

**American College of Radiology  
ACR Appropriateness Criteria®**

**Clinical Condition:**                      **Pretreatment Staging of Invasive Bladder Cancer**

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
X-ray chest	9	Effective screen of site of most common hematogenous metastasis.	Min
CT abdomen and pelvis without and with contrast (CT urography)	8	Pre- and post-contrast with excretory phase.	High
MRI pelvis without and with contrast	8	See comments regarding contrast in text under "Anticipated Exceptions."	None
X-ray intravenous urography	5		Med
CT abdomen and pelvis with contrast	5	May be appropriate if done in combination with IVU.	High
NUC Tc-99m bone scan whole body	3	Probably not indicated unless bone pain is present.	Med
MRI abdomen without and with contrast	3	Probably not indicated unless CT is inconclusive or in patients with renal failure.	None
CT chest with contrast	3	Probably not indicated unless chest radiograph is suspicious.	Med
US pelvis (bladder)	3	Limited visualization beyond the bladder wall.	None
FDG-PET whole body	2		High
CT pelvis without contrast	2		Med
MRI pelvis without contrast	2		None
X-ray radiographic survey whole body	1		Med
<b>Rating Scale:</b> 1=Least appropriate, 9=Most appropriate			<b>*Relative Radiation Level</b>

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## PRETREATMENT STAGING OF INVASIVE BLADDER CANCER

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### **Summary of Literature Review**

In 2006, an estimated 61,420 new cases of bladder cancer will occur in the U.S., and 13,600 will die of the disease. The lifetime probability of developing invasive bladder cancer is 1 in 28 for men and 1 in 88 for women in the U.S. [1]. Bladder cancer has a high tendency toward multifocality at presentation and at recurrence after treatment [2]. Transitional cell carcinoma of the bladder (TCCB) is the most common cell type, accounting for greater than 90% of all cases of bladder cancer [3]. The average age of patients with TCCB in the U.S. is 65 at diagnosis. Almost 80% of patients with TCCB present with hematuria, which is either gross or microscopic and is usually painless and intermittent [4].

TCCB 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. The most common sites of hematogenous spread are lung, bone, liver, and brain [5,6]. Superficial lesions do not metastasize until they invade deeply and may remain indolent for many years. 70%-85% of TCCB is superficial at presentation, confined to the mucosa or submucosa, without muscle invasion [3,4]. Only invasive tumors will be considered here. The imaging workup begins after the bladder tumor has been identified cystoscopically and has been proven by biopsy.

TCCB is staged by its extension at presentation and graded I-IV according to microscopic (pathologic) criteria of aggressiveness. The standard staging systems for bladder cancer are the Jewett Strong Marshall (JSM) system and the Tumor Node Metastasis (TNM) system. In the classic JSM staging system, stage A tumors are

confined to the lamina propria, while stage B involves the muscularis propria. Stage B is divided into superficial and deep infiltration of the muscularis. Extension of tumor beyond the serosa is stage C, and stage D is characterized by involvement of regional then distant nodes or other organ involvement. The division of stage B into superficial and deep is based on Jewett's observation of an 80% 5-year survival rate for patients with B1 lesions compared with 8% for patients with B2 lesions in a small series [4-7]. The TNM system, which is now being used more commonly, encompasses the status of the primary tumor (T), the lymph nodes (N), and any metastasis (M) (Appendix I).

Tumor grade relates directly to depth of invasion but inversely to curability, so that the 5-year survival rate of patients with grade III and IV superficial tumors is only half that of patients with low-grade I and II superficial tumors (37% vs 71%) [4]. Patients with invasive tumors with no nodal involvement have a 5-year survival rate of 28%, and those with nodal involvement have a 5-year survival rate of 11% [8].

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 [3,4,8]. Radical cystectomy with pelvic lymphadenectomy remains the standard treatment for muscle-invasive urothelial tumors of the bladder. [9].

