Understanding the Lymphatics: An Updated Review of the N Category of the AJCC 8th Edition for Urogenital Cancers

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Genitourinary Imaging · Review

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OBJECTIVE. Organ-specific nonregional and regional lymph nodes vary considerably among tumors. Nonregional lymph node involvement equals metastasis, which is critical to detect to ensure correct tumor staging, management, and prognosis. Knowledge of nodal nomenclature and anatomy is therefore essential in every cross-sectional imaging study.

CONCLUSION. This article reviews the most important changes and highlights of the N category of the American Joint Committee on Cancer 8th edition of the TNM classification for urogenital cancers.

Diagnosis, treatment, and prognosis of urogenital cancers depend on cancer staging, which is made according to severity of cancer in the body. The TNM cancer staging system was developed by the American Joint Cancer Committee (AJCC) and the Union for International Cancer Control and remains the most widely used system worldwide. Staging is determined by the local extent of the primary tumor (category T), degree of lymph node (LN) involvement (category N), and presence of metastasis (category M), which typically occur by lymphatic or hematogenous pathways. Knowledge of lymphatic pathways of tumor spread and regional lymphatic drainage pathways is essential because nonregional lymphadenopathy is considered distant metastasis even if the disease spread is limited to LNs. Imaging is central for nodal staging and complements clinical and surgical examination. MRI can be used advantageously for assigning T category, contrast-enhanced CT (CECT) and FDG PET/CT for nodal and distant metastasis, and ultrasound to evaluate LNs in the groin and provide image guidance for biopsy. Any clinician involved with urogenital cancers must be aware of the many important updates in the 8th edition of the AJCC TNM classification [1]. This review article will describe the most important updates affecting staging, prognosis, and management of urogenital cancers.

When Is a Lymph Node Suspicious?

Imaging-based evaluation of an LN must consider size, morphology, nodal border, internal architecture, number of abnormal LNs, and tumor-specific characteristics. Despite modern advancement in imaging, there are still shortcomings to nodal evaluation by imaging, such as failure to detect micrometastasis and limited differentiation of benign and malignant LNs.

Size remains an important criterion to distinguish a metastatic from a nonmetastatic LN using a short-axis diameter of 8 mm in the pelvis and 10 mm in the abdomen [2, 3]. Measurements are more reliable in the axial plane [4]. Although size matters, exceptions are common, for example, retroperitoneal LNs larger than 8 mm in short axis are considered abnormal in testicular cancer [5], nonregional inguinal LNs smaller than 15 mm in short axis are typically benign, and perivisceral LNs in rectal cancer less than 5 mm in short axis may be metastatic [4]. Additionally, LN enlargement may be caused by benign conditions such as infection and reactive hyperplasia. Size alone is insufficient to differentiate benign and malignant LNs because nodes may be enlarged in benign conditions like infection. To help avoid potential confusion, RECIST 1.1 criteria use different measurement criteria [6]. Morphologic indicators of malignancy include irregular borders indicating extranodal extension, round or irregular shape, and loss of fatty hilum [2, 4, 7–9]. Extranodal extension is defined as nodal cancer metastasis growing beyond the confines of an LN capsule, for example, regional LN metastasis invading a distant organ. An increased number of involved LNs is important to determine the N category for most cancers and is discussed in detail below. Several studies for various tumors have indicated the LN ratio (ratio of nodes

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that are positive for metastatic disease relative to total number of LNs harvested) as a good predictor of survival [10–14]. Central necrosis on CT and heterogeneity on T2-weighted MRI are suspicious indicators of metastasis [4, 15], although tuberculosis and fungal infections may lead to a low-density appearance [16, 17]. Rim or heterogeneous enhancement increase suspicion of malignancy, whereas homogeneous enhancement is seen in both benign and malignant conditions [2]. Macroscopic fat and calcifications within LNs are typical benign characteristics, although calcification occurs in serous ovarian carcinoma, bladder carcinoma, and treated metastatic LNs in testicular cancer. DWI and ADC mapping have shown promise in LN evaluation especially in prostate cancer but are currently insufficient to replace invasive diagnostic techniques [18].

Accurate interpretation also entails a detailed understanding of tumor-specific spread, because nodes along a specific tumor pathway of dissemination are more often metastatic. Finally, locally advanced, biologically aggressive, and larger tumors tend to have a higher incidence of lymphatic involvement [19]. In summary, a combination of size, shape, border, internal architecture, and tumor-specific characteristics should all be used to differentiate between malignant and benign LNs.

Pelvic Lymph Nodes and Nomenclature

The most important pelvic nodal groups include bilateral spermatic and ovarian nodes along the gonadal vessels, common external and internal iliac groups along the respective iliac arteries, paraaortic and perivisceral nodes, and inguinal nodes (Fig. 1). Because most pelvic cancers arise from midline organs, laterality typically does not affect the N category. A categorization of Nx indicates that LNs cannot be assessed, N0 indicates no involvement, and N1–N3 indicate increasing levels of regional lymphadenopathy.

