

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

Clinical Condition: Follow-up Imaging of Bladder Carcinoma

Variant 1: Superficial TCC—no invasion or risk factors.

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen and pelvis without and with contrast (CT urography)	3		High
X-ray intravenous urography	3	Utilization of intravenous urography has continued to decline with the increasing widespread use of CT urography.	Med
X-ray chest	2		Min
FDG-PET whole body	1		High
US pelvis (bladder)	1		None
MRI abdomen and pelvis without and with contrast	1		None
CT chest with contrast	1		Med
CT abdomen and pelvis with contrast	1		High
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

Variant 2: Invasive TCC with or without cystectomy.

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9		Min
CT abdomen and pelvis without and with contrast (CT urography)	8		High
X-ray abdomen loopogram	8	In patients with an ideal loop post cystectomy.	Med
X-ray intravenous urography	5	Utilization of intravenous urography has continued to decline with the increasingly widespread use of CT urography.	Med
MRI abdomen and pelvis without and with contrast	5	See comments regarding contrast in text under “Anticipated Exceptions.”	None
CT abdomen and pelvis with contrast	5	Appropriate if MDCT urography is not available. Visceral/nodal status evaluated during CT urography.	High
CT chest with contrast	3	Performed if chest x-ray is equivocal.	Med
US pelvis (bladder)	3		None
FDG-PET whole body	2	Indicated for suspected nodal or distant metastasis.	High
Rating Scale: 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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Clinical Condition:**Follow-up Imaging of Bladder Carcinoma****Variant 3:****Superficial TCC—no invasion with risk factors.**

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen and pelvis without and with contrast (CT urography)	8		High
X-ray intravenous urography	5	Utilization of intravenous urography has continued to decline with the increasingly widespread use of CT urography.	Med
X-ray chest	5		Min
CT abdomen and pelvis with contrast	3	Visceral/nodal status evaluated during CT urography.	High
FDG-PET whole body	1		High
US pelvis (bladder)	1		None
CT chest with contrast	1		Med
MRI abdomen and pelvis without and with contrast	1		None
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

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FOLLOW-UP IMAGING OF BLADDER CARCINOMA

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Summary of Literature Review

Transitional cell carcinoma (TCC) of the bladder accounts for 95% of all bladder cancer in the United States [1]. It is the second most common genitourinary malignancy and the fifth leading cause of cancer deaths in American males over 75 years of age [2]. In 2006, approximately 61,420 new cases were expected to occur. Bladder cancer occurs about four times more commonly in men than in women and with double the frequency in whites compared to African Americans. According to the American Cancer Society [3], “An estimated 13,060 deaths will occur in 2006. For all stages combined, the 5-year relative survival rate is 82%. When diagnosed at a localized stage, the 5-year survival rate is 94%; 75% of cancers are detected at this early stage. For regional and distant stages, 5-year relative survival rates are 48% and 6%, respectively. Beyond 5 years, survival continues to decline, with a rate of 75% at 10 years and 70% at 15 years after diagnosis.” Patients who have been diagnosed and treated for TCC require follow-up evaluation, which is usually based on the type of treatment as well as accurate initial grading and staging of the tumor.

The purposes of follow-up imaging evaluation are to detect new or previously undetected tumor, to detect recurrent or metastatic disease, and to monitor the effects and/or complications following urinary diversion surgery [4]. Recommendations for tumor surveillance can be based on the classification of patients into three groups; 1) those with superficial bladder cancer but no additional risk factors and treated by local therapy; 2) those with superficial bladder cancer with additional risk factors but still treated by local therapy; and 3) those with invasive bladder cancer, usually treated with cystectomy [5].

In patients with newly diagnosed TCC, the median time to the first recurrence is 31 months. Subsequent recurrences present with increasing frequency [6,7].

The likelihood of recurrent or metastatic disease increases with the presence of one or more of the following risk factors [1-26]:

