Appendix H: Review of Current Recommendations for Anatomic Imaging in Clinical Nodal Staging of Various Cancers

REVIEW OF CURRENT RECOMMENDATIONS FOR ANATOMIC IMAGING IN CLINICAL NODAL STAGING OF VARIOUS CANCERS

This is a summary of information from the American College Of Radiology ACR Appropriateness Criteria, Supplement to Radiology June 2000 Volume 215(S) and from The National Comprehensive Cancer Network Practice Guidelines in Oncology National Comprehensive Cancer Network Rockledge PA 19046 or the Bethesda Handbook of Clinical Oncology, J. Abraham & C. J. Allegra, Eds., Lippincott Williams & Wilkins, 2001 (These practice guidelines were chosen for their wide availability—other similar guidelines are available)

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A. Overview

Review of current recommendations for anatomic imaging in clinical nodal staging of various cancers

The table on the next page summarizes information on the use of anatomic imaging for the evaluation of lymph node status for clinical staging from the American College Of Radiology ACR Appropriateness Criteria, Supplement to Radiology June 2000 Volume 215(S), from The National Comprehensive Cancer Network Practice Guidelines in Oncology National Comprehensive Cancer Network Rockledge PA 19046, and the Bethesda Handbook of Clinical Oncology, J. Abraham & C. J. Allegra, Eds., Lippincott Williams & Wilkins, 2001 (These practice guidelines were chosen for their wide availability—other similar guidelines are available).

Only the recommendations for anatomic imaging for evaluation of lymph node status in a variety of common cancers is summarized in this table. The ACR Criteria, NCCN Guidelines and Bethesda Handbook are not limited to lymph node evaluation, but also outline diagnosis, TMN clinical staging, TNM pathological staging, treatment and follow up. The ACR Criteria is specifically oriented to the role of imaging procedures in cancer workup and treatment; the other two references are more global. The ACR and NCCN are consensus documents, recommend procedures to be used in routine clinical practice and are updated on a regular basis by expert committees of practicing clinicians. This **Appendix** includes verbatim excerpts from the various monographs for each cancer. The entire guides from ACR and NCCN are on the CD included with this document; the Handbook is not available electronically. There are extensive references in both sources on the CD.

It can be seen from this table that either CT or MR are routinely recommended as part of the clinical evaluation in a number of staging evaluation schemes for the initial clinical staging. In general, CT (or CECT) and MR are recommended similarly. ACR generally considers them interchangeable, but more often recommends CT first as it is more widely available and tends to be less expensive. In some cases, the recommendation depends on the initial tumor diagnosis, as in the NCCN recommendation for bladder cancer. Recommendations are particularly nuanced for prostate cancer, depending on PSA level and Gleason score. Recommendations for cervical and uterine cancer are complicated by the international FIGO scheme, which is reluctant to recommend technology that is not widely available in all countries; practice in the United States is generally to use imaging in pre-surgical clinical staging. It is standard practice for all clinical staging schemes that whenever medically possible, clinical staging of tumors, nodes, and distant metastases is followed by pathological staging.

Summary Of Recommendations For Evaluation Of Lymph Nodes With Anatomic Imaging In Initial Clinical Staging

	ACR (appropriateness score out of 9)	Bethesda Handbook	NCCN Guidelines
Kidney	MRI Abdominal 8; CECT Abdominal 8	CECT or MRI of the abdomen and pelvis	Same as Bethesda
Bladder	MRI: pelvis 8 CT: pelvis/abdomen 6 Also recommended in follow up of invasive TCC	CT of Abdomen and pelvis	Only for muscle invasive primary T2 or higher: CT or MRI of the abdomen and pelvis followed by nodal biopsy if enlarged nodes are seen
Prostate	PSA ≤ 10 and/or Gleason 2-6: MRI 3; CT 3 PSA > 10 and/or Gleason 7-10: MRI 7; CT 7 ProstaScint 7 followed by CT guided FNA Also recommended in follow up in some cases: MRI 5, CT 4	Pelvic CT or MRI for primary T1-T2 if nomogram indicates probability of lymph node involvement of > 20% or if primary is T3 or T4. If enlarged nodes, then FNA.	Same as Bethesda
Testicular	MRI: pelvis/abdomen 5 CT: pelvis/abdomen 9	After orchiectomy, abdominopelvic CT	Same as Bethesda
Ovarian	CT 9; MRI 4	Ultrasound or CT of the abdomen & pelvis	Abdominopelvic CT
Cervical	MRI 8; CT 6	CECT or MRI	Debatable (FIGO)
Uterine	MRI 8; CT 8 Either CT or MRI is appropriate.	Rarely CT or MRI	Debatable (FIGO)
Breast	Not rated for nodes	Not usually used for lymph node staging	Not usually used for lymph node staging
Lung, small cell	CT Thorax 8; MRI Thorax 6	CT chest	Same as Bethesda
Lung, non-small cell	CT Chest 9; MRI abdomen 2	CT chest, MRI	CT chest, PET
Head & Neck	Not in ACR Criteria	CT, MRI	Same as Bethesda
Lymphoma	CT chest/abdomen/pelvis 9; MRI 2	CT chest, abdomen, pelvis	Same as Bethesda
Colorectal	MR endorectal coil 6 Abdominal/pelvic CT 6	CT abdomen & pelvis	CT or MRI abdomen & pelvis

Note: ACR almost always considers MRI a substitute for CT for patients allergic to iodide contrast, with renal insufficiency or pregnant.

These are direct excerpts dealing with evaluation of lymph nodes: verbatim, but without surrounding sentences. Text in italics or bold are not from the references. The Criteria, Bethesda Handbook and Practice Guidelines are not limited to lymph node evaluation, but cover diagnosis, clinical staging, pathological staging, treatment and follow up. The entire from ACR and NCCN are on the CD included with this document; the Handbook is not available electronically. There are extensive references in both sources on the CD.