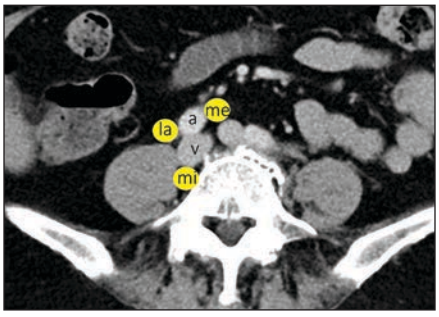
Pelvic Lymphatic Pathways

Lymphatic spread in urogenital tumors typically follow a sequential pattern without skip metastases [20]. There are four major pelvic lymphatic pathways (Fig. 2). The lateral pathway drains pelvic organs to the obturator group of the external iliac chain. The internal iliac (hypogastric) pathway drains most of the pelvic organs along the internal iliac vessels to the junctional nodes between the internal and external iliac nodes. Cancer arising from prostate, cervix, endometrium, ovaries, and upper two-thirds of the vagina often metastasize by the lateral and internal iliac pathways [16]. The presacral pathway drains to the presacral lymphatic plexus of the internal iliac group. Cervical cancer may rarely spread via the sacrouterine ligament to the presacral nodes [20–22]. The anterior pathway drains from the anterior bladder wall along the umbilical artery to the hypogastric group of the internal iliac nodes.

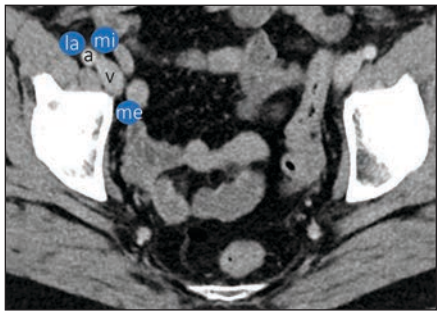
All groups converge to the common iliac nodes [16, 23]. The lateral pathway is the most common pathway, the anterior the least common. The paraaortic pathway, which bypasses the pelvic pathways, is the main regional pathway for ovarian and testicular cancer spread. Finally, cancer from the penis, ovary, vulva, and lower third of the vagina may spread by the inguinal pathway to the sentinel LNs for the superficial inguinal subgroup located where the great saphenous vein drains into the common femoral vein at the saphenofemoral junction. From here, cancer cells may reach the deep inguinal and external iliac groups.



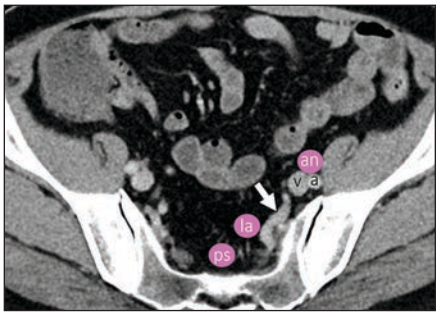
A



B



C



D

Fig. 1—Lymph node (LN) groups in pelvic cancers. a = artery, v = vein, la = lateral group, me = medial group, mi = middle group, ps = presacral group, an = anterior group.
A, Volume-rendered reformation of contrast-enhanced CT shows major LN groups. Inguinal LNs are located below inguinal ligament and divided into deep group within femoral sheath along common femoral vessels and superficial group anterior to inguinal ligament along saphenous vein and femoral vein. White circles show paraaortic nodes; yellow circles, common iliac nodes; blue circles, external iliac nodes; purple circles, internal iliac nodes; and orange circles, inguinal nodes.
B, Axial contrast-enhanced CT image of pelvis shows common iliac nodes and their relationship to common iliac artery and vein. Common iliac nodes are located caudad to aortic bifurcation and craniad to iliac bifurcation and subdivided into lateral and medial groups according to their location relative to common iliac arteries. Middle subgroup is located in lumbosacral fossa.
C, Axial contrast-enhanced CT image shows external iliac group with lateral, medial, and middle subdivisions and their relationship to external iliac artery and vein. External iliac nodes are located between common iliac bifurcation and inguinal ligament along external iliac artery.
D, Axial contrast-enhanced CT image shows internal iliac group subdivided in four major groups closely related to internal iliac artery and vein and branches. Presacral group is located anterior to sacrum and posterior to mesorectal fascia, anterior group is located anterior to proximal internal iliac arteries, and lateral sacral group is situated adjacent to lateral sacral artery (*arrow*). Hypogastric node is most cephalic nodal group located just inferior to sacral joint in **A**.