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 [4,10,11]. The principal task is to identify extravesical spread. Unfortunately, none of the imaging modalities can identify microscopic spread to muscle layer, perivesical fat, lymph nodes, or other organs.

Cystography, pelvic angiography, lymphangiography (LAG) with or without percutaneous fine-needle aspiration (FNA) biopsy, and radiographic whole-lung laminography are no longer routinely used in staging TCCB since the advent of cross-sectional imaging [5-7,12].

### **Radiographic Skeletal Survey**

Because radiographic skeletal survey sensitivity is so low, in the range of 17%-60%, it is also no longer used [6]. Radiographs are only useful at a site of increased activity on radionuclide bone scan or local bone pain [6].

### **Intravenous Pyelography**

Intravenous pyelography (IVP) was once the best screening exam for upper-tract disease and was the most

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sensitive test in detecting small urothelial lesions [4,5,7,10,11,13]. With widespread use of CT urography, the role of IVP in evaluating the renal collecting system and ureter is declining [14]. Although only 60% of known bladder tumors are visualized by IVP, obstruction of a ureteral orifice at the level of the ureterovesical junction is usually due to invasive bladder tumor, if urolithiasis is excluded [15,16]. Any degree of ureteric obstruction is significantly associated with both decreased overall survival rates and decreased tumor-free interval [17]. Ureteral obstruction can be demonstrated by CT urography.

Yousem et al [13] found synchronous TCC above the bladder in 14 of 597 (2.3%) patients with TCCB, 8 (1.3%) with ureteral TCC, and 6 (1.0%) with renal TCC. They reported a range of incidence of synchronous upper-tract lesions between 0% and 6.4% and stated that IVP “must be performed” when TCCB is first diagnosed. Retrograde ureteropyelography is also excellent for detailed study of the urothelium, especially when IVP is contraindicated or the results are equivocal [13]. However, recent studies have reported an incidence of 1.1% in which IVP was able to diagnose only 66% of cases [18].

### **Chest Radiograph and Computed Tomography**

All patients with invasive TCCB need pulmonary evaluation. The chest radiograph is an effective, inexpensive, low-morbidity screen [6,7,19]. Patients with equivocal chest radiograph and those thought to be at high risk should have standard chest computed tomography (CT) [6].

### **Radionuclide Bone Scan**

Radionuclide skeletal scintigraphy has a sensitivity ranging from 69%-100% but is highly nonspecific [6,7]. Solitary bone lesions in patients with underlying primary malignancies are due to metastases in only 55% of cases. The incidence of bone metastases in bladder cancer patients increases with tumor stage at time of diagnosis, from 5% of patients with early-stage invasive tumors to 15% of patients with locally advanced disease [6]. A 4.6% positive rate was found in 458 bone scan studies [20]. Since therapy was affected in only 0.9%, the conclusion was that scintigraphy has “no place in the routine preoperative staging of bladder carcinoma” [20]. Bone scanning may be limited to patients with bone pain and/or elevated levels of serum alkaline phosphatase [6]. Further evaluation with radiographs and/or magnetic resonance imaging (MRI) can be helpful, and, if necessary, guided needle biopsy can be definitive [6].

### **Ultrasound: Transabdominal, Transrectal, and Transurethral**

The distended bladder is a superb acoustic window. Size and location of the tumor affect detectability with ultrasound (US). Lesions smaller than 0.5 cm that are flat and/or near the bladder neck can be easily missed [7].

Nevertheless, detection rates of over 95% are reported [7]. US is limited in visualization beyond the bladder wall and cannot detect nodal enlargement [7,21]. Also it cannot differentiate wall edema, prominent mural folds, postoperative changes, blood clots, or benign masses [7]. Color Doppler with transrectal ultrasound (TRUS) adds nothing to evaluation of stage or grade [22].