B. Kidney

1. ACR

The most effective treatment for RCC is radical nephrectomy, which involves node dissection and complete removal of the kidney and Gerota's fascia.

Preoperative staging is important to the surgeon in planning the procedure.

For TxN+ disease (lymph node involvement), CT and MRI are approximately equal and both are superior to US. US is often obscured by bowel gas. However, from a surgical perspective, the identification of nodes is less important because the nodes must be sampled at the time of surgery. CT-guided aspiration biopsies can be performed if desired for documenting nodal metastases, however; this is rarely needed. Imaging is important for the preoperative detection of bulky adenopathy, which might complicate the surgical approach. This is especially true for laparascopic nephrectomies in which both the vascular anatomy and the nodal pathology may be poorly visualized. Accurate preoperative information becomes even more important, emphasizing the need for computed tomography angiography (CTA) or magnetic resonance angiography (MRA) prior to such a procedure.

2. NCCN

In the initial work up algorithm, abdominopelvic CT with contrast is recommended. Lymph node dissection at nephrectomy is considered optional.

In the manuscript:

Computed tomography of the abdomen and pelvis and a chest radiograph are essential studies in the initial work-up. A CT scan of the chest is obtained when the chest radiograph is abnormal or advanced disease is suspected. Magnetic resonance imaging (MRI) is used in evaluating the inferior vena cava when tumor involvement is suspected, or it can be used as a substitute for CT for detecting renal masses and for staging when contrast material cannot be administered because of allergy or renal insufficiency.

Surgery is advised for patients with clinical stage I or II tumors, as well as selected patients with clinical stage III disease (ie, patients who have a tumor involving the renal vein or vena cava). Patients with minimal regional adenopathy may also be considered for surgery, as lymph nodes suspicious for disease on CT may be hyperplastic and may not be involved with the tumor.

A radical nephrectomy--defined as a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland--remains the mainstay of surgical resection. The lymph node dissection may not be therapeutic but provides prognostic information, since virtually all patients with nodal involvement subsequently relapse with distant metastases despite lymphadenectomy.

3. Bethesda

CT abdomen and pelvis with contrast.

C. Bladder

1. ACR

Transitional cell carcinoma of the bladder spreads by local extension through the basement membrane into the muscular layer, then to the perivesical fat. Progressive extension into the muscular layer allows vascular and lymphatic invasion and more distant spread. Treatment ranges from cystoscopic local excision or segmental bladder resection with pelvic lymphadenectomy for early tumors to irradiation, chemotherapy, and/or radical extirpation for deep invasion. Cystectomy and conduit with pelvic lymphadenectomy are usually not performed on those with known extension beyond the bladder (1,2,6). Since clinical staging by cystoscopy and bimanual examination under anesthesia is inaccurate in more than 50% of patients, imaging is vital to the proper treatment of these patients. The principal task is to identify extravesical spread.

Computed Tomography of the Pelvis and Abdomen
The primary contribution of CT is distinguishing tumors that are organ confined from those with extravesical extension (3,5,7). It demonstrates bulky thickening of the bladder wall, perivesical extension, lymph node enlargement, and distant metastases very well.

Barentsz et al reviewed 437 cases in the literature using CT to stage TCCB. Overall accuracy ranged from 40%-85%, with correct staging of nodes and metastases 82 to 97%.

Magnetic Resonance Imaging
Magnetic resonance imaging (MRI) is superior to CT in demonstrating the lower pelvic anatomy. Barentsz et al also reviewed 340 cases using MRI. The staging of tumor was correct in 73%-96% of cases, and the staging of nodes and metastases was 73% to 98% correct

CT versus MRI
Both CT and MR imaging rely on enlargement of lymph nodes as a criterion for metastasis. Lymph node metastasis in patients with superficial tumors (less than T3) is rare, but if deep muscle layers are involved (T3a) or if extravesical invasion is seen, the incidence of lymph node metastasis rises to 20%-30% and 50%-60%, respectively. If a lymph node is considered to contain metastasis, an FNA biopsy should be considered. Both CT and MRI are considered similar in their ability to detect nodal enlargement.

Follow up imaging of Bladder cancer
CT scan is recommended at 6, 12, and 24 months for follow-up of patients with minimal muscle invasion (T2) in patients who either elect cystectomy or other types of therapy without cystectomy, since most recurrences become evident within the first 2 years after surgery. There is a different recommendation for follow-up on patients treated with a

bladder-preserving surgery. In these patients with transurethral resection of localized muscle-invasive TCC and follow-up combined neoadjuvant chemotherapy and radiation therapy, CT scans of the abdomen and pelvis are performed at 3 months after completion of radiation therapy and then every 6 months or "as otherwise indicated".

2. NCCN

In work up and staging algorithms for muscle invasive and metastatic CT and/or MRI of the pelvis and abdomen are specified, as it is for T4b and metastatic. Nodes ≥ 2 cm are biopsied.

In manuscript:

Treatment of muscle invasive disease
Before any treatment is advised, the patient should be assessed for the presence of regional and/or distant metastases. This evaluation should include a cystoscopy, EUA/TURBT, chest x-ray, evaluation of the upper tracts with an IVP or retrograde pyelogram, and CT of the abdomen and pelvis. Some physicians advocate performing an MRI scan

Assuming that the metastatic work-up is negative and the patient does not have medical comorbidities that preclude surgery, the treatment may proceed directly with surgery. An exploratory laparotomy with pelvic lymph node dissection is performed. If extensive disease is found in the lymph nodes or elsewhere in the pelvis, the cystectomy is generally not completed, and the patient is referred for systemic therapy. If there is no gross disease in the lymph nodes, the cystectomy is completed.

T4b Disease
Patients with unresectable disease, defined as a fixed bladder mass, or those with positive nodes prior to laparotomy are considered for chemotherapy alone or chemotherapy with radiation therapy. An initial stratification is based on the results of transaxial imaging. For patients who show no nodal disease on CT scanning, chemotherapy followed by cystoscopy and CT. If the tumor has responded, options include consolidation chemotherapy, RT or surgery. If no response is noted, chemotherapy/RT or a new chemotherapy regimen can be used.