1. **Depth of invasion**—Most TCCs of the bladder (75%-85%) are superficial. Although the risk of recurrence is approximately 75%, most remain superficial, with only 10%-15% progressing to invasive carcinoma. There is evidence to indicate that cancers that invade the lamina propria (stage T1) should not be regarded as superficial. High-grade stage T1 tumors may progress to invade muscle in 30%-50% of cases. When this occurs, the prognosis is as poor as it is for those presenting initially with invasive cancer. More than 50% of patients who are treated locally for invasive cancer manifest distant metastases, and they usually die of their disease within 2 years [1,2,6,20,25].
2. **Tumor size**—Various studies have shown that tumors greater than 3 cm have up to a 35% chance of progression, and tumors greater than 10 grams are also associated with a poor prognosis [1,11,12,16,17,22,23].
3. **Grade**—Progression from grade I to III in patients without interval intravesical chemotherapy, cystectomy, or radiation therapy has been associated with an increased incidence of invasive disease and a decreased 5-year survival rates [12,18]. In one study, fewer than 10% of grade I tumors but as many as 50% of grade II tumors and more than 80% of grade III tumors were found to be invasive at the time of initial diagnosis [1,13]. In another study, the 5-year survival rate of patients with grade I tumors was 94%, but only 40% for patients with grade III tumors [1,5,13,22,23].
4. **Adjacent or remote bladder mucosal changes**—If there are adjacent or distant changes of atypia or dysplasia, there is a significant chance of progression to muscle invasion (more than 30% within 4 years of diagnosis). Carcinoma in situ (CIS), in patients with low-grade, low-stage lesions may be associated with progression to muscle invasion (greater than 80% within 4 years of diagnosis) [9,15-17].
5. **Multiplicity of foci**—A finding of multiple tumors is seen in approximately 30% of cases and is associated with a recurrence rate that is almost one-third higher than it is in patients with single lesions. This finding is generally associated with a shortening of the average time until recurrence [22,23]. Two of three patients with single lesions but nine of ten with

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multiple lesions developed recurrent carcinoma [1,5,7,12,16,17,26]. In a randomized clinical trial evaluating the prognostic factors associated with recurrence of T1 cancers, the number of tumors (worst for those with three or more) at the time of presentation was most important followed, in order of importance, by the number of recurrences (significantly greater chance of future recurrence for those patients with more than one recurrence per year) and the size of the largest tumor (worst for those over 3 cm) [11].

6. **Upper tract obstruction** has been associated with a decreased 5-year survival rate. Patients with bilateral hydronephrosis had a 5-year survival rate of 31%, compared with 45% for those who had unilateral involvement and 63% for those with no hydronephrosis [27].
7. **Lymphatic invasion** in the lamina propria is a very poor prognostic sign [8], and most patients so affected die within 6 years [7,16,23]. Solid (nonpapillary) lesions have a greater tendency for lymphatic invasion [15].
8. **TCC involvement of the prostate**—When TCC of the bladder is associated with involvement of the prostate (and it has been observed in 29%–43% of cystectomy specimens), particularly with stromal invasion, there is a substantially increased risk of urethral recurrence. Sixty-seven percent of men with urethral recurrence had prostatic TCC in cystectomy specimens. Urethral recurrence can be expected in only 1%–4% of cases when there is no TCC in the prostate. Those patients who are not candidates for cystoprostatectomy with urethrectomy are best followed up with urethral washings. Urethroscopy is performed in those having positive cytologic results [4,19,21,24,26].
9. **Laboratory tests and chromosomal abnormalities**—A number of laboratory tests have been used to prognosticate tumor progression. These include tests for Thompson-Friedenreich (T) antigen expression, lectin-binding carbohydrate structures, ABH blood group antigens, oncofetal protein expression, and epidermal growth factor receptors. According to Catalonia [10], “these tests have not been adopted into clinical practice to influence treatment decisions in individual patients.” Chromosomal abnormalities in tumors (marker chromosomes and a large proportion of aneuploid tumor cell lines) have also been used to predict tumor recurrence or progression [10].

Cystoscopic and Virtual Cystoscopic Surveillance

Recommended surveillance for patients treated for superficial bladder TCC includes cystoscopy every 3 months for 2 years, then every 6 months for 2 years, and then yearly thereafter. There has been interest in

developing virtual cystoscopic or cystographic techniques using magnetic resonance imaging (MRI) and computed tomography (CT) both for problem solving in cases that are suboptimal for standard cystoscopy (narrow-necked diverticula) and as a way to avoid the patient discomfort associated with standard cystoscopy. Browne et al [28] demonstrated CT cystography to have a 100% sensitivity in identifying 0.5 cm masses and a sensitivity of 95% for all patients in detecting neoplasm with an accuracy of 88%. Beer et al [29] examined MR cystography (multiplanar reconstructions) and cystoscopy demonstrating a combined sensitivity and specificity of 90.7% and 94.0% respectively. Multiplanar MR reconstructions (cystography) alone demonstrated sensitivity of 92.3% and specificity of 91.1% and MR cystoscopy demonstrated sensitivity of 90.7% and specificity of 90.4%. Both CT and MR cystoscopy provide views comparable to standard cystoscopy.