TRUS is excellent for evaluating prostate and seminal vesicles [7]. Transurethral ultrasound (TUUS) is more sensitive than transabdominal ultrasound (TAUS), and TRUS and is more accurate in staging depth of wall involvement but is not widely available [6,7,22]. TRUS provides local staging information with 62%-100% accuracy, highest for superficial tumors [5,21,23]. TRUS staging is unreliable for tumors larger than 3 cm and tumors with calcifications, largely because of acoustic shadowing [21]. It is poor (70%) for evaluating extravesical spread [23]. Three-dimensional US rendering is yet another new diagnostic tool with potential to aid in discriminating superficial from muscle-invasive tumors [24].

Endoluminal ultrasound (ELUS), also known as intravesical ultrasound (IVUS), uses a miniature, high-frequency transducer introduced by a rigid cystoscope for intravesical evaluation [25,26]. ELUS is both sensitive and specific in detecting muscle invasion in bladder cancer, with rates comparable to those of TUUS, and it provides greater bladder wall detail. Limitations include difficulty in depicting the tumor base in certain locations and in depicting the depth of invasion in tumors larger than 2 cm with broad bases [25,27].

With progression from TAUS to TRUS to TUUS and ELUS, the diagnostic accuracy of US has improved [6]. In 214 new cases of TCCB with pathological correlation, Fang et al [28] reported overall accuracy of 78.6% in local staging with TAUS. They had 9.8% overstaging and 11.7% understaging. Their accuracy was 87% for stage A, 60.5% for stage B, 41.2% for stage C, and 83.3% for stage D. Akdas et al [29] reported an overall accuracy of 96.5% in diagnosing and staging bladder tumors with TUUS in 104 patients: 96.2% in stage Ta-T1 lesions, 100.0% in T2 lesions, 91.7% in T3 lesions, and 100.0% in T4 lesions. There was no discussion of N or M staging.

Studies have shown ELUS to be 100% sensitive, 75% specific, and 84% accurate in detecting muscle invasion in bladder cancer, with both a positive and negative predictive value of 100% [25,26]. 3-D rendering had a 66% staging accuracy for pTa tumors, 83% for pT1 tumors, and 100% for >pT1 or muscle invasive tumors [24].

### **Computed Tomography of the Pelvis and Abdomen**

The primary contribution of conventional CT is distinguishing tumors that are organ-confined from those with extravesical extension [6,7,10]. It demonstrates

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bulky thickening of the bladder wall, perivesical extension, lymph node enlargement, and distant metastases very well [7,8,30,31]. Identification of the primary lesion can be difficult in the areas of the bladder neck and dome [30]. CT cannot distinguish inflammatory postoperative or postradiation edema or fibrosis from tumor and cannot assess depth of invasion of the bladder wall [7,8,10,30]. CT is also unable to detect microscopic or small-volume extravesical tumor extension and metastases in nonenlarged lymph nodes [32].

Voges et al [31] found an accuracy of 50% in CT staging of pT2(B1) and pT3a(B2) (*p*=pathologic) lesions, understaging of 29.5% of cases, and overstaging of 20.5% of cases. Staging of pT3b(C) lesions was 46.2% accurate, with 53.8% understaged. Of 16 pT4 lesions, one (6.3%) was correctly diagnosed and 15 were understaged. All had infiltration into prostate or seminal vesicle.

Barentsz et al [21] reviewed 437 cases in the literature using CT to stage TCCB. Overall accuracy ranged from 40%-85%, with correct staging of nodes and metastases ranging from 82%-97%. For extravesical extension, accuracy ranged from 40%-92% with a mean of 74%. Paik et al found overall accuracy of 54.9%, with 39% understaging and 20.7% false negative for extravesical spread. Preoperative CT staging altered planned surgical management in only 3.7% of cases [32]. Multi-detector row helical CT with IV contrast and 60-second delayed images is a highly sensitive and specific method for detecting bladder cancer and associated perivesical invasion, particularly when there is a greater than 7-day time interval between intervention and CT. Its sensitivity and specificity are up to 92% and 98% in this setting, respectively. [33].