If pelvic lymph nodes greater than 2 cm are documented, a biopsy is advised to exclude nodal spread. Baseline renal function, the presence or absence of cardiac disease, and overall performance status must also be considered when making a treatment recommendation. Patients with a good performance status and no significant comorbid disease may be considered for chemotherapy with or without radiation therapy if their nodes are positive.

3. Bethesda

A computed tomography (CT) scan of the abdomen and pelvis is useful in assessing the extent of the primary tumor, pelvic and paraaortic lymphadenopathy, and liver and adrenal metastases.

D. Prostate Cancer

1. ACR

Clinically localized disease (Stage A or B) is amenable to cure. Treatment methods include radical prostatectomy and radiation therapy. Tumor transgressing the capsule into the periprostatic space, even if microscopic, is considered Stage C disease. While some urologists will consider such patients for extirpative surgery, they are often treated with radiation therapy. Positive lymph nodes categorize the tumor as Stage D. Such patients are not candidates for curative therapy and are usually treated with hormonal manipulation.

The major difficulty in staging prostate cancer is determining microscopic penetration of the capsule. Another major issue is determining the presence or absence of tumor in normal-appearing pelvic lymph nodes.

However, a recent study reports a 93.7% accuracy for CT in detecting positive lymph nodes, which increases to 96.5% if CT-guided fine-needle aspiration biopsy is added. This degree of accuracy was obtained by considering every node 6 mm or larger as pathologic; this is a departure from previous CT criteria for positive nodes. Summarizing the current use of CT in staging prostate cancer, it appears to have little value in determining the direct extension of the tumor, but if the newer criterion for positive nodes is adopted, it may prove to be accurate in detecting nodal disease.

ProstaScint: A review of two recent multicenter clinical trials found a sensitivity of 52 and 62% and a specificity of 72 and 96% as confirmed by pelvic lymphadenectomy results. When used in conjunction with other diagnostic methods, ProstaScint offers the possibility of defining the extent of disease in high-risk (PSA greater than 10 ng/ml), newly diagnosed prostate cancer patients.

Summary
Imaging should perhaps depend to some degree upon PSA levels and tumor grade in individual patients. The likelihood of direct extension or distant metastases is low in patients with low-grade tumors and low levels of PSA. Patients with high-grade tumors or significantly elevated PSA levels have a high risk of capsular transgression, positive nodes, or bony metastases. Therefore, even in the face of a DRE that suggests localized disease, such patients should have a more detailed preoperative staging evaluation. Unfortunately, none of the current imaging modalities can detect microscopic spread of the tumor through the prostatic capsule. MRI using endorectal coil techniques shows promise but needs further development, and there is a steep learning curve in interpretation of the images. For determining nodal involvement in these high-risk patients, CT with fine-needle aspiration biopsy has proven accurate in at least one report, and radionuclide bone scans are useful for detecting bony metastases. ProstaScint may also play an important role in detecting nodal metastases.

Follow-up
A rising PSA level prompts a bone scan. If this is positive, no other imaging is indicated. An equivocal bone scan may lead to more refined imaging such as a quantitative bone scan or MRI. A negative bone scan requires further investigation such as biopsy (post prostatectomy and radiation therapy) and lymph node evaluation (post radiation therapy and ADT).

Another ACR monograph addresses staging prior to radiation therapy with similar recommendations.

2. NCCN

In Initial Clinical Assessment Staging Work-Up Algorithm:
For life expectancy >5years or symptomatic: Pelvic CT or MRI if T1 or T2 in cases where nomogram indicated probability of lymph node involvement of > 20% or if T3, T4 If Positive nodes, then FNA

In Manuscript

For patients with a life expectancy of more than 5 years and a PSA level greater than 10 ng/mL, a bone scan is appropriate in the presence of a Gleason score of 8, 9, or 10. A T3 or higher tumor is an additional factor influencing the need to perform further evaluation. Scanning of the pelvis for the presence of lymph node metastases, using either computed tomography (CT) or magnetic resonance imaging (MRI), is also recommended for this subset of patients. These procedures may also be indicated for patients with T1 -2 tumors if a higher rate of lymph node involvement is predicted by one of the available nomograms (Partin, 1997; Blute, 2000). If enlarged lymph nodes are discovered, a fine needle biopsy should be performed for pathologic examination.

Follow up: For patients who have undergone a radical prostatectomy, there are two groups to consider: those whose PSA level fails to fall to 0 ng/mL and those with a rising PSA level (based on two laboratory determinations).

For patients who develop a rising PSA level, the work-up options include a bone scan, biopsy, CT/MRI, and ProstaScint examination. If the tests are negative for distant or nodal disease, radiation therapy with or without androgen ablation, observation, or androgen ablation alone is acceptable.

For patients not responding to prior radiotherapy who present with a rising PSA level or positive DRE, it is again appropriate to define the extent of recurrent disease with a bone scan, pelvic CT or MRI scan, and/or a ProstaScint examination.

3. Bethesda

Computed tomography (CT) or magnetic resonance imaging (MRI) is obtained for T3, T4 lesions to detect the presence of enlarged lymph nodes for men in whom surgery is

considered. If lymph nodes appear enlarged, a fine-needle aspiration (FNA) can be performed, potentially sparing surgery. CT scans are often needed for treatment planning for radiation therapy, especially 3-D conformational approaches.

E. Testicular Cancer

1. ACR

Testicular tumors spread or metastasize either by the hematogenous or lymphatic route. Most follow the regional lymphatic chain alongside the spermatic vessels. Typically, the first order of metastases is the "sentinel" lymph node, which on the left is located at the renal hilar region and on the right in the paracaval region below the renal artery and vein. Left-sided tumors typically spread to the periaortic nodes and preaortic nodes and right-sided tumors most commonly involve interaortocaval, precaval, and preaortic nodes. Crossover is not uncommon, but typically is from the right to the left. Further drainage is through the thoracic duct, resulting in more widespread metastases.