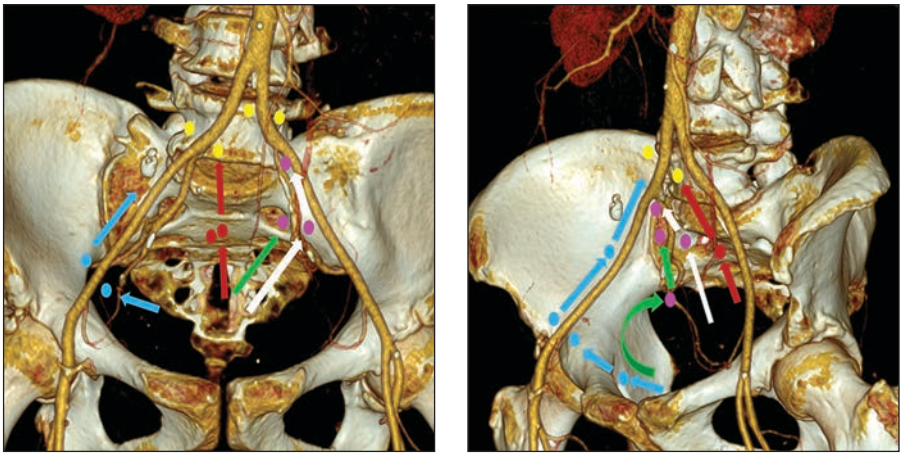


Fig. 2— Major lymphatic drainage pathways. **A** and **B,** Coronal (**A**) and left anterior oblique (**B**) volume-rendered reformation images of pelvis show lateral pathway (*blue arrows*) draining to obturator group of external iliac group (*blue circles*) from which lymph can reach rest of external iliac group. Internal iliac pathway (*white arrows*) drains to hypogastric nodes of internal iliac group at junction between external and internal iliac nodes (*purple circles*). Presacral pathway (*red arrows*) drains to presacral plexus (*red circles*), which is part of internal iliac chain. Anterior pathway (*green arrows*) drains to internal iliac chain and then further to hypogastric nodes. All nodes ultimately reach common iliac nodes (*yellow circles*).

TABLE 1: Regional and Nonregional Lymph Nodes in Common Pelvic Cancers

Nodes	Location of Cancer					
	Prostate	Testis	Ovary	Cervix	Endometrium	Bladder
Perivisceral	Regional	Regional	Regional	Regional[a]	Regional	Regional
Paraaortic	Nonregional	Regional	Regional	Nonregional	Regional	Regional
Common iliac	Nonregional[b]	Nonregional[c]	Regional	Regional	Regional	Regional
External iliac	Regional	Nonregional[c]	Regional	Regional	Regional	Regional
Internal iliac	Regional	Nonregional[c]	Regional	Regional	Regional	Regional
Inguinal	Nonregional	Nonregional[c]	Regional	Nonregional	Nonregional	Nonregional

Note—Data from [2] and [29].
[a]Perivisceral nodes for cervical cancer include paracervical and parametrial nodes.
[b]Common iliac lymph nodes represent secondary drainage lymph nodes in prostate cancer.
[c]Intrapelvic and inguinal nodes are considered regional only after inguinal or scrotal surgery [2].

Prostate Adenocarcinoma

The regional LNs for prostate adenocarcinoma are the true pelvic nodes below the bifurcation of common iliac arteries, whereas the common iliac, inguinal, and abdominal LNs are nonregional (Table 1). The lateral pathway to the obturator group and the internal iliac pathway to the hypogastric nodes is most commonly involved [24–26]. The obturator nodes are the most common sentinel LN group [27], from which disease can reach other external iliac nodes. When the obturator, external iliac, internal iliac, and presacral nodes are negative for metastatic disease, second-level skip metastases to common iliac or retroperitoneal nodes are usually not present [28]. Lymphatic spread by the presacral pathway is considered less common [26]. Bilateral nodal involvement is common and laterality does not affect the N category [1, 25]. Risk factors for LN involvement are high PSA and Gleason grade or score, number of biopsies positive for metastatic disease, and bilobar involvement [25, 29–31]. Pelvic CECT or MRI are typically used for LN evaluation in intermediate and high-grade disease and may be used to target biopsies [32]. Sentinel LN biopsy is not routinely used because of high variability in primary prostatic lymphatic drainage. Presence of lymphatic metastasis worsens biochemical and metastasis-free survival as well as overall survival [33, 34]. The N category has been emphasized in the AJCC 8th edition because N1 disease is automatically stage IV, whereas a T4N0M0 tumor has been downgraded to stage III. Therefore, presence of nodal metastasis may alter the treatment regimen to include adjuvant androgen-deprivation therapy. The natural lymphatic channels are disturbed after prostatectomy, which complicates classification between regional and nonregional nodes (Fig. 3). Nonetheless, nonregional adenopathy (e.g., mesorectal) should still be classified nonregional even after prostatectomy.

Testicular Cancer

Paraaortic LNs and their subdivisions (interaortocaval, periaortic, retroaortic, preaortic, paracaval, precaval, retrocaval nodes) and nodes along the spermatic vein are regional for testicular cancer. Lymphatic drainage is composed of superficial vessels carrying lymph from the tunica vaginalis testis and deep vessels draining the epididymis and body of testis. The lymph then follows the testicular blood vessels in the spermatic cord to reach the paraaortic nodes. Intrapelvic and inguinal LNs are considered regional only after inguinal or scrotal surgery [1]. Importantly, the greatest measurement in any dimension and not the maximal shortest nodal diameter should be reported. Presence of nodal metastasis upstages to minimum stage II, whereas N0 disease (stage I) may undergo active surveillance after initial radical orchiectomy. The differentiation of N1 to N3 is important because N3 equals stage IIC leading to a different treatment algorithm and prognostic group