Urinalysis and cytologic evaluation should be performed at the time of each cystoscopy. Positive cytologic findings are followed by examination of the remaining bladder or upper tracts [1,2,4,10,30]. There has been interest in developing quantitative tests to complement or even replace urinary cytology in follow-up of bladder carcinoma. Kumar et al [31] demonstrated 85% sensitivity in detecting recurrent bladder cancer using the NMP22 marker detection device versus 41% sensitivity for traditional cytology, suggesting that it may substitute for urinary cytology. Additional studies demonstrate similar sensitivities for detecting bladder cancer with various molecular markers and Messing et al [32], Varella-Garcia et al [33] and Bhuiyan et al [34] suggest that, due to its sensitivity, immunohistochemical testing may increase the time period between cystoscopies or even replace cystoscopy.

Intravenous pyelography (IVP) was once the most common imaging modality used to evaluate the urothelium of the upper collecting system [35]. CT urography has begun to supplant IVP as its use becomes increasingly widespread [36,37]. Although some suggest an upper urinary tract imaging study such as these every one or two years, most believe that, in the absence of risk factors, urine cytologic evaluation and cystoscopy are sufficiently accurate, especially since the risk of upper-tract TCC in all patients treated for bladder carcinoma is only about 2%–5% [3,10,30,38–42] and the mean interval between initial treatment of bladder tumor and detection of subsequent upper-tract cancer is 70–80 months [10,30]. This low risk may not be sufficient to justify routine upper-tract screening [39,43], in spite of the fact that not all recurrences give positive cytologic results or are associated with hematuria [10].

In a study limited to patients who had their initial bladder cancer treated with radical cystectomy only, the mean interval between cystectomy and detection of upper-tract

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tumors was approximately 40 months (range 8-100) [40]. Surveillance of the upper tracts is appropriate in patients with positive urine cytology results or every one to two years in patients with the following risk factors (usually postcystectomy) [1,44]:

1. **Carcinoma in situ (CIS)**—When found in the cystectomy specimen, patients had a 9%-13% incidence of upper-tract TCC, with a correlation between the extent of the CIS and the risk of upper-tract TCC [4,30,38-42].
2. **Urethral CIS**—When present, the likelihood of upper-tract TCC increases to 20-30% [4,26,38,40-42].
3. **Multiple tumors.**
4. **Recurrent tumors.**
5. **Tumors involving the ureteral orifices** [4,10,38-42,44].
6. **Tumors arising in bladder diverticula** as a result of later detection and earlier transmural tumor extension [45].

If a documented recurrence is invasive, the patient is then staged [1,10,46].

If CT urography [47] cannot be done if there is incomplete visualization or nonvisualization of the collecting structures, evaluation can be supplemented with retrograde pyelography or, in those patients with ileal conduits, replaced by loopogram. CT urography is also promising in those patients with urinary diversions and may provide additional diagnostic information as it provides examination of the entire abdomen and pelvis unlike a standard loopogram. A preliminary study by Sudakoff et al [48] demonstrated that CT urography with 3D rendering depicted both normal and abnormal postoperative findings in patients with urinary diversions. The addition of digital radiography enhanced visualization of the urinary collecting system to a statistically significant degree [48]. Antegrade pyelography is uncommon but occasionally performed for diagnosis when the above techniques fail or if the collecting system is directly accessed to perform urine cytology or nephroscopy [4,10,44].

Modern imaging techniques have led to more accurate tumor staging and detection of recurrences [35]. These results in stage migration as patient with "...silent or early metastases, [move] from lower into higher..." TNM (tumor, nodes, metastases) categories [2]. When CT is used to evaluate patients following cystectomy, the pelvis is the most common site of recurrence. In these cases, the CT should include evaluation of the abdomen and perineum so that unsuspected, isolated abdominal metastases and recurrent perineal tumor will not be missed. Most metastases are detected within the first 18-24 months following surgery. Bladder cancer deaths occur

within 2 years of the initial diagnosis in over 80% of cases [14]. The most common sites of metastatic TCC are lymph nodes, liver, lung, bone, and adrenal glands [49].

Computed Tomography

CT is recommended at 6, 12, and 24 months for follow-up of patients with minimal muscle invasion (T2) who elect either cystectomy or other types of therapy without cystectomy, since most recurrences become evident within the first 2 years after surgery [4,25]. There is a different recommendation for follow-up of 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" [50].

Magnetic Resonance Imaging

MRI of the bladder may be used to evaluate of superficial bladder tumors. CT provides limited visualization of the depth of tumor invasion within the bladder wall [9,24,51,52]. MRI, even without intravenous contrast enhancement, has been noted to be "superior to clinical staging" and to allow distinction between advanced T3a tumors and the less invasive T1, T2, and early T3a lesions [53,54]. Tekes et al [55] 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 [55]. Hayashi et al [56] 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.