Computed Tomography (CT)
Computed tomography is probably the most common study used for assessing the retroperitoneum for the presence of metastatic testicular malignancy. This study is noninvasive and reproducible and provides excellent imaging of the periaortic and pericaval regions. Difficulties with computed tomography are that many young men have little peritoneal fat, which tends to be an impediment to the study, and that CT cannot detect the presence of metastatic disease in lymph nodes of normal size. Additionally, inflammatory lymph nodes cannot be differentiated from those that are enlarged secondary to malignant disease. CT interpretation is aided by understanding the lymphatic drainage of the testicles. Node involvement is usually limited to the side of the primary tumor and crossover is usually present only in the presence of advanced disease. Various benign conditions have also been found to mimic metastases from testicular tumors. Lymph nodes larger than 1 cm are suspicious for metastatic disease, particularly if they are located in the hilar regions of the kidney or in the periaortic or caval areas. Various studies have established the accuracy of computed tomography in the detection of metastatic retroperitoneal lymph nodes, which ranges from 73- 97%. Sensitivity ranges from 65-96% and specificity from 81-100%. Experience also indicates that accuracy declines in patients with limited disease (stage N1 and stage N2) and also if the upper limit of normal lymph node size is lowered to 4 mm.

Lymphangiography
Lymphangiography is used with decreasing frequency because of the disadvantages of the study, which include its invasiveness, its inability to opacify the sentinel lymph node, and its inability to demonstrate the upper limits of involvement in patients with extensive disease. The accuracy of bi-pedal lymphangiography has been shown to be comparable to computed tomography and varies from 62-89%. Sensitivity ranges from 54-90% and specificity from 67-100%. Studies have also indicated that a combination of lymphangiography and CT improve accuracy, but evidence indicates that this approach is not cost-effective.

Magnetic Resonance Imaging (MRI)
Magnetic resonance imaging (MRI) has also been used in the staging of testicular tumors; however, evidence indicates that it is comparable to CT. MRI does offer an advantage, allowing for the differentiation of blood vessels from lymph nodes and may also have the potential of distinguishing residual tumor from fibrosis.

2. NCCN

If an intratesticular mass is identified, further evaluation includes measurement of the serum concentrations of AFP and beta-hCG and a chest x-ray, followed by a radical inguinal orchiectomy. If a germ cell tumor is found, then an abdominopelvic computed tomographic (CT) scan is performed.

Stage IA Non-seminoma
Two management options exist for patients with stage IA disease-- observation or nerve-sparing retroperitoneal lymph node dissection (RPLND). The cure rate with either approach exceeds 95% (Hoskin et al, 1986; Klepp et al, 1990). However, the high cure rate associated with surveillance is predicated on adherence to periodic follow-up examinations and subsequent chemotherapy for the 20% to 30% of patients who relapse. (Approximately 20% of patients with clinical stage I non-seminoma who do undergo RPLND are found to have regional lymph node metastases at the time of surgery.) If observation is chosen for patients with stage IA disease, patients must be compliant with follow-up. The follow-up examination includes an abdominopelvic CT scan every 3 months for the first 2 years. Noncompliant patients are managed with RPLND.

3. Bethesda

Imaging
•Ultrasound: to detect the presence of testicular parenchymal abnormality.
•Radiographic studies: standard two-view chest radiograph to rule out pulmonary metastases.
•Computed tomography (CT) scans of chest, abdomen, and pelvis: to establish extent of disease dissemination.
•Magnetic resonance imaging (MRI): especially when results of the physical examination and testicular ultrasound are equivocal.

F. Ovarian Cancer

1. ACR

Ovarian cancer is the sixth most common malignancy among women in the United States, accounting for more than half of all deaths from genital tract cancer. Most women with this tumor present with advanced stage III-IV disease. The role of diagnostic imaging has been ovarian mass characterization, determination of preoperative disease extent, and prediction of tumor resectability. Surgical staging is both diagnostic and therapeutic, and

an experienced gynecologic surgeon is critical in optimum debulking of this tumor.

For the past 15 years, CT has been considered the imaging modality of choice in the preoperative evaluation of ovarian cancer. CT has been validated as an accurate method to predict successful surgical cytoreduction. CT has been useful for detecting local tumor involvement of the pelvic ureter and uterine serosa and metastases to the peritoneum, omentum, mesentery, liver, spleen, and lymph nodes. Current high-resolution CT scanners can detect 50% of peritoneal implants as small as 5 mm [sensitivity 63%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 52%]. The most important limitation of CT in staging ovarian cancer is its inability to reliably detect bowel surface, mesenteric or peritoneal tumor implants smaller than 5 mm, especially in the absence of ascites.

Few studies have evaluated MR in staging ovarian cancer. Two studies found no statistical difference between CT and MR in defining disease extent. Thus, CT is currently the recommended modality to stage ovarian cancer. MR imaging is recommended to patients with a contraindication to the use of iodinated contrast agents (allergy, renal insufficiency), who are pregnant, and in whom CT findings are inconclusive.

2. NCCN

There was general agreement on the primary work-up of a patient with an undiagnosed pelvic mass, and there have not been any significant changes made to the previous guidelines. The standard work-up for such patients should include an ultrasound or abdominopelvic computed tomography (CT) scan (if clinically indicated) after a complete physical examination and appropriate laboratory studies, including a CA 125 determination, have been completed. A consultation for a family history of ovarian and breast cancer should also be obtained.