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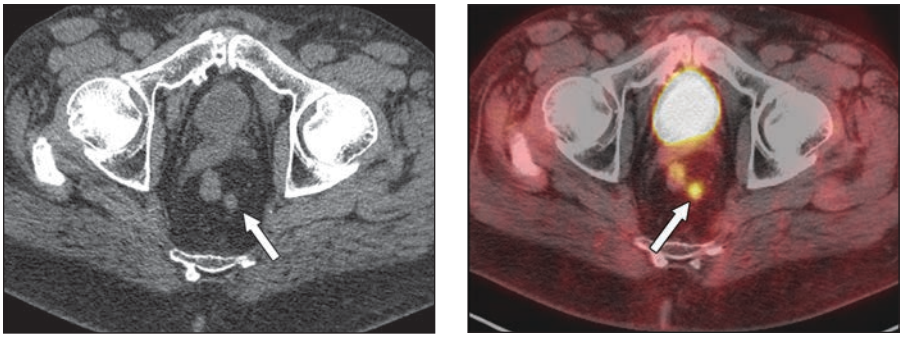


Fig. 3—73-year-old man with history of radiation therapy for prostate and lung cancer.
A and **B,** Whole-body CT (**A**) and fused FDG PET/CT (**B**) show single, round, FDG-avid (SUV_{max}, 5.5) mesorectal lymph node (*arrows*) that most likely represents recurrent nonregional prostate cancer lymph node metastasis.

[35]. CECT is used as the main modality for staging; MRI is mainly reserved for problem solving. Lymphatic spread is the most common pathway for testicular cancer because local invasion is hampered by the tunica albuginea testis. This has important clinical implications, because abdominal adenopathy may be the only manifestation of occult testicular cancer detectable in cross-sectional imaging of the abdomen and pelvis. Male patients with unexplained paraaortic adenopathy should therefore undergo testicular ultrasound (Fig. 4). LN metastases are typically soft-tissue density or necrotic in seminomas, whereas complex cystic nodes are common with nonseminomatous germ cell tumors [36]. Retroperitoneal LN dissection may be used as an alternative to chemotherapy or as part of a multimodality treatment regimen if sufficient surgical expertise is available [37]. Solid-to-cystic change after chemotherapy is associated with tumor differentiation to mature teratoma perhaps indicating need for surgery [36]. Staging of testicular cancer also includes serum markers α-fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase in addition to regular T, N, and M categories, because serum marker elevation has important prognostic implications [1, 38].

Penile Cancer

Regional LNs for penile cancer are the superficial and deep inguinal nodes. The N category primarily depends on clinical evaluation to determine palpability, visibility, mobility, and fixation rather than imaging [1]. Bilateral LN involvement signifies a worse prognosis. N1 disease is at least overall stage III, whereas N3 is stage IV. Like with vulvar cancer, there is a rich network of lymphatic ducts crossing the midline. The saphenofemoral node is the sentinel node. Skip metastases to the external iliac group are rare. CT and MRI may allow detection of pelvic adenopathy not amenable to palpation. Although most patients have palpable inguinal nodes at time of presentation, about half are reactive because of comorbid infection or inflammation [39]. On the contrary, small nodal metastases are present in approximately 20% of patients without palpable nodes [40]. Dynamic sentinel node biopsy has shown promising results although is not yet confirmed in larger studies [41].

Ovarian, Fallopian Tube, and Primary Peritoneal Cancer of Müllerian Duct Origin

Regional LNs for ovarian cancer include common iliac, external iliac, and internal iliac nodes and paraaortic, retroperitoneal, and inguinal nodes. Similar to testicular cancer, the greatest measurement in any dimension and not the shortest maximal diameter must be reported [1]. Importantly, laterality does not play a role in staging [42]. Certain tumors may have specific characteristics such as calcifications in serous ovarian carcinomas [43]; however, this is not included in the guidelines from the Federation of Gynecology and Obstetrics (FIGO) [44] or TNM classification [1]. The two main pathways are the paraaortic pathway following the gonadal vessels in the suspensory (infundibulopelvic) ligament to the paraaortic and paracaval nodes and the pelvic pathway in the broad ligament to the internal and external iliac nodes. The paraaortic LNs are most frequently involved (75–83%) as are the external iliac (59–60%) and obturator (53–55%) nodes in advanced ovarian cancer [45, 46]. Lymphatic metastasis may spread up or down in a retrograde fashion toward the aortic bifurcation from the paraaortic LN [22]. A third, less common pathway is spread along the round ligament to the deep inguinal LN and further to the external iliac nodes. CECT of the chest, abdomen, and pelvis can be used to evaluate for extent of disease and for posttreatment follow-up [47]. Laparoscopic evaluation, FDG PET scan, or MRI with DWI may also be used in nodal staging. Ascites caused by lymphatic obstruction is associated with increased risk of supradiaphragmatic LN involvement [48].

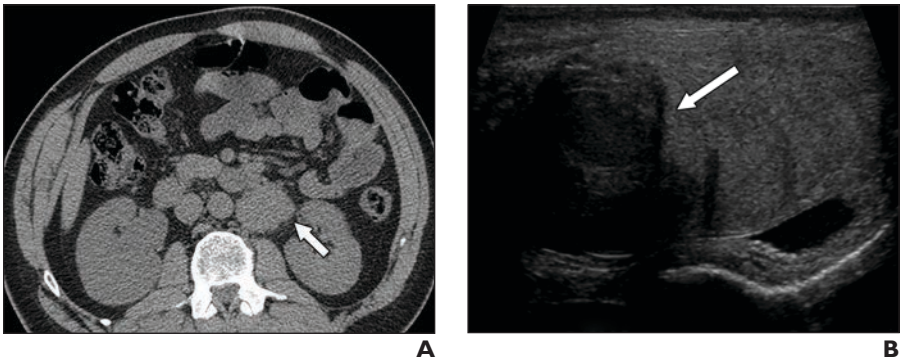


Fig. 4—47-year-old man with right flank pain and no significant medical history.
A, Unenhanced axial CT of abdomen shows isolated left paraaortic lymphadenopathy (*arrow*).
B, Subsequent gray-scale testicular ultrasound shows occult left testicular tumor (*arrow*).