Various methods for bladder distension have been studied to increase the accuracy of detecting muscle invasion in bladder cancer on CT imaging. These include evaluating the bladder filled with urine, urine opacified with iodinated contrast material, and air [34]. These methods have accuracies of approximately 84%, 89% and 93% respectively, with overstaging and understaging percentages comparable, ranging from 4%-7% for overstaging and 2%-4% for understaging [34].

In addition to conventional CT, helical CT with multiplanar reformation (MPR), 3-D reconstruction (3DR), and virtual cystoscopy (CTVC) have also been described in the literature. Using helical CT and MPR, Wang et al [35] found an overall accuracy of 87.7% in CT staging of all stages of bladder cancer and, more specifically, 76.9% for Ta-T2 lesions and 94.7% for T3-T4 lesions. Pathologic lymph nodes were confirmed in six of seven cases. MPR was shown to be useful in evaluating the origin and extent of extravesical invasion, as well as tumor relationship to the ureter. A study by Browne et al [36] found that the sensitivity of 3DR in detecting bladder carcinomas of all stages was 76.9%. CT cystography and

virtual cystoscopy may find use in patients unable to tolerate traditional cystoscopy, in those for whom traditional cystoscopy failed, or in those with narrow-necked bladder diverticula that may contain lesions [36]. Sensitivity for identifying 0.5 mm masses has been reported to be 100%, and for all patients' sensitivities of 95% in detecting neoplasm with an accuracy of 88% have been reported with CT cystography. Virtual cystoscopy provides comparable views to traditional cystoscopy but may not add additional diagnostic data in patients able to tolerate traditional cystoscopy [36].

Multidetector CT urography provides collecting system opacification comparable to that of IVP [37].

A recent 200-patient study conducted at a fast-track hematuria clinic demonstrated 93% sensitivity and 99% specificity for bladder cancer detection by CT urography, rates similar to those of traditional cystoscopy. As upper tracts are increasingly evaluated by CT for hematuria, the addition of lower-track evaluation adds negligible cost and avoids the discomfort that may be associated with traditional cystoscopy, thereby streamlining the evaluation of patients with hematuria [38].

Absolute degree of contrast enhancement of tumor may correlate with histologic grade in bladder transitional cell carcinoma, as demonstrated in a study of 65 patients. Although interesting, this finding may find greater application in research of tumor angiogenesis and regression post antiangiogenesis therapy [39].

### Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is superior to CT in demonstrating the lower pelvic anatomy. There is striking inherent contrast between the bright perivesical fat and the intermediate-signal-intensity bladder wall on T1-weighted images. Multiplanar imaging and gadolinium enhancement improve visualization of tumors on T1-weighted images [21,40-44]. Fat suppression techniques can help identify perivesical extension [44]. Deep-muscle invasion presents as disruption of the low-signal-intensity bladder wall by tumor, which usually is of higher signal intensity [7,10,30,41,45]. After intravenous gadolinium chelates, TCCB shows earlier and greater enhancement than normal bladder or nonmalignant tissue [40,41].

Most recently, Tekes et al [46] demonstrated staging accuracies of 85% and 82% in differentiating superficial from muscle invasive tumors and organ-confined from non-organ-confined tumors, respectively. Additionally, the accuracy of pathologic lymph node detection was 96%. Overstaging occurred in 32% of cases. The length of time elapsed between transurethral resection and MRI did not affect staging accuracy [46]. Barentsz et al [21] reviewed 340 cases using MRI. The T staging of tumor was accurate in 73%-96% of cases, and the staging of nodes and metastases was accurate in 73%-98% of cases. The best staging results were with gadolinium-enhanced

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T1-weighted fast spin-echo sequences 14 seconds after injection. These authors suggest that following cystoscopic identification of tumor, MRI should be used as the initial imaging modality to stage the tumor. Hayashi et al [9] reviewed 71 patients using gadolinium-enhanced endorectal surface coil and reported an 83% overall staging accuracy. Muscle invasion was diagnosed with 87% accuracy, 91% sensitivity, and 87% specificity. Deserno et al [47] found that MRI performed with ferumoxtran-10 (ultrasmall superparamagnetic iron oxide) contrast demonstrated an accuracy in pathologic lymph node detection of up to 92% and a sensitivity of up to 96%.