3. Bethesda

The workup of an undiagnosed pelvic mass should include a complete history and physical examination, laboratory work including CA125, and an ultrasound or computed tomography (CT) scan of the abdomen/pelvis (if clinically warranted). If the woman is younger than 30 years, an α-fetoprotein and β-human chorionic gonadotropin (β-HCG) should be performed to rule out germ cell tumors. A pelvic radiograph can be used to look for the presence of a mature teratoma, which can appear as a calcified mass. Preoperative endometrial sampling should be performed in women with abnormal vaginal bleeding. A chest radiograph is warranted before surgical intervention.

G. Cervical cancer

1. ACR

The prognosis of cervical carcinoma is primarily determined by the stage of disease, volume of the primary tumor, and histologic grade. The International Federation of Gynecology and

Obstetrics (FIGO) has defined the clinical staging system for cervical carcinoma based on findings from physical examination, colposcopy, lesion biopsy, chest radiograph, cystoscopy, sigmoidoscopy, intravenous urography, and barium enema. When compared with surgical staging, FIGO clinical staging is inaccurate. Staging errors are 28% in stage Ib disease and 50%-64% in stage IIa-IIb disease. Clinical evaluation underestimates the surgical stage in 15%-36% of patients. In clinically staged Ib disease, underestimation of tumor extent occurs in 21% and overestimation in 6% of patients. Inaccuracy in clinical staging is predominantly due to difficulties in the evaluation of parametrial and pelvic side wall invasion and in the evaluation of primary endocervical (endophytic) tumors. Evaluation of lymph node metastasis, an important prognostic factor and a determinant in treatment planning, is not included in the clinical staging system. In spite of these limitations of clinical FIGO staging, modern cross-sectional imaging modalities have not been incorporated into recommendations for diagnostic workup.

Computed Tomography
The staging accuracy of CT ranges from 32%-80%. The sensitivity for parametrial invasion ranges from 17%-100% with an average of 64%. Specificity ranges from 50%-100% with an average of 81%. There is a consensus in the literature that the value of CT increases with higher stages of disease, and that CT has limited value (a positive predictive value of 58%) in the evaluation of early parametrial invasion. The positive predictive value of CT for nodal involvement is 65% with a negative predictive value of 86%.

Magnetic Resonance Imaging
The staging accuracy of MRI ranges from 75%-90%. The sensitivity of MRI in the evaluation of parametrial invasion is 69%, and the specificity is 93%. In five studies that compare MRI and CT in the evaluation of parametrial invasion, MRI was superior to CT. In the evaluation of nodal disease, the sensitivity and specificity of MRI, 50% and 95% respectively, are similar to those of CT. In the assessment of local tumor invasion, T2-weighted images are superior to contrast-enhanced T1-weighted images.

Lymphangiography
Although lymphangiography has been routinely used in the past for the pretreatment evaluation of lymph node metastases, it has been mostly replaced, in this role, by CT and MRI. Single studies that have compared lymphangiography and CT have shown similar accuracy (72%-91% and 71-88%, respectively) for both modalities. CT may have a slightly higher specificity than lymphangiography (88%-95% versus 59%-93%), but lymphangiography is more sensitive than CT (63%-88% versus 53%-72%), especially in early stages (I-II) of disease. A meta-analysis compared the utility of lymphangiography, CT and MRI in patients with cervical cancer. Although summary-receiver-operator characteristics revealed no significant differences in the overall performance of LAG, CT and MRI, there was a trend toward better performances for MRI than for LAG or CT.

2. NCCN

There is debate as to the value of a noninvasive work-up, such as intravenous pyelography (IVP) or lymphangiography, versus computed tomography (CT) or magnetic resonance

imaging (MRI). The appropriate stage for performing cystoscopy and/or proctoscopy
The use of lymphangiography, MRI, and/or CT scans may aid in treatment planning but is not accepted for staging purposes. In addition, FIGO has always maintained that staging is intended for comparison purposes only and not as a guide for therapy. As a result, although the panel uses the FIGO definitions as the stratification system for this guideline, the findings on imaging studies, such as CT and MRI, are used to substratify treatment options.

3. Bethesda

Radiologic Studies

- Chest radiograph (CXR)
- Intravenous pyelography or computed tomography (CT) scan with i.v. contrast.
- Barium enema (stage III, IVA, and earlier stages if there are symptoms referable to colon or rectum).
- Magnetic resonance imaging (MRI) if needed for better disease evaluation.

H. Uterine/endometrial

1. ACR

In the evaluation of lymph node metastases, compared with either CT or MRI, ultrasound has a significantly lower sensitivity for the detection of pelvic lymph node metastases. The efficacy of CT and MRI in the evaluation of lymph node metastases is similar, and both modalities rely on anatomic findings of nodal size, (equal to or greater than 1 cm on short axis). Lymphography is not recommended for the evaluation of cancer of the endometrium. Not only is the modality invasive (and very few imaging centers offer this service) but its performance, because of the difficulties in the evaluation of pelvic nodes, also is slightly inferior and is not statistically significant to that of CT and MRI.

2. NCCN

Other ancillary tests such as cystoscopy, sigmoidoscopy, ultrasound, computed tomography, and magnetic resonance imaging should be reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.

Lymph Node Dissection
The most controversial component of surgical staging is pelvic and aortic lymphadenectomy and whether it should be required for all patients with disease confined to the uterus. Among issues to be considered are the need for the operating surgeon to be familiar with gynecological cancer surgery, the required extent of lymphadenectomy, the contention of some physicians that low-grade and noninvasive endometrial cancers do not justify routine lymphadenectomy, and the reality that some obese patients are not technically suitable for nodal dissection. The incidence of pelvic and aortic node metastasis is related to the grade of tumor and the depth of myometrial invasion.