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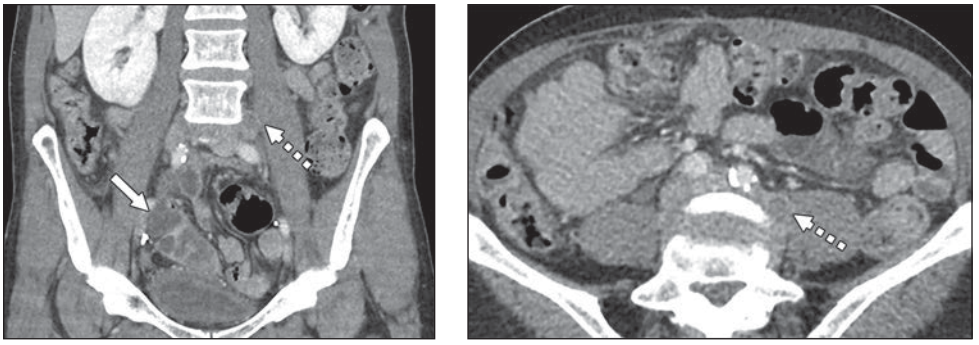


Fig. 5—54-year-old woman with no significant medical history presenting with pelvic pain.
A and **B,** Contrast-enhanced coronal (**A**) and axial (**B**) CT images of abdomen and pelvis show multilocated right ovarian primary cancer (*solid arrow*). Retroperitoneal lymphadenopathy (*dashed arrows*) measuring less than 10 mm in greatest dimension was only disease manifestation outside pelvis, which is classified as N1a (Federation of Gynecology and Obstetrics IIIA1i) and carries better prognosis than retroperitoneal adenopathy with concomitant peritoneal metastasis.

Isolated supradiaphragmatic LNs without ascites are more likely benign [48]. In patients with advanced ovarian cancer undergoing debulking surgery, ovarian metastases have been shown in mesenteric nodes by retrograde spread from the paraaortic to the mesenteric nodes or by tumor implants in the small bowel serosa [22, 49–51]. The incidence of ovarian metastases varies with histologic subtype and tumor grade. For well-differentiated and low-grade epithelial ovarian cancers, the incidence of LN metastases is around 3–4% and may increase to 20% in grade III tumors [52, 53]. Detection of extrapelvic disease is important because malignancy limited to the pelvis classifies as stage II, whereas spread outside the pelvis is at minimum stage III. Spread exclusive to the retroperitoneal nodes happens in less than 10% of ovarian carcinomas [54] and now classifies as stage IIIA1 instead of IIIC—an important update because of significantly better prognosis with overall survival of 58–84% [1, 55], compared with patients with concomitant retroperitoneal LN and peritoneal involvement in which overall survival is only 18–36% (Figs. 5 and 6) [44, 55–62]. Surgical management of ovarian epithelial cancer may involve sampling of both pelvic and paraaortic LNs in addition to hysterectomy and oophorectomy depending on the stage. Regional LNs and staging for fallopian tube cancers and cancers of the peritoneum (of Müllerian duct origin) are similar to ovarian cancer [1].

Cervical Cancer

Regional LNs for cervical cancer include paracervical, parametrial, internal iliac, external iliac, common iliac, presacral, and lateral sacral nodes. Contrary to ovarian cancer, the paraaortic LN are nonregional. Bilateral LN involvement is common and spread is typically sequential with common iliac, paraaortic, and inguinal nodes considered secondary metastatic sites. Skip metastases to the paraaortic LNs are rare [63]. The N category is divided into presence (N1) or absence (N0) of LN involvement. In early cancers, obturator and external iliac nodes are the most commonly involved and comprise around 80% of all detected nodal metastasis [64, 65] (Fig. 7). Lymphatic spread most commonly occurs via the lateral pelvic route along the lateral parametrium to reach the obturator nodes and the anterior route along the vesicouterine ligament to the hypogastric nodes. A smaller proportion of cancers may spread by the presacral route along the uterosacral ligament. Risk of pelvic adenopathy is correlated to the T category and parametrial involvement and implies a significantly worse prognosis [66]. Five-year-survival rate decreases from 57% in patients without LN involvement to 34% in patients with pelvic adenopathy and to 12% in patients with paraaortic LN involvement [67]. The FIGO staging system, traditionally made according to clinical examination, now allows imaging to play a more central role in assigning an N category [68]. FIGO subdivides stage IIIC to include regional and paraaortic LNs, whereas TNM classification considers paraaortic LN involvement to be nonregional metastasis and stage IVB [1]. Pelvic MRI may complement the clinical evaluation of local invasion, whereas FDG PET/CT or CECT of the chest, abdomen, and pelvis is typically used to detect LN metastasis [69]. Suspicious LNs may be further evaluated with imaging-guided biopsy before surgical LN debulking or radiation treatment. FDG PET/CT may also be used in locally advanced disease to assess for LN involvement before initiating primary chemotherapy. If surgical expertise is available, sentinel LN biopsy may help to reduce morbidity from complete pelvic LN dissection [70, 71].