Although more costly than CT, MRI is more accurate in differentiating between T3b and T4a, between T4a and T4b, and between marrow and no marrow infiltration [53,54,57,58]. MRI performed with ferumoxtran-10 (ultrasmall superparamagnetic iron oxide) contrast demonstrated accuracies in pathologic lymph node detection of up to 92% and sensitivities of up to 96% [59]. These improved techniques for detecting new, recurrent, or metastatic tumors in patients with proven invasive TCC [25,60] have sometimes been associated with decreased morbidity, although not with increased curability [4,44].

Ultrasonography

Abdominal and transurethral ultrasonography (US) have had "limited success" in the evaluation of bladder cancer for determining its local extent [10]. Transabdominal US has "important limitations," particularly for tumors that are flat, smaller than 5 mm, or near the bladder neck and when there has been both understaging and overstaging [15,61]. However, using transrectal US (TRUS), it is

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possible to detect almost all lesions in the region of the bladder neck and dome, as well as a number of small tumors (<5 mm). Some evidence suggests that there is improved bladder tumor staging when TRUS is used in conjunction with MRI. TRUS has also been effective for monitoring tumor response or recurrence following neoadjuvant chemotherapy [62].

Chest Radiography

Chest radiography (PA and lateral) to search for occult metastases should be obtained at 6, 12, 18, and 24 months and then yearly for up to 5 years following cystectomy [3]. A lung lesion suspected on chest radiography may be appropriately followed by a CT scan of the chest for improved definition.

Positron Emission Tomography

Currently, there is a limited role for positron emission tomography (PET) imaging in the assessment of bladder cancer. According to Shvarts, et al [63] “It has a high positive predictive value and can be used for problem solving in patients with indeterminate findings on conventional imaging.” Kosuda et al [64] used PET in 12 patients with histologically proven bladder cancer. “The study demonstrated a true-positive rate of 66.7% and a false-negative rate of 33.3%. PET was able to identify 100% (17/17) of distant metastases (lung, bone, and remote lymph node) as well as 66.7% (2/3) of local pelvic lymph nodes [63].” Therefore, “fluorine-18 fluorodeoxyglucose (FDG-PET) might be useful in detecting perivesical tumor growth or distant metastasis in patients with advanced bladder cancer, and for the early detection of recurrent cancer following therapy, although a major remaining pitfall is the intense FDG accumulation due to excretion in the urine [64].”

Likewise, a review of PET imaging in patients with bladder, prostate, and renal cancer concluded that ¹⁸F-FDG is unsuitable for imaging bladder tumors because of its high urinary excretion, although there may be a role in detection of recurrent disease [65]. A study correlating ¹⁸F-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 [66]. Preliminary studies show that ¹¹C-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 lymph nodes due to reactivity when compared with CT. In addition there is negligible urinary excretion of ¹¹C-choline [67].

Summary

Routine imaging follow-up is **NOT** indicated for patients with superficial TCC and no invasion of the lamina propria or additional risk factors. Patients with superficial TCC require careful observation and IVP or CT

urography every 1-2 years **IF** any of the following risk factors for recurrent tumor are present:

1. tumor size greater than 3 cm or 10 grams,
2. higher than grade I tumor, or
3. adjacent or remote bladder mucosal changes or dysplasia or CIS. Additional imaging may be necessary if there are positive urine cytologic findings, hematuria, or abnormal cystoscopy.

Patients with invasive TCC—especially those with evidence of: 1) lymphatic or 2) hematogenous invasion; those with associated 3) dysplasia or 4) CIS in the cystectomy specimen; those with associated 5) urethral TCC, 6) multifocal bladder tumors, 7) recurrent bladder tumors, and 8) tumors in bladder diverticula or 9) involving the ureterovesical junctions—should have an IVP or CT urography every 1-2 years. If IVP is inadequate or not possible, CT urography, loopogram, or pyelography (retrograde or antegrade) can be used as a substitute or supplement. Patients requiring cystectomy for invasive bladder cancer should have an MRI or a CT scan at 6, 12, and 24 months and a chest x-ray at 6, 12, 18, 24, 36, 48, and 60 months postoperatively. If recurrent bladder cancer is found and considered invasive, new staging may be required (see the ACR Appropriateness Criteria® topic [Pretreatment Staging of Invasive Bladder Cancer](#)) [46].

Anticipated Exceptions

Patients treated with bladder-preserving surgery and follow-up neoadjuvant chemotherapy and/or radiation therapy for localized muscle-invasive TCC may require more frequent CT and/or MRI. TRUS may be used in selected cases when it is considered helpful. PET imaging may be helpful in cases of advanced bladder cancer, particularly for detecting regional lymph node spread or distant metastases.

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 [68-70], 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

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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).

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/1.73m²), 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) [69].

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 [71]

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, ≤ 2 cm in greatest dimension
N2		Metastasis in a single lymph node, >2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, ≤ 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 Groupings [71]

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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