Original Article

Comparison of dynamic contrast-enhanced and diffusion weighted magnetic resonance image in staging and grading of carcinoma bladder with histopathological correlation

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Abstract

Background: Bladder cancer is the second most common neoplasm of the urinary tract worldwide. Dynamic contrast-enhanced and diffusion-weighted MRI has been introduced in clinical MRI protocols of bladder cancer because of its accuracy in staging and grading.

Aim: To evaluate and compare accuracy of Dynamic contrast enhanced (DCE) and Diffusion weighted (DW) MRI for preoperative T staging of urinary bladder cancer and find correlation between apparent diffusion coefficient (ADC) and maximum enhancement with histological grade.

Materials and Methods: Sixty patients with bladder cancer were included in study. All patients underwent Magnetic Resonance Imaging (MRI) on a 1.5-T scanner with a phased-array pelvic coil. MR images were evaluated and assigned a stage which was compared with the histolopathological staging. ADC value and maximum enhancement curve were used based on previous studies. Subsequently histological grade was compared with MR characteristics.

Results: The extent of agreement between the radiologic staging and histopathological staging was relatively greater with the DW-MRI (κ=0.669) than DCE-MRI (κ=0.619). The sensitivity, specificity, and accuracy are maximum and similar for stage T4 tumors in both DCEMRI (100.0, 96.2 and 96.7) and DW-MRI (100.0, 96.2 and 96.7) while minimum for stage T2 tumors - DCEMRI (83.3, 72.2, and 76.7) and DWI-MRI (91.7, 72.2, and 80).

Conclusion: MRI is an effective tool for determining T stage and histological grade of urinary bladder cancers. Stage T2a and T2b can be differentiated only by DCE-MRI. Results were more accurate when both ADC and DCE-MRI were used together and hence a combined approach is suggested.

Key Words: Digits, hand, upper limb, varicosities, varicose veins

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INTRODUCTION

Bladder cancer is the second most common neoplasm of the urinary tract worldwide, prostate cancer being first.[1] It accounts for 6-8% of overall malignancy in men and 2-3% in women, with the highest incidence rates in North American and Europe, as well as in areas with endemic schistosomiasis (Africa and the Middle East). It is more common in men

than women (3:1) and typically occurs in patients over the age of 50.[2] They are broadly classified as either epithelial or nonepithelial (mesenchymal) tumor. On an average 90-95% of bladder neoplasms arise from the epithelium, the most common subtype is transitional cell carcinoma (90%).[1] Mesenchymal tumors represent the remaining 5% of bladder tumors, with the most common subtypes being rhabdomyosarcoma, in children, and leiomyosarcomas, in adults. Many chemicals are thought to be carcinogens for bladder cancer includes aniline dyes, benzidine, B-naphthylamine and other potential bladder cancer carcinogens.[3-5] Cigarette smoking is the strongest risk factor for bladder cancer.[6] Age is also a risk factor for developing bladder cancer, which occurs more commonly in the elderly.[7]