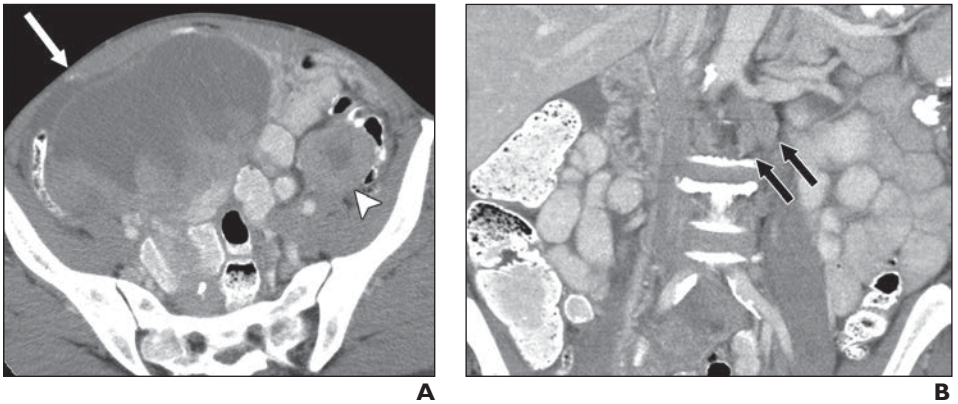


Fig. 6—53-year-old woman with abdominal pain and cachexia.
A and **B,** Contrast-enhanced axial (**A**) and coronal (**B**) CT images show large complex cystic and solid right adnexal mass (*arrow*, **A**) with ascites and heterogeneous mass (*arrowhead*, **A**) in left hemipelvis, most consistent with right ovarian cancer and left intrapelvic metastasis, indicating stage IIB (disease limited to pelvis). However, patient also had suspicious left paraaortic lymph nodes (*arrows*, **B**) outside pelvis, which upgrades overall stage to stage IIIA1.

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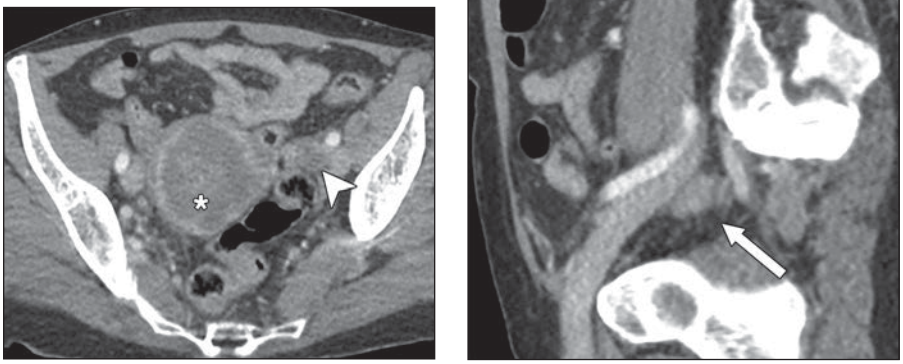


Fig. 7—61-year-old woman with no significant medical history presenting with abdominal pain. **A** and **B,** Contrast-enhanced axial (**A**) and sagittal (**B**) CT images show heterogeneous cervical mass (*asterisk*, **A**) with invasion into uterus, consistent with primary cervical carcinoma. Enlarged left parametrial (*arrowhead*, **A**) and right external iliac (*arrow*, **B**) regional nodes were seen (category N1).

Endometrial Cancer

The regional LNs for endometrial cancer are the perivisceral, internal iliac, external iliac, common iliac, and paraaortic nodes. Lymphatic dissemination is the most common means of dissemination and is more complex and less orderly than in other pelvic cancers. The middle and inferior aspects of the uterus typically drain via the lateral pathway (parametrial nodes) to the obturator group, which is the most commonly affected group. Fundal and upper corpus uteri cancers use the internal iliac pathway to the hypogastric, common iliac, and paraaortic nodes [72, 73]. Isolated paraaortic nodes may also be directly involved by lymphatic spread following the gonadal vessels [16]. Although the inguinal LNs may potentially receive lymph drainage along the round ligament, these nodes are considered nonregional (category M1, stage IVB). The most common pathways of spread are the lateral and the internal iliac pathways. Presence of LN metastasis is an important prognostication factor and correlates with tumor size and grade, presence and depth of invasion into the myometrium, invasion into the cervical stroma and adnexa, patients aged older than 60 years, nonendometrioid histology, and lymphovascular involvement (Fig. 8) [74, 75]. Paraaortic involvement (category N2) is more serious than pelvic involvement alone as indicated by the FIGO and TNM classifications [1, 74]; overall survival has been reported to decrease from 75% in patients with isolated pelvic LN metastasis to 38% if paraaortic nodes were also involved [76]. Contrast-enhanced pelvic MRI may be valuable for local assessment but less helpful to detect nodal metastases. As a consequence, pelvic nodal evaluation with or without paraaortic dissection is recommended by National Comprehensive Cancer Network to stage apparent uterine-confined disease [77, 78], although a meta-analysis found no survival benefit in early-stage uterine cancer undergoing nodal dissection [79]. Sentinel LN mapping may also be used in centers with sufficient surgical expertise to reduce the morbidity from LN dissection. CECT of the chest, abdomen, and pelvis is reserved for staging of higher grade or incompletely staged carcinomas and FDG PET/CT for cases with suspected metastasis.