As with CT cystography and virtual cystoscopy, there has been interest in MR cystography (including multiplanar reconstructions and virtual cystoscopy) as a replacement for traditional cystoscopy and to assist in staging. High diagnostic accuracy has been demonstrated, with sensitivity of 90.7% and specificity of 94.0% using combined virtual cystoscopy and multiplanar reconstructions. These results are comparable to those of CT, and MR cystography is especially promising in special cases where traditional cystoscopy may be contraindicated (urethral stricture), or suboptimal (narrow-necked bladder diverticula) [48]. Similar conclusions were previously drawn by Lammle, et al [2].

### **Computed Tomography versus Magnetic Resonance Imaging**

Noting that MRI appears to have slightly better sensitivity and specificity than CT, See and Fuller [6] felt that its benefits were offset by its increased cost and the length of exam. They limited their use of MRI to equivocal cases. Cummings et al [4] felt that use of CT and MRI may be limited to tumors larger than 5 cm and to solid rather than papillary lesions. Klein and Pollack [10] stated that MRI and CT have similar accuracy for detecting perivesical fat invasion and that the most notable advantage of MRI is its apparent ability to differentiate between superficial and deep invasion of the bladder wall. Barentz et al [21] concluded that MRI is the best technique for staging invasive tumors, as it was slightly better than or equal to CT at differentiating T3a from T3b lesions and superior to CT for tumors at the bladder dome or base. In deeply infiltrating tumors (stages T3b-T4b), they asserted that MRI “is generally agreed to be the most accurate staging technique,” and “when MRI is available, CT is no longer needed.” Recently, MacVicar [8] in a review article stated that MRI is the investigation of choice for local staging and is the preferred technique in postcystectomy and radiation therapy follow-up. Robinson et al [49] in a review of 143 patients prior to radiotherapy confirmed that MRI is superior to clinical staging and provided additional prognostic information.

Both CT and MRI rely on enlargement of lymph nodes as a criterion for metastasis, but they are limited in detecting

metastases to normal-sized nodes. This may change as further studies may corroborate the early results of using lymphotropic nanoparticle-enhanced MRI for detecting micrometastasis in nonenlarged lymph nodes [50]. Lymph node metastasis in patients with superficial tumors (less than T3) is rare, but if deep muscle layers are involved (T2b) 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, a fine-needle aspiration (FNA) biopsy should be considered. Both CT and MRI are equivalent in their ability to detect nodal enlargement [51].

### **Positron Emission Tomography and Radioimmunoscintigraphy**

Conventional positron emission tomography (PET) using <sup>18</sup>F-fluorodeoxyglucose (FDG) is unsuitable for imaging bladder tumors because of its high urinary excretion, although it may have a role in detection of recurrent or metastatic disease [52]. FDG-PET is 67% sensitive, 86% specific, and 80% accurate in detecting pathologic lymph nodes in patients with bladder cancer, which exceeds both CT and MRI [53]. A study correlating FDG-PET and CT results in the same patients reported sensitivity, specificity, and accuracy of 60%, 88%, and 78%, respectively, in nodal and metastasis staging, suggesting improved distant metastatic and locoregional node staging [54]. <sup>11</sup>C-choline PET when compared with CT promises slightly increased accuracy of lymph node staging (63.0% vs 88.9%,  $p < 0.01$ ) and may avoid false positive results for lymph nodes due to reactive hyperplasia when compared with CT, although further evaluation with this agent is needed to confirm these findings [55].