Hematuria is the most common symptom.[8] Irritative voiding symptoms such as frequency or dysuria can also be the presenting symptoms. The clinical assessment consists of urine cytology for malignant cells, urine for tumor marker, hemograms, liver and kidney function tests, cystoscopic examination and examination under anesthesia. Radiological evaluation is a significant part of diagnosis and staging of bladder cancer. Grey scale sonography is initial modality to confirm the presence of the lesion, evaluate morphology of tumor, perivesical extension, lateral pelvic wall involvement, lymph node status, to exclude metastasis and to look for back pressure changes in kidneys. Intravesical US is more promising than noninvasive transmission assessment surveys.[9] Computed tomography (CT) and magnetic resonance imaging (MRI) are the main radiologic examinations used in the evaluation of patients with bladder cancer. There is still controversy about which imaging modality is better. The advantages of CT include shorter acquisition time, wider coverage in a single breath hold, and lower susceptibility to various patient factors. However, CT scan is unable to differentiate between stage T2a and T2b.[10-12] MRI has superior soft tissue resolution and poorer spatial resolution compared with CT. Faster dynamic contrast enhanced (DCE)-MRI helps to differentiate bladder tumor from surrounding tissues as enhancement of the tumor occurs earlier than the normal bladder wall due to neovascularization.[13] On the other hand, diffusion-weighted MRI has been introduced in clinical MRI protocols because of its higher contrast resolution and ability to detect and reflect molecular diffusion restriction in malignant tissue.[14,15] In general, gadolinium enhancement is most useful in detecting and staging early-stage disease. Microscopic extravesical spread (T3a disease) cannot be reliably identified, but MRI readily shows macroscopic extravesical extension (T3b disease). Direct bony invasion should also be detectable. According to Tekes *et al.*, gadolinium-enhanced MRI has accuracy of 85% in differentiating noninvasive versus invasive disease and of 82% in differentiating organ-confined from nonorgan-confined disease.[16]

MATERIALS AND METHODS

The retrospective study was given clearance by Institutional Ethical Committee. During the period between January 2011 and November 2012, 60 patients with presumed diagnosis of the urinary bladder carcinoma either clinically or by other investigations like ultrasound, underwent DCE-MRI within 3 weeks of diagnosis. Patient with previous biopsy/resection were excluded from the study. Urinary bladder carcinoma was subsequently confirmed on histopathology of the operated specimen. Staging and grading of tumors were analyzed on MRI and compared with the operative and histopathological findings.

The MRI technique

Patients were instructed to start drinking water 2 h before the MRI study and to present with a full bladder. Patients were imaged using Philips 1.5 T whole body MRI Intera Achieva machine using dedicated pelvic coil, with a field of view of 26-28 cm. T1-weighted images were obtained in axial and sagittal planes with a T1-weighted turbo spin-echo sequence. Similarly, T2-weighted images obtained in both axial and sagittal planes. These sequences were used to locate tumoral lesions and to reveal their morphologic characteristics.

Diffusion-weighted MRI

Before gadolinium-enhanced imaging, respiratory-triggered diffusion-weighted images were obtained in a transaxial plane using a single-shot echo-planar sequence (TReff/TEeff = 2790-4560/88 ms); b factors, 0 and 1000 s/mm; 5-mm section thickness with a 2-mm intersection gap. Spectral inversion recovery fat suppression technique was used to eliminate chemical shift artifacts.

Dynamic contrast-enhanced MRI

Performed in the axial plane and if required in the sagittal plane using two-dimensional T1FFE sequences with an intravenous bolus injection. The contrast was administered by hand injection of 0.1 mmol/kg of body weight of a gadolinium chelate followed by a flush of 20 ml of saline solution. 8-10 dynamic scans, each lasting 20-30 s, were performed sequentially in 5 min using parameters identical to those of the unenhanced sequence. The onset of the contrast injection and the data acquisition was triggered synchronously.

STAGING AND GRADING

Diffusion weighted MRI]

Diffusion-weighted images (DWI) were interpreted referring to T1- and T2-weighted images. The bladder wall was identified as a thin line of slight hyperintensity on DWI.[17,18]

- Stage T1: Hyperintensity of tumor within the bladder lumen

- StageT2: Hyperintensity of tumor partially seen in the bladder wall
- StageT3: Hyperintensity of tumor disrupting the bladder wall
- StageT4: Hyperintensity of tumor extending into the adjacent organs, abdominal or pelvic wall.

The mean ADCs of G1, G2, and G3 tumors in our study were:

G1: >1400 × 10^{-3} mm^2/s; G2: 1400-1000 × 10^{-3} mm^2/s and G3: <1000 × 10^{-3} mm^2/s.

Dynamic contrast-enhanced MRI

With DCE-MRI, bladder tumors, mucosa, and submucosa enhance early, but[17-19] the muscle layer maintains its hypointensity.

- Stage T1: Intact muscle layer at the base of the tumor that shows low signal intensity on T2-weighted MRI and no early enhancement on DCE-MRI
- Stage T2a: Irregular inner margin of the bladder wall muscle's hypointense line with or without enhancement difference
- Stage T2b: Disrupted hypointense line and early enhancement without perivesical fat infiltration
- Stage T3b: Lesion with an irregular shaggy outer border and streaky areas in perivesical fat of the same signal intensity as the tumor
- Stage T4: Lesion extending into an adjacent organ or abdominal and pelvic side walls with the same signal intensity of the primary tumor.

Time-intensity curves

Time–intensity curves were also constructed from signal intensity values obtained[18,19] from freely drawn regions of interest selected on the basis of optimal visualization of the lesion and the region of greatest enhancement.

- Grade1: Time-intensity curve shows enhancement, followed by a slow increase
- Grade 2: Time-intensity curve shows enhancement, followed by a plateau
- Grade 3: Time-intensity curve shows enhancement, followed by washout.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) Version 17.0. Manufactured by IBM. Chi-square test, Friedman test, Wilcoxon signed rank test, analysis of variance and Kappa statistic was applied for comparison of data. Diagnostic efficacy was depicted in terms of sensitivity, specificity, negative predictive value, positive predictive value and diagnostic accuracy. The level of confidence was kept at 95% hence a $P < 0.05$ indicated a significant association. Sensitivity, specificity, and accuracy of MRI were assessed on a stage-by-stage basis, and the gold standard was pathologic confirmation in all cases. Histologic staging conformed to the updated TNM system of the International Union against Cancer.

In addition, data were regrouped to evaluate the accuracy of MRI staging in distinguishing superficial (≤T1) from invasive (≥T2) tumors and organ-confined (≤T2b) from nonorgan-confined (≥T3) tumors.

RESULTS

Study was performed on 60 patients, clinically suspected to have bladder cancers based on clinical presentation, urine cytology and ultrasound findings. The age range in the study group was 35-89 years similar results reported by Lynch and Cohen *et al.*[20] and Horner *et al.*[7] There were 48 male and 12 female patients. The male to female ratio in the study was 4:1, similar results described by Jemal *et al.*[2] The most common presenting symptom in the study was hematuria (86.7%) with or without other symptoms such as poor stream, hesitancy, and dysuria. Few patients were asymptomatic and detected during investigation unrelated to the disease. The similar findings were described by Varkarakis *et al.*[21] and Wakui *et al.*[8]

Histopathological examination (HPE) revealed 58.33% of cases presented with Stage I disease. The detailed number of patients with staging and grading is represented in Tables 1 and 2. Staging accuracy of DCE-MRI found to be 73.3%. Statistically, the extent of agreement between HPE and DCE-MRI was substantial (κ =0.690) and significant ($P < 0.001$). The detailed results of comparison of DCE-MRI staging with HPE staging is represented in [Table 3]. Diagnostic accuracy of DW-MRI for local (T) staging found to be 76.7%. Statistically, the extent of agreement HPE and DW-MRI was substantial (κ =0.669) and significant ($P < 0.001$). The detailed results of comparison of DW-MRI staging with HPE staging is

Table 1: Distribution of patients according to HPE staging

HPE stage	No. of patients	Percentage
T1	35	58.33
T2a	9	15
T2b	4	6.66
T3a	5	8.33
T3b	4	6.66
T4a	3	5