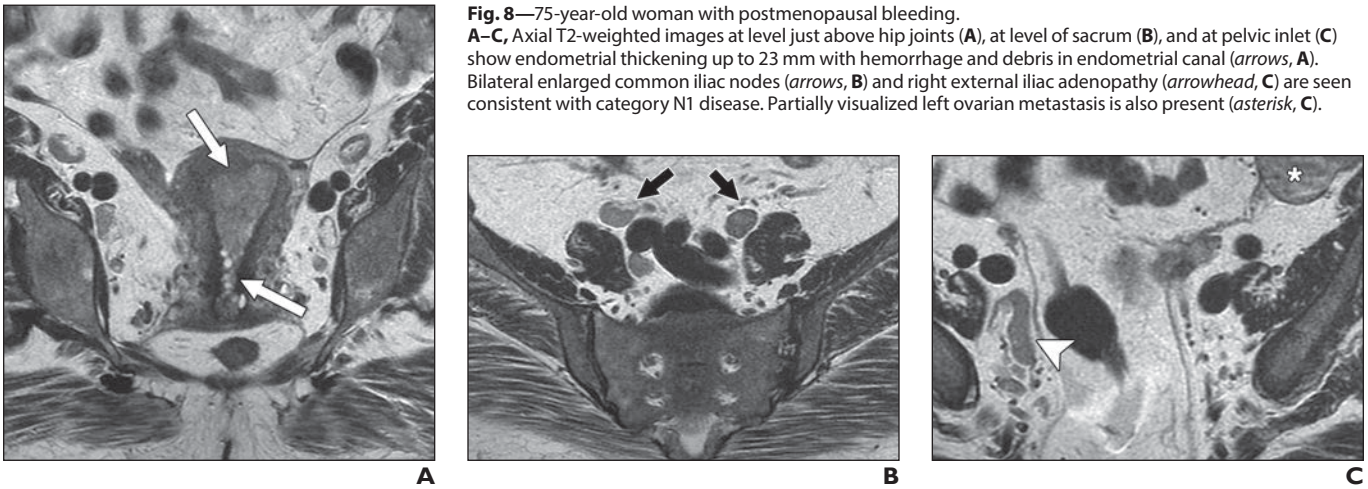


Fig. 8—75-year-old woman with postmenopausal bleeding.
A–C, Axial T2-weighted images at level just above hip joints (**A**), at level of sacrum (**B**), and at pelvic inlet (**C**) show endometrial thickening up to 23 mm with hemorrhage and debris in endometrial canal (*arrows*, **A**). Bilateral enlarged common iliac nodes (*arrows*, **B**) and right external iliac adenopathy (*arrowhead*, **C**) are seen consistent with category N1 disease. Partially visualized left ovarian metastasis is also present (*asterisk*, **C**).

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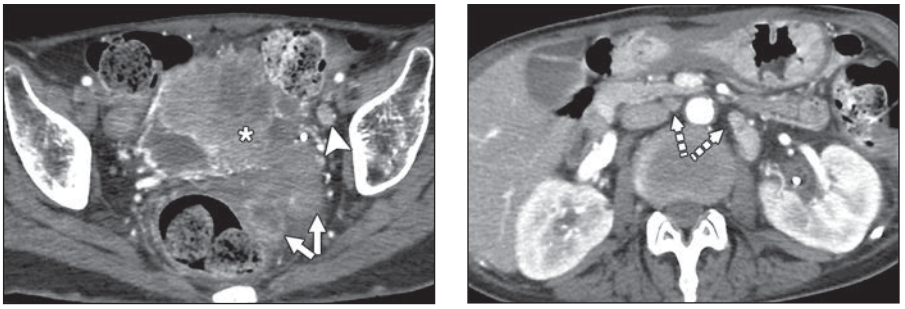


Fig. 9—59-year-old woman with left flank pain. **A** and **B,** Axial contrast-enhanced CT images of pelvis (**A**) and abdomen (**B**) show fungating urinary bladder tumor (*asterisk*, **A**) with extravesical extension and obstruction of left ureterovesical junction causing left hydronephrosis (partially visualized). Regional left internal nodes (*arrows*, **A**) and left external node (*arrowhead*, **A**) and bilateral nonregional paraaortic nodes (*dashed arrows*, **B**) are involved (category M1a).