Based upon retrospective analysis of patients who have undergone full surgicopathologic

correlation, it has been suggested that patients with grade 1 tumors and invasion of less than one third of the myometrium may be spared the risks associated with lymph node dissection, whereas nodal sampling is recommended for all patients with grade 2 to 3 tumors, deep myometrial invasion, cervical involvement, or suspect nodes at surgery. Other intraoperative and postoperative considerations must be factored into the decision of whether or not to perform lymphadenectomy. In 15% to 20% of cases, the preoperative grade, as assessed by endometrial biopsy or curettage, is upgraded on final fixed pathologic evaluation of the hysterectomy specimen (Daniel and Peters, 1988). In addition, the intraoperative evaluation of myometrial invasion by gross examination of fresh tissue becomes increasingly inaccurate as the grade of tumor increases. In one study, the depth of invasion was accurately determined by gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions. A further indication for complete surgical staging is suggested in a recent report demonstrating statistically improved survival in patients with complete node dissection versus no node dissection or limited node sampling, even after adjusting for other clinicopathologic variables .

Nodal Involvement
Based upon a prospective evaluation of surgicopathologic patterns of spread in endometrial cancer by the Gynecologic Oncology Group (GOG) and others, it is now recognized that much of the adverse prognosis associated with intrauterine risk factors is mediated through nodal involvement. The incidence of pelvic nodal metastases is 5% or less for grade 1 and 2 tumors with inner one third myometrial invasion. For patients with outer third infiltration, nodal disease was found in 19% of grade 2 cancers and 34% of grade 3 cancers. Given the wider acceptance of formal surgicopathologic evaluation and the adoption of the 1988 FIGO staging classification, clinical stage I and stage II patients with adverse intrauterine features who were once deemed at risk for nodal metastases are now upstaged to stage III and stage IV when extrauterine disease is documented. The implications of this "stage migration" should be considered when evaluating historical data.

3. Bethesda

• Routine use of U/S, computed tomography (CT) scan, magnetic resonance imaging (NUU), and bone scan rarely adds useful information and is not recommended.

I. Breast

1. ACR

Not included in ACR.

2. NCCN

Sentinel node and/or limited axillary dissection recommended.

3. Bethesda

CT recommended, but not necessarily for nodes.

J. Lung

1. ACR

Bronchogenic carcinoma, non-small cell carcinoma

Evaluation of Nodal Metastasis (the N Factor)
CT has become the method of choice for the assessment of mediastinal nodes in bronchogenic carcinoma. Previously, patients with mediastinal nodal metastasis from bronchogenic carcinoma were not considered to benefit from surgical therapy. However, numerous studies have consistently documented improved survival of selected patients after resection of mediastinal nodal disease and, in most cases, adjuvant radiation therapy. The new American Joint Committee on Cancer Staging now considers patients with ipsilateral mediastinal lymph node metastasis (N2) as potentially surgically resectable stage IIIa disease. Included in this group are patients with: (1) intracapsular rather than extracapsular involvement; and: (2) positive nodes identified at thoracotomy after negative mediastinoscopy. In addition, early reports have indicated that even patients with gross and bulky ipsilateral nodal metastasis (N2) may benefit from surgery if it is combined with neoadjuvant chemotherapy and radiation therapy. However, patients with contralateral mediastinal nodal involvement (N3) are considered to have nonoperable stage IIIb disease.

Several studies have addressed the accuracy of CT in the staging of mediastinal nodal metastasis in lung cancer. Some early investigations reported a high sensitivity in the range of 88%-94%, values that were equivalent to the sensitivity of mediastinoscopy. Opinions based on such data suggest that mediastinoscopy was unnecessary in cases in which the CT scan showed no evidence of enlarged nodes. However, these early studies suffered from faulty methodology which included: (1) the lack of an adequate lymph node mapping system; and (2) the failure of complete mediastinal nodal sampling at surgery. More recent studies that have used total nodal sampling and the American Thoracic Society Lymph Node Classification have generally shown a lower sensitivity of CT in the detection of nodal metastasis. McLoud et al reported that the sensitivity and specificity of CT was 64% and 62% respectively. This study used 1 cm as the upper limit of normal diameter for the short axis of lymph nodes and also used extensive lymph node sampling that was correlated closely with CT nodal stations. Staples et al. used similar methodology and showed a somewhat higher sensitivity of 79%, which approached that of mediastinoscopy. However, they used the long axis for lymph node measurement. They concluded that CT and mediastinoscopy were complementary, particularly because CT often showed enlargement of lymph nodes in groups that were inaccessible at mediastinoscopy. Daly et al found that in detecting mediastinal nodal metastasis, CT had a sensitivity of CT of 81% with central tumors and 71% with peripheral tumors. The negative predictive index, however, was 93%. Based on this figure, they suggested that mediastinoscopy was not necessary when the CT scan was negative. However, they did recommend careful nodal sampling at the time of

thoracotomy. Their study suffered from the fact that a nodal sampling scheme was not used in the correlation between radiologic and pathologic findings.

In summary, controversy still exists on the value of CT scanning in staging the mediastinum in lung cancer. A negative CT scan for mediastinal adenopathy may provide useful information, particularly in institutions in which mediastinoscopy may not be available or preferred. If patients are selected immediately for thoracotomy without preceding mediastinoscopy, careful nodal sampling must be done at the time of surgery. Because of the low specificity of CT, enlarged lymph nodes must be biopsied for accurate staging. Despite the limited sensitivity and specificity of CT, it appears to be used almost universally for staging the mediastinum in lung cancer. This use appears to be appropriate because of the additional information that CT provides. It provides a map of enlarged nodes prior to mediastinoscopy, as well as information on enlarged nodes that are out of reach of the mediastinoscope or that are contralateral in position and suspect for N3 disease.

The issue of CT staging of the mediastinum in T1 lesions is controversial. T1 tumors are defined as lesions <3 cm in greatest diameter surrounded by lung or visceral pleura without evidence of invasion proximal to the lobar bronchus. Several studies have suggested a low prevalence of mediastinal nodal metastatic disease with T1 cancers (5-15%). Because of this low prevalence, it has been suggested that CT may not be necessary in such patients and that the preoperative staging should be limited to plain chest radiographs. However, Seely et al (10) found a 21% prevalence of nodal metastasis among 104 patients with T1 lesions. The sensitivity of CT was 77% for the detection of these metastases and the study's authors recommended that CT be performed in such patients. Pearlberg et al , in a study of 23 patients with T1 lesions, found only one patient who had CT evidence of noncurative disease. Because of the low yield, CT was not recommended. In a larger series of 63 patients, Duncan et al found that 14% of patients with T1 lung cancers had inoperable disease correctly detected by CT. However, in this study pathologic proof of inoperability was lacking. In summary, the issue remains controversial, and none of the studies appears to be definitive.