HPE: Histopathological examination

Table 2: Distribution of patients according to HPE grading

HPE grade	No. of patients	Percentage
I	25	41.66
II	20	33.3
III	15	25

HPE: Histopathological examination

represented in Table 4. An absolute agreement between DW and DCE methods was observed for 50/60 (83.3%) cases. Measure of agreement (κ =0.764) showed substantial agreement between DCE and DW methods for 'T' staging [Figures 1-4]. Accuracy against gold standard was of relatively higher order in DCE (73.3%) and DWI (76.7%) and the difference between two methods was not significant statistically (P = 0.655). For grading, diagnostic accuracy of DCE-MRI was observed to be 73.3%, maximum for Grade II (90%), and minimum for Grade I (58.3%). Statistically, the extent of agreement between HPE and DCE-MRI was substantial (κ =0.600) and significant (P < 0.001). Diagnostic accuracy of DW-MRI (ADC value) for grading of bladder cancer observed to be 80%, maximum for Grade I (91.7%) and minimum for Grade II (60%) [Figure 5].

Table 3: Diagnostic efficacy of DCE technique for HPE staging

HPE stage	Diagnostic efficacy of DCE				
	Sensitivity	Specificity	PPV	NPV	Accuracy
T1	62.5	100.0	100.0	88.0	90.0
T2	83.3	72.2	66.7	86.7	76.7
T3	50.0	91.7	60.0	88.0	83.3
T4	100.0	96.2	80.0	100.0	96.7
≤T1->T2	62.5	100.0	100.0	88.0	90.0
≤T2b-≥T3	90.0	80.0	90.0	80.0	86.7

HPE: Histopathological examination, PPV: Positive predictive value, NPV: Negative predictive value, DCE: Dynamic contrast-enhanced

Table 4: Diagnostic efficacy of DWI criteria for HPE staging

HPE stage	Diagnostic efficacy of DWI criteria				
	Sensitivity	Specificity	PPV	NPV	Accuracy
T1	62.5	100.0	100.0	88.0	90.0
T2	91.7	72.2	68.8	92.9	80.0
T3	50.0	95.8	75.0	88.5	86.7
T4	100.0	96.2	80.0	100.0	96.7
≤T1->T2	62.5	100.0	100.0	88.0	90.0
≤T2b-≥T3	95.0	80.0	90.5	88.9	90.0

HPE: Histopathological examination, PPV: Positive predictive value, NPV: Negative predictive value, DWI: Diffusion-weighted imaging

DISCUSSION

Accurate preoperative evaluation of bladder carcinoma is important because therapy depends on the clinical stage of disease. Stage T1 lesions can be treated adequately with fulguration on transurethral resection, and low-grade stage T2 lesions are often treated with segmental cystectomy. Radical cystectomy is performed for stage T3a and T3b lesions, whereas palliative radiation therapy is the common management for stage T4 disease.

Ultrasonography is good for detection, but has relatively lower performance with substantial risk of overstaging of superficial lesions and understaging of muscle-infiltrating tumors.[22] In our study, on DCE-MRI overall agreement with HPE stage was observed on 73.3% cases. Diagnostic accuracy was greater for Stage T4 disease (96.7%).

Statistically, the extent of agreement between DCE and HPE staging was substantial (κ =0.619) and significant (P < 0.001). An overall accuracy of 73.3% was noted in our study which is definitely higher than reported in literature. Tuncbilek *et al.*[23] have reported accuracy of 62.5%, 62% by Tekes *et al.*[16] and 60% by Buy *et al.*[24] This is possibly because MRI was done within few days of after doing TURP, making differentiation between acute edema or hyperemia and tumor difficult. In the study, diagnostic accuracy for superficial versus invasive disease (<T1Vs >T2 stage) was found to be 90% which is slightly higher than the reported accuracy of 85% (90% if small lesions excluded) by Tanimoto *et al.*[25] This was lower than that of