Vaginal Cancer

Regional LNs for the upper two-thirds of the vagina are the pelvic nodes. The lateral and internal iliac pathways drain into the obturator and internal iliac nodes, which are the primary drainage sites. Inguinal and femoral nodes are regional for cancers in the lower third of the vagina. Primary vaginal cancer is rare and comprises about 3% of all gynecologic cancers [80]. Secondary vaginal involvement from cervical, vulvar, and metastatic cancer is much more common and accounts for more than 80% of vaginal tumors and should be carefully considered before diagnosing vaginal cancer [16]. Only cancers confined to the vagina without extension to the cervix or vulva are considered primary vaginal cancers [80]. The N category is simplified into presence or absence of regional LN metastasis and neither laterality nor number of LNs are taken into account [1]. N1 upgrades overall stage to stage III or IV depending on the T and M categories. Radiation therapy is the preferred treatment used alone or in combination with surgery [80, 81].

Vulvar Cancer

The inguinofemoral nodes are regional for vulvar cancer. The saphenofemoral junction node is the sentinel node, from which disease can reach the deep inguinal nodes. Pelvic lymphadenopathy is considered M1 disease. Lymphatic networks around the vulva extend across the midline and laterality of LN metastasis is therefore excluded as a TNM criterion [1]. Staging of vulvar cancer includes both clinical and imaging evaluation of the inguinal nodes because clinical evaluation is not always reliable [82, 83]. Ultrasound can help guide inguinal node biopsy, whereas CT is typically included in T2 (tumor size > 2 cm) or N3 disease because of greater risk of pelvic metastasis. MRI is preferred to evaluate the primary tumor and inguinal nodes. Although FDG PET/CT may be used to detect distant metastases, limited data are available on the utility in detection of groin metastasis, and false-positive results for LNs occur [84]. The N category is the most essential prognostic factor and is divided into several categories depending on size, number, morphology, and extracapsular spread [1]. The 5-year-survival rate for patients without lymphadenopathy is around 90%, which drops to 36% in patients with three to four affected LNs and 0% when seven or more nodes are involved [85]. Similarly, patients with metastatic nodes smaller than 5 mm in maximal short-axis diameter have a 5-year-survival rate of 90%, which decreases to 45% for 5–15 mm nodes, and 20% with metastases larger than 15 mm or extracapsular extension [86]. Extracapsular extension is perhaps the most important prognostic factor and decreases 5-year-survival rate from 80–81% in patients with intranodal involvement to 25–31% with extranodal extension [86–88]. Sentinel node techniques have minimized risk of lymphedema and wound infection compared with radical groin excision [89].

Urinary Bladder Cancer

The true pelvic nodes below the bifurcation of the common iliac arteries are regional for urinary bladder cancer [1]. Even when the tumor is unilateral, it is common to see bilateral nodal involvement [90]. The classic lymphatic pathway of spread uses the perivesical nodes to reach the internal and external iliac nodes, which represent primary regional drainage stations [1, 91]. The obturator group of the external iliac nodes and internal iliac group are the most common sentinel node groups [90, 92]. Bladder cancers from the superolateral wall tend to involve the obturator nodes, whereas tumors located in the anterior wall, neck, and fundus primarily drain to the internal iliac nodes. A minority of bladder neck and fundus cancers may use the presacral route to reach the presacral nodes [16, 20]. If the iliac nodes are free of tumor, more cranial metastases are unlikely. The N category is unchanged in TNM classification and distinguishes between presence of one (N1) or more (N2) true pelvic LN metastasis and involvement of common iliac nodes (N3), which constitutes secondary drainage pathways [1]. CT and MRI are used for staging; MRI is particularly useful to assess local invasion and nodal involvement [93]. FDG PET/CT is of limited value because of excretion of tracer in urine. Patients with more advanced locally invasive disease have greater risk for LN involvement and need further staging. If no nodal metastases are identified, the patient may be a candidate for curative treatment with radical surgery or radiation [94]. The M category has been updated to include nonregional LNs above the common iliac nodes (M1a) and other distant metastasis (M1b), usually lung, bones, and liver (Fig. 9). Presence, size, and number of involved nodes and extracapsular extension has significant negative impact on prognosis and can change treatment from surgery to chemoradiotherapy [95, 96]. Noninvasive superficial tumors may be treated with either resection, intravesical chemotherapy, or both. These patients do not need further staging given the low risk of tumor metastasis.

Urethral Cancer

Inguinal and pelvic LNs are regional nodes for urethral cancer. Laterality does not affect the N category. Anterior tumors are more likely to reach the inguinal nodes whereas posterior tumors tend to spread to pelvic nodes first [97]. Regional LN involvement is seen in 25–33% of cases [98, 99], and distant metastasis at the time of presentation is rare and seen in up to 6% [97]. CT and MRI are useful to evaluate local invasion and nodal disease.

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The N category has been updated to distinguish between metastasis in single (N1) or multiple (N2) nodes. A combination of chemotherapy, radiation treatment, and surgery may be needed for optimal treatment although the exact regimens are less clearly defined because of sparsity of literature given the disease rarity. Locoregional disease control remains the most important aspect of management.

Conclusion

A combination of size, shape, border, internal architecture, number, and tumor-specific characteristics should be used to differentiate between malignant and benign LNs. Knowledge of organ-specific nonregional and regional LNs is essential to provide accurate staging for urogenital cancers. Lymphatic metastasis is an important mode of tumor dissemination because presence of nodal involvement may significantly alter management. Staying up to date with the 8th edition of AJCC TNM classification helps ensure appropriate management.

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