Small cell

Small cell lung cancer accounts for 20%-25% of lung cancer cases in the United States. Although the TNM staging system has been useful, the alternative staging system widely applied is a two-stage system based on studies of the Veterans Administration Lung Study Group. In this system, patients are classified as having either limited disease (i.e., tumor confined to one hemithorax and to the regional lymph nodes) or extensive disease (i.e., tumor beyond this area in contralateral lung or extrathoracic sites.) Extensive disease is present in 60%-80% of newly diagnosed patients with small cell lung cancer. Conventional staging for extrathoracic metastasis in patients with small cell lung cancer includes CT of the abdomen and head, bone scintigraphy, and bilateral bone marrow biopsy.

2. NCCN

Non-small cell

The chest CT scan can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, key determinants of stage II and stage III disease). This determination will influence the steps in further pretreatment evaluation. Recently, positron emission tomography (PET) scans have been used to evaluate the mediastinal nodes because CT scanning has known limitations for evaluating these lymph nodes.

As noted above, evaluation of the mediastinal nodes is a key step the further staging of the patient. Mediastinoscopy is considered gold standard. Thus, its use is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high based on tumor size and location. Therefore, mediastinoscopy is appropriate for patients with T3 lesions even if the chest CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive CT scan. In contrast, due to the low prior probability of lymph node involvement in patients with peripheral T1 or T2 lesions, some NCCN institutions do not use routine mediastinoscopy in these cases (category 2B). The risk for mediastinal lymph node involvement increases in patients with central T1 or T2 lesions with negative CT scans. In this situation, mediastinoscopy is recommended.

Small cell

Small-cell lung cancer consists of two stages: (1) limited disease, defined as disease confined to the ipsilateral hemithorax within a single radiation port, and (2) extensive disease, or obvious metastatic disease. Chest radiotherapy is important for at least a subset of limited-stage disease. However, contralateral hilar and supraclavicular nodes and pericardial or malignant pleural effusions are frequently excluded from protocols for limited-stage patients. Approximately 67% of patients present with overt metastatic disease, which includes spread to the liver, adrenal glands, bone, bone marrow, and brain. Staging should always include a chest radiograph, chest and liver CT scans that encompass the adrenal glands.

3. Bethesda

Non-small cell

- CT and MRI can provide information regarding hilar and mediastinal nodal involvement by tumor. Size is the criterion used to distinguish normal from abnormal nodes, with a short- axis nodal diameter of 1 cm typically used as the upper limit of normal. However, nodal enlargement may relate to hyperplastic reactive nodes, particularly after obstructive pneumonia.
- The accuracy of CT and MRI for detecting metastatic hilar (NI) or mediastinal disease is only 62% to 68% and 68% to 74%, respectively. Thus mediastinoscopy remains an important staging procedure.
- MRI is the investigation method of choice in evaluating superior sulcus tumors, because CT is limited by axial plane and streak artifact from the shoulders.

Small cell
•Chest imaging: a chest radiograph; chest computed tomography (CT) scan, particularly if thoracic radiotherapy is planned; bronchoscopy if no evaluable tumor is found on chest radiograph/CT scan.

K. Head & Neck

1. ACR

Not in ACR.

2. NCCN

Each tumor type has a separate algorithm, most of which require CECT and/or MRI with or with out gadolinium.

3. Bethesda

Computed tomography (CT) scan remains the primary imaging study for the evaluation of metastatic adenopathy. Magnetic resonance imaging (MRI) may complement the CT scan

Once the diagnosis of cancer is established, the patient should be evaluated for extension of tumor, lymph node involvement, presence of metastasis, and secondary tumors to determine the clinical stage. In general, besides a thorough physical examination, CT scan and/or MRI of the primary tumor and neck are indicated. CT scan is cheaper and faster, has better definition for cortical bone, and is better than MRI for evaluating metastatic adenopathy. MRI has superior soft tissue contrast, does not involve radiation, and may be better than CT scan for primary tumor staging. A chest radiograph is indicated for all patients, mostly because of the risk of a second malignancy in this high-risk population. Additional studies will vary according to the primary site.

L. Lymphoma

1. ACR

Hodgkin's
In Hodgkin's disease, the purpose of staging is to define the anatomic extent of detectable disease. This provides prognostic information and can serve as the basis of rational treatment decisions.

Computed Tomography
Contrast-enhanced computed tomography (CT) should be performed of the chest, abdomen, and pelvis in all patients.

Thoracic CT scans can result in upstaging of the patient by demonstrating abnormalities not appreciated on routine chest radiographs. Demonstration of intrathoracic abnormalities may also result in alteration of treatment fields or clinical management. Adenopathy in the mediastinal, hilar, subcarinal, and internal mammary areas may be detected with a thoracic CT scan that can influence radiation treatment planning. Detection of extensive pericardial involvement or pulmonary parenchymal involvement can occasionally be demonstrated on chest CT scans which may render a patient ineligible for treatment with radiation therapy alone.