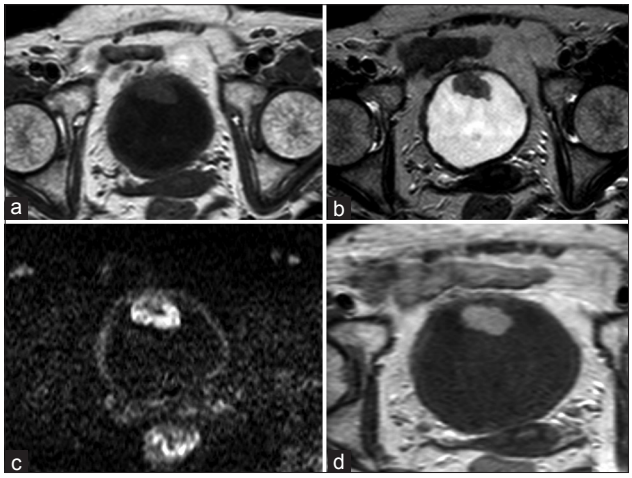

Figure 1: Stage 1 Grade 2 transitional cell carcinoma (a and b) T1- and T2-weighted image shows a single polypoidal intraluminal anterior wall mass (c) diffusion-weighted images a single polypoidal intraluminal anterior wall mass with diffusion restriction (d) dynamic contrast-enhanced imaging shows a single polypoidal intraluminal anterior wall mass showing intense enhancement

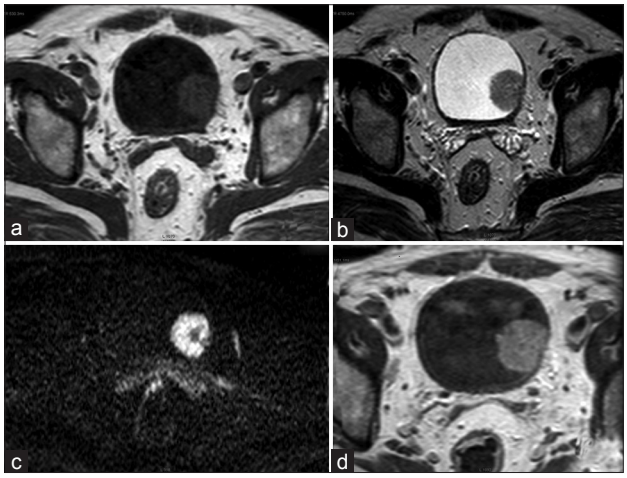

Figure 2: Stage 2 Grade 1 transitional cell carcinoma (a and b) T1- and T2-weighted image showing single intraluminal mass near left VesicoUreteric Junction (L-VUJ) (c) diffusion-weighted images shoes restricted diffusion (d) dynamic contrast-enhanced image showing rapidly enhancing single intraluminal mass near L-VUJ followed by slow increase

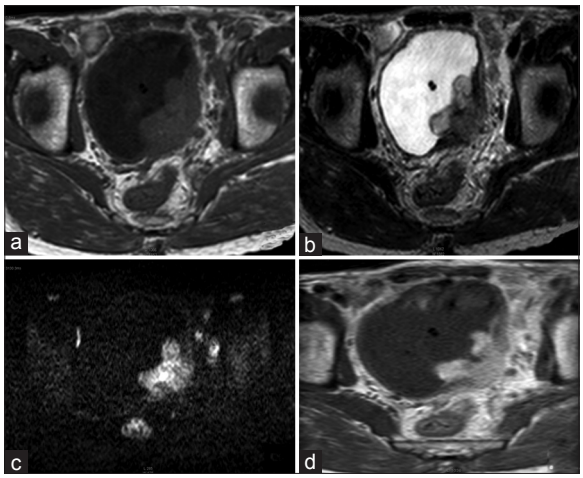

Figure 3: Stage T3b and Grade 3 carcinosarcoma (a) T1-W image showing left posterolateral wall mass abutting left VesicoUreteric Junction (L-VUJ) (b) T2-W image showing left posterolateral wall mass abutting L-VUJ with Foley's *in situ* (c) diffusion weighted image showing diffusion restriction with perivesical extension (d) dynamic contrast-enhanced image shows enhancing L-posterolateral mass abutting L-VUJ and perivesical extension

