marrow involvement									
Buchmann, 2001 (3)	untreated HD or NHL	52	CT	bone marrow biopsy	90	38	100	100	90
Tesoro-Tess, 1991 (4)	untreated HD or NHL	72	MRI	bone marrow biopsy	83	56	87	39	93

HD, Hodgkin's Lymphoma; NHL, Non-Hodgkin's Lymphoma; MALT, Non-Hodgkin's Gastric Lymphoma; Acc, accuracy; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; MRI, magnetic resonance imaging; CT, computed tomography

Treatment Response Assessment

Accurate remission assessment and restaging are crucial in the management of treatment because they identify patients who may benefit most from the minimal standard conventional therapy and those for whom alternative treatment strategies may be needed. Response assessment needs to be able to discriminate between active residual disease and benign fibrous tissue. Treatment therapy included either chemotherapy or radiation therapy or a combination of both. The results of four studies evaluating tumour response assessment are summarized in Table 2.

Luker et al (5) used CT to differentiate benign fibrosis from residual disease in children with HD treated with chemotherapy and/or radiotherapy. Twenty-three patients underwent serial CT at least three times over a three-year period (means, 4.1 times, 2.6 years). Eighteen patients experienced complete remission after an average of 6.3 months (range, 0.5-20 months), and five had residual benign mediastinal masses shown by CT confirmed with biopsy and Ga-67 scintigraphy. The conclusion was that continued follow-up with CT might allow for the detection of recurrent disease.

Mikhaeel et al (6) assessed the accuracy of CT to be 58% in 33 patients with aggressive NHL. The authors stated that a weakness in using CT with aggressive NHL may be its inability to correctly identify an early response since it depends largely on the reduction in size of enlarged lymphadenopathy or masses. Functional imaging reflects the metabolic activity of tissues that precede anatomical changes, allowing for a more expedient change to an alternative treatment.

In a study by Zinzani et al (7), 59 patients with NHL, presenting abdominal involvement, had CT scans at diagnosis and during follow-up (median, 24 months). The accuracy of CT was found to be very low, at 25%, because of the many false positives, which may be due to the CT scan inability to differentiate between active residual disease and fibrotic changes from curative therapy in patients with abdominal masses.

Zinzani et al (8) used 33 consecutive patients to compare CT to MRI in detecting the difference between residual tumour tissue and fibrosis. CT and MRI scans were done before and six months after treatment. MRI was conducted on only 16 patients because of logistical problems. The mediastinal disease was monitored using Ga-67, MRI, and CT. Accuracy was 81% for MRI and 61% for CT. The conclusion was that CT was able to provide valuable information about tumour size and distribution but could not differentiate between fibrosis and inflammation, whereas Ga-67 and MRI were capable of discriminating between active residual disease and fibrosis or necrosis. However, because of MRI cost, lack of accessibility, and low specificity, the authors suggested that MRI should only be used in special patients who present with allergic reactions to radiographic dye.

In order to assess the diagnostic value of mediastinal sonography, Wernecke et al (9) in their clinic compared CT to mediastinal sonography in the follow-up of patients with mediastinal lymphomas (one-48 months after therapy). They assessed 40 patients with sonography (mean, 5) and 31 patients with CT (mean, 3). The accuracy rate for sonography was 100% compared to 81% in CT.

Table 2. Detecting response after chemotherapy and/or radiotherapy

Study	Patients	N	Imaging test	Gold standard	Complete response on imaging test				
					Acc (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Mikhaeel, 2000 (6)	aggressive NHL	33	CT	clinical outcome & follow-up	58	54	64	75	41
Zinzani, 2002 (7)	HD (n=16) or aggressive NHL (n=43)	59	CT	clinical outcome & follow-up	25	15	72	70	16
Zinzani, 1996 (8)	HD (n=17) or high-grade NHL (n=16)	33	CT	clinical outcome & follow-up	61	61	50	95	8
		16	MRI	clinical outcome & follow-up	81	87	0	93	0
Wernecke, 1991 (9)	HD (n=29) or NHL (n=11)	31	CT	clinical outcome & follow-up	81	94	62	77	89
		40	mediastinal sonography	clinical outcome & follow-up	100	100	100	100	100

HD, Hodgkin's Lymphoma; NHL, Non-Hodgkin's Lymphoma; Acc, accuracy; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; MRI, magnetic resonance imaging; CT, computed tomography

Follow-up

No evidence-based guidelines concerning the follow-up of patients with lymphoma met the inclusion criteria for this report. Although consensus-based guidelines were not systematically sought, four recent guidelines from established groups consistently recommended the periodic use of CT for the evaluation of suspicious symptoms or clinical findings (1, 10-12). Four studies investigated the use of CT in follow-up.

Drossman et al (13) investigated the role of Ga-67 imaging and CT in differentiating between active disease and fibrotic changes in 18 patients, aged eight to 23, with childhood lymphoma involving the mediastinum or neck. Clinical evaluation, CT, and Ga-67 imaging were performed at initial presentation, at three-month intervals for the first year, and then at various intervals during follow-up, and more frequently if clinically warranted. Only the evaluations involving all three study components were included in the statistical analysis (See Table 3).

Table 3. Detecting recurrent disease.

Study	Patients	N	Imaging test*	Acc (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
Drossman, 1990 (13)	childhood lymphoma involving mediastinum or neck	18	CT	56	100	50	20	100
			Ga-67	83	100	81	40	100

* confirmed by clinical findings, follow-up.

Acc, accuracy; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography; Ga-67, gallium-67-citrate

The prospective study by Guppy et al (14) followed all 117 patients with diffuse large B-cell NHL who were treated at their institution and had complete response. The follow-up policy was a physical examination (PE) and history every three months for the first year after therapy, every six months for the second year, and yearly afterwards. CT scans were performed at three months and one year. In the 35 patients who relapsed, the relapse was detected by new signs and symptoms in 86% (30 cases), by CT in 5.6% (two cases), and by colonoscopy or abnormal blood results in 8.6% (three cases). Seven patients (20% of cases) relapsed before three months, as ascertained through symptoms, illustrating that alternatives other than CT were used to detect relapses.

Weeks et al (15), in the follow-up of a clinical trial, retrospectively evaluated 139 patients with large-cell NHL in complete remission. Assessments including a PE, history, lactate dehydrogenase (LDH) serum test, CXR, CT, US, and BMB were conducted every two to three months. The majority of relapses were detected at unscheduled visits promoted by symptoms (32/35, 91%). Only the serum test for LDH was sensitive to preclinical relapse. An analysis of the relapse patterns found that 75% of relapses occurred in at least one old site. The median time between CT scans was 5.6 months, and those scans did not detect any of the relapses. Of the 67% of patients who relapsed in a new site, 42% relapsed in both old and new sites and 25% in new only. Thirty-three percent relapsed in sites of previous involvement only, and 75% recurred in at least one old site. The investigators noted that the tests most sensitive to recurrent disease at clinical relapse were not targeted to specific disease sites but were full-body studies.

Dryver et al (16) performed a retrospective review of all patients treated for HD at their centre between 1990 and 1999. The follow-up protocol was assessment every three months for two years, every six months for the next three to five years and every 12 months thereafter. Of the 107 patients, relapses were suspected in 109 instances, involving 68 patients. Of these, twenty-two patients truly experienced a relapse (See Table 4). Sixty-four percent of the relapses were identified through signs or symptoms, 27% through radiological studies, and 9% through laboratory findings.

A cost analysis revealed that the 211 routine CT scans conducted detected two of 22 relapsed patients (9%) but accounted for 29% of the total follow-up costs. The positive predictive value (PPV) of the CT scan was 14%. The authors suggested that the high false-positive rate could be caused by the difficulty in discriminating between residual fibrotic masses and viable tumour, and therefore, the routine use of CT scans in follow-up should be eliminated.

Table 4. Summary of suspected and true relapses.

Modality	Suspected Relapse	True Relapse
Patient	46	10
Physician	28	4
Radiological	31 (7-CXR, 12-CT)	6 (4 -CXR, 2-CT)
Laboratory abnormalities	4	2

V. EXPERT CONSULTATION

Input was sought from the CCO Hematology DSG as well as clinical radiologists involved in the investigation of patients with lymphoma. The Panel reviewed the available evidence and determined that there was insufficient evidence to allow for definitive recommendations. Where data was not available, the Expert Panel considered published consensus guidelines and statements.

Staging

No published data provided insight on the utility of either ultrasound or CT in staging of lymphoma. Some early data suggested that MRI might be more sensitive than CT in some situations; however, whether this had an impact on treatment decisions or patient outcomes is not clear. The role of Ga-67 or PET scanning lies outside of the scope of this document.

In the absence of an evidence-based optimal staging strategy, the Expert Panel recommends that the Cotswold modification of the Ann Arbor staging system be used for staging (17). This system relies on CT as the primary imaging modality for most patients. In selected cases, additional modalities such as ultrasound and MRI may be used. In most cases CT scanning of the chest, abdomen, and pelvis +/- neck is recommended. For patients being managed with palliative intent, more limited staging may be appropriate in some cases.

Response Assessment

Documenting response to treatment is an important use of diagnostic imaging in lymphoma. While currently available data does not suggest that any one imaging modality is optimal for that purpose, no modality appears to be clearly superior to CT. One limitation of CT, however, is the difficulty of differentiating fibrosis from residual disease in cases of apparent incomplete response. In such circumstances, serial CT scanning and, if necessary, MRI or other modalities such as Ga-67 or PET scanning may be of use in selected cases. For most patients, the Panel recommends CT scans involving at least initially involved areas after the completion of treatment. The Panel also recommends the use of the International Workshop

Response Criteria for non-Hodgkin's Lymphoma to classify response (12) and notes that these criteria are currently being revised to incorporate the use of PET scanning (18). In patients for whom the treatment plan may be adapted based on the speed of response, interim restaging involving CT scanning of involved areas at a time point midway through treatment is appropriate.

Follow-up

The routine use of imaging in follow-up offers the possibility for the early identification of relapse before it presents clinically. Potential disadvantages include cumulative radiation exposure over time, the false identification of relapses, and the impact on resource utilization. While no published studies allow for the identification of an optimal follow-up approach, more data are available on the use of imaging in follow-up than for the other purposes. Available data suggest that imaging modalities such as CT scanning appear to have high false-positive rates, while being relatively insensitive. Even in series where routine imaging is performed, most relapses are identified clinically through reported symptoms (13-15). In some series, however, a significant minority of relapses were detected through routine follow-up imaging (16). In such cases, it was unclear whether earlier detection led to improved outcome.

A number of agencies have developed consensus-based guidelines on the use of imaging in the follow-up of lymphoma. The American College of Radiology (ACR) publishes the ACR Appropriateness Criteria, practice guidelines with a strong consensus component. The ACR Criteria *Follow-up of Hodgkin's Disease* strongly recommended that, for those patients with IIA subdiaphragmatic HD, chest/abdomen/pelvic CT be performed either every six months for two years, then yearly for three years, or once a year for five years, citing the potential for early curative salvage therapy (10). The Canadian Association of Radiologists recommended that, if there is clinical suspicion of relapse or progression, a chest, abdomen, and pelvis examination would be appropriate, especially for NHL, and that MRI is not indicated initially but may help to assess the nature of a residual mass detected by CT (1). The National Comprehensive Cancer Network (NCCN), an alliance of 19 American Cancer treatment institutions, publishes consensus-based guidelines electronically (11). That body recommends that imaging be performed in follow up every three to six months for two to three years and annually, subsequently, based on clinical circumstances. The NCCN categorizes this recommendation as 2B, indicating that there is non-uniform consensus based on the lower level evidence, including clinical experience, that the recommendation is appropriate. The International Primary CNS Lymphoma Collaborative Group criteria for NHL do not make

definitive recommendations regarding the use of imaging studies in follow-up (12) They indicate that imaging studies may be added for relevant clinical indications, but specific tests could not be recommended.

The Panel perception is that follow-up practices in Ontario are highly variable. The group recognizes that the possibility of an earlier identification of relapse could be of benefit to patients. The group also recognizes that the routine use of follow-up imaging identifies true relapses relatively infrequently and has a high false-positive rate. In addition, frequent CT scanning can lead to significant radiation exposure over time and is highly resource intensive. Given this, the Panel recommends that the use of imaging for routine follow-up is not required in all patients with lymphoma following completion of therapy. The yield would appear to be particularly low in patients treated with curative intent with a favourable prognosis who attain a complete response to treatment. The Panel considered routine follow-up imaging to be reasonable in selected patients at high risk of recurrence, particularly those who fail to achieve a complete response to therapy (especially if PET is unavailable), those at risk of recurrence in anatomically sensitive areas (such as the spinal cord, ureters, or biliary tree), and those with incurable lymphomas. The recommendation is that clinicians have a low threshold to use CT, or MRI if necessary, for the investigation of symptoms suggesting relapse. The selection of an imaging modality will depend on the physician's discretion and the anatomical position of the suspected relapse.

VI. EXTERNAL REVIEW

The draft report, with recommendations developed by a small panel of experts in oncology and radiology, was distributed with a four-item survey in February and March 2006 for review, as part of an external evaluation process, to a broader group of Ontario radiologists and oncologists. The external review included 20 Ontario health care providers. All six respondents (30%) were medical oncologists and completed the survey, with three providing written comments. Five agreed and one neither agreed nor disagreed that the methods used in the report development were appropriate. Four agreed with the draft recommendations as stated, would follow the recommendations of the report, and agreed that the recommendations should be approved as guidelines for practice. However, one respondent neither agreed nor disagreed with those statements, and one respondent disagreed with them.

The major points of the comments included a remark by one respondent for the need for gallium scanning and PET scans in the guideline. The Panel recognizes that mounting evidence exists addressing the role of these two modalities in lymphoma but notes that this lies outside

the scope of this document. Another major item was concern about the paucity of evidence on which the recommendations were based. However, it was acknowledged that the evidentiary qualities of the data were poor, and so it was decided to look to well-established existing recommendations and guidelines. CT was chosen as the primary mode because of these existing practice guidelines. One respondent commented that, at best, MRI might be more accurate than CT and allow differentiation between residual scar tissue and tumour and, at the very worst, it is as good as CT, yet felt that the risk of radiation exposure in a young population by repeated CT scans over many years could be very real and that under the circumstances, more attention should have been given to MRI as the preferred diagnostic test. The Expert Panel considered the data on the use MRI in staging to be promising but noted that the data are very early and are based on the study of a small number of patients. Given the primacy of CT in the published guidelines and response criteria, the Panel considers this to be the modality of choice in staging and assessment of response. The Panel acknowledges that a concern may exist over radiation exposure with the use of serial CT scanning in follow-up but considers this can best be addressed by limiting follow-up imaging studies, particularly in patients at low risk of relapse.

The PEBC Report Approval Panel (RAP) review resulted in no major changes to the document. The RAP remarked, however, that, because standard practices are based on scant literature and the incorporation of this literature does not provide meaningful contributions to practice recommendations, it is therefore necessary to develop guidelines using a process that is principally built on consensus rather than upon published literature.

VII. RECOMENDATIONS

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

Table 4. Summary of recommendations.

Lymphoma			
Clinical/ Diagnostic Problem	Investigation	Recommendation	Comment
Staging	CT	Indicated (primary)	<ul style="list-style-type: none"> • CT chest/abdomen/pelvic ± neck in all patients is generally accepted as the primary modality for suspected lymphoma. • Useful in selecting the site for surgical tissue diagnosis.
	MRI	Specialized study	
	US	Specialized study	
Response Assessment	CT	Indicated (primary)	<ul style="list-style-type: none"> • CT of at least involved area partway through treatment where this information will alter the treatment plan. • CT of at least involved area upon completion of treatment where this information will alter the treatment plan.
	MRI	Specialized study	<ul style="list-style-type: none"> • In select cases where indicated clinically.
	US	Specialized study	<ul style="list-style-type: none"> • In select cases where indicated clinically.
Follow-up	CT	Indicated (primary)	<ul style="list-style-type: none"> • Routine radiologic follow-up may be appropriate in following selected cases: <ul style="list-style-type: none"> ○ High-risk at presentation. ○ Those in PR or CR (unconfirmed) after initial therapy if PET not available. ○ Those felt to be at risk of recurrence in anatomically sensitive areas (where ever CT is felt to be most appropriate). ○ Patients with incurable lymphomas.
	MRI	Specialized study	<ul style="list-style-type: none"> • When CT is unclear, MRI may be useful in identifying solid organ involvement, but does not prevent the need for surgical staging. In some cases, may show extra-nodal disease, such as bone marrow involvement when bone scan is equivocal.
	US	Specialized study	<ul style="list-style-type: none"> • Useful in select cases for abdominal and pelvic nodes, solid organ, etc.
Investigation of suspected relapse	CT	Indicated (primary)	<ul style="list-style-type: none"> • Physician should have a low threshold for signs and symptoms suggesting relapse. • The selection of imaging modality depends on physician discretion and anatomical position.
	MRI	Specialized study	<ul style="list-style-type: none"> • In select cases where indicated clinically.
	US	Specialized study	<ul style="list-style-type: none"> • In select cases where indicated clinically.

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Appendix A. Literature search terms.

MEDLINE

exp lymphoma/
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/

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

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-analyis/

EMBASE

exp lymphoma/
exp metastasis/di
cancer staging/
cancer recurrence/
diagnostic imaging/
echography/
exp computer assisted tomography/
nuclear magnetic resonance imaging/

"sensitivity and specificity"/
case control study/
prospective study/
retrospective study/
clinical trial/
multicenter study/
randomized controlled trial/
systematic review.mp.
systematic review/
meta-analysis/

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Disclaimer

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