CT scans of the abdomen have an advantage over bipedal lympangiography in their ability to assess the upper abdominal nodes, the liver, and the spleen. Investigators at the University of Florida and the Joint Center for Radiation Therapy (10) analyzed the positive and negative predicted value of CT for pelvic and para-aortic adenopathy compared with staging laparotomy. They confirmed earlier results from Stanford University demonstrating a high negative predictive value (89%-93%). Investigators from the University of Florida demonstrated a lower positive predicted value of 20%, compared with a value of 60% obtained at Stanford. The negative predicted value and positive predicted value for splenic disease was approximately 77% and 43%, respectively. All three institutions concluded that CT evaluation of the spleen was not reliable. Investigators at Stanford University and the University of Florida have examined size of the spleen based on CT dimensions of the product of transverse, vertical, and anteriorposterior dimensions with differing conclusions. Hancock et al, concluded that splenic size, whether assessed radiographically or by weight, was not a sensitive predictor for Hodgkin's disease involvement. However, Mendenhall (4) noted that increasing splenic size as measured by weight or index correlated with an increase probability of splenic involvement.

Magnetic Resonance Imaging
Magnetic resonance imaging (MRI) may be an alternative to chest or abdominal CT scanning for initial evaluation of the patient. MRI has been evaluated as an initial staging tool compared with CT scan in a prospective study by Skillings and colleagues. Employing laparotomy to define pathologic extent of abdominal disease, these investigators demonstrated MRI was more sensitive but less specific than CT with similar accuracy rates. They concluded MRI could not replace laparotomy as a staging procedure. Tesoro-Tess et al, investigated the role of MRI in the initial staging of Hodgkin's disease and found this procedure to be a useful adjunct to staging thoracic disease and assessing the spleen. MRI has been employed in evaluating the bone marrow to identify areas of abnormality for biopsy. Because of its low sensitivity (55.6%) and its low positive predictive value (38.5%) it is not a substitute for bone marrow biopsy in appropriate patients. Some investigators have found MRI to be of benefit in restaging patients after definitive treatment to help differentiate fibrosis from tumor.

2. NCCN

Non-Hodgkins:–Most variants require abdominopelvic CT in the work up
Hodgkins–Chest x-ray and chest/abdominopelvic computed tomography (CT) scans are

appropriate imaging studies. If the CT is equivocal, gallium scan or positron emission tomography (PET) imaging may be helpful in selected cases (category 2B).

3. Bethesda

Staging evaluation usually includes chest radiograph (CXR), whole-body computed tomography (CT) scans, and bone marrow (BM) biopsies. Lumbar puncture with cytology should be performed in patients at risk of central nervous system (CNS) disease [i.e., aggressive NHL with elevated lactate dehydrogenase (LDH) and more than one extra- nodal site and/or positive BM biopsy]. Baseline gallium or positron emission tomography (PET) scans are useful for staging and for comparison with posttreatment scans during response assessment.

M. Colorectal

1. ACR

Studies correlating pathological staging (e.g., Dukes') with radiological assessment consistently yield poor results for radiology; thus preoperative formal staging of the colonic neoplasm should not be a goal of the imaging study. Most surgeons rely on preoperative abdominal/pelvic imaging to evaluate the abdomen and retroperitoneum for the presence of either local complications and/or distant metastases. However, preoperative staging assessment of rectal carcinoma has significant therapeutic implication. Patients with node negative rectal carcinomas that have not reached the serosa may be adequately treated by radiation therapy with or without transanal excision. Furthermore, clinical trials combining preoperative radiation followed by primary resection have shown improved survival in patients who present with either transmural invasion or are lymph node positive. Thus preoperative imaging for local staging of rectal cancer is routinely employed. Radiologic pretherapeutic staging of colorectal carcinoma has not been widely accepted by either referring clinicians or diagnostic radiologists, because of poor correlation with Dukes' staging resulting in relatively minimal impact in initial operative therapy. Furthermore, preoperative adjuvant therapy is controversial. However, most surgeons rely on preoperative

On the basis of currently available results, routine CT staging is not recommended for primary colorectal tumors; however, CT is the procedure of choice for preoperative global assessment of the abdomen and retroperitoneum because of its high negative predictive value and because of its increasing accuracy in advanced disease. In patients with colonic neoplasm, CT is sufficient to screen for local extension and distant metastases, because staging is less important. Detection of nodes involved with tumor remains a difficult problem. If a colonic resection is planned, local node groups are encompassed in a properly performed cancer operation. Transrectal ultrasound may be used to determine local tumor extent; however, up to 14% of patients with locally limited tumors confined to the bowel wall may have regional node metastases. Although TRUS can frequently detect regional lymph nodes and is superior to CT at this task, to date, it cannot predict the histology of the visualized lymph nodes.

Magnetic resonance imaging may be beneficial in determining involvement of the pelvic musculature and adjacent organs. It is possible that endorectal coils and contrast-enhanced MR imaging could improve staging of colorectal tumors. Magnetic resonance imaging holds promise in the evaluation of perirectal nodes and offers comparable results with CT in the liver. Newer studies are necessary to reassess the utility of newer breath-hold MR sequences. While MR imaging may offer other advantages over CT in patients with primary colorectal cancer, it is uncertain and more comprehensive studies are needed.

2. NCCN

Patients who present with invasive colon cancer require a complete staging work-up, including pathologic tissue review, total colonoscopy, a CEA determination, chest x-ray, and a CT scan of the abdomen and pelvis.

Patients with rectal carcinoma should be fully staged. Endoscopic biopsy of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If available, endorectal ultrasound can assist the surgeon in determining the extent of disease. Computed tomography or magnetic resonance imaging of the abdomen and pelvis are recommended because they might provide additional information about the extent of the disease.

The NCCN Guidelines recommend thorough evaluation in any patient with a suspicious lesion in the anal canal. This includes a careful digital rectal exam plus anoscopic visual examination with biopsy of suspicious lesions and palpation of the inguinal lymph nodes. A CT scan or an MRI scan of the pelvis is necessary to evaluate pelvic lymph nodes or suspicious inguinal lymph nodes.

3. Bethesda

Diagnostic Evaluation

•Basic laboratory studies including complete blood count, electrolytes, and liver and renal function tests, chest radiograph, and computerized tomography of the abdomen and pelvis are useful in initial cancer diagnosis, although the relative contributions of these various modalities are undefined.