The experimental modality of radioimmunoscintigraphy using anti-MUC1 mucin monoclonal antibody C595 labeled with various radiotracers has been shown to be up to 90% sensitive in detecting invasive cancer and 88% sensitive in detecting distant metastases in sites such as lymph node, bone, and lung. [56,57].

### **Recommendations**

With the increasingly widespread use of CT urography, the role of IVP is declining. CT urography not only is effective for local staging but also provides concomitant evaluation of the liver as well as nodal status. Chest CT can be limited to those with equivocal chest radiographs. Radionuclide bone scan is not indicated without bone pain and/or elevated serum alkaline phosphatase levels. Radiographs can be limited to sites of increased uptake and/or bone pain. US is useful for local tumor (T) staging; TUUS and ELUS appear to be equally effective in this regard. Contrast-enhanced MRI is preferred over CT for local staging and is equivalent in assessing regional lymph nodes. CT or MR virtual cystoscopy may be used in specific cases such as evaluation of narrow-necked bladder diverticula, which may be poorly evaluated by traditional cystoscopy, but they are not indicated in the

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majority of patients. CT and MR virtual cystoscopic techniques may also be of use in those unable to tolerate traditional cystoscopy and may be considered to streamline evaluation of hematuria, combining staging and screening. MRI of the head is needed only if neurological symptoms are present. PET studies to date are not proven to enhance pretreatment staging and are not indicated until further validation and studies are completed.

### Anticipated Exceptions

Nephrogenic systemic fibrosis (NSF), also known as nephrogenic fibrosing dermopathy) was first identified in 1997 and has recently generated substantial concern among radiologists, referring doctors and lay people. Until the last few years, gadolinium-based MR contrast agents were widely believed to be almost universally well tolerated, extremely safe and non-nephrotoxic, even when used in patients with impaired renal function. All available experience suggests that these agents remain generally very safe, but recently some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed NSF [58-60], a syndrome that can be fatal. Further studies are necessary to determine what the exact relationships are between gadolinium-containing contrast agents, their specific components and stoichiometry, patient renal function and NSF. Current theory links the development of NSF to the administration of relatively high doses (eg, >0.2mM/kg) and to agents in which the gadolinium is least strongly chelated. The FDA has recently issued a “black box” warning concerning these contrast agents ([http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca\\_200705HCP.pdf](http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705HCP.pdf)).

This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated GFR <30 mL/min/1.73m<sup>2</sup>), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s) [59].

### Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document.

Relative Radiation Level Designations	
Relative Radiation Level	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv

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## Appendix 1. Staging of Bladder Cancer [61]

### Primary tumor (T)

Stage	Sub-Stage	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary carcinoma
Tis		Carcinoma in situ (ie, flat tumor)
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
	T4a	Tumor invades the prostate, uterus, vagina
	T4b	Tumor invades the pelvic wall, abdominal wall

[Note: The suffix “m” should be added to the appropriate T category to indicate multiple lesions. The suffix “is” may be added to any T to indicate the presence of associated carcinoma in situ.]

### Regional lymph nodes (N)

Stage	Sub-Stage	Definition
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single lymph node, $\leq 2$ cm in greatest dimension
N2		Metastasis in a single lymph node, $>2$ cm but $\leq 5$ cm in greatest dimension; or multiple lymph nodes, $\leq 5$ cm in greatest dimension
N3		Metastasis in a lymph node, $>5$ cm in greatest dimension

### Distant metastasis (M)

Stage	Sub-Stage	Definition
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

## Appendix 2. Stage Grouping [61]

Stage 0a	Ta, N0, M0
Stage 0is	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2a, N0, M0
	T2b, N0, M0
Stage III	T3a, N0, M0
	T3b, N0, M0
	T4a, N0, M0
Stage IV	T4b, N0, M0
	Any T, N1, M0
	Any T, N2, M0
	Any T, N3, M0
	Any T, Any N, M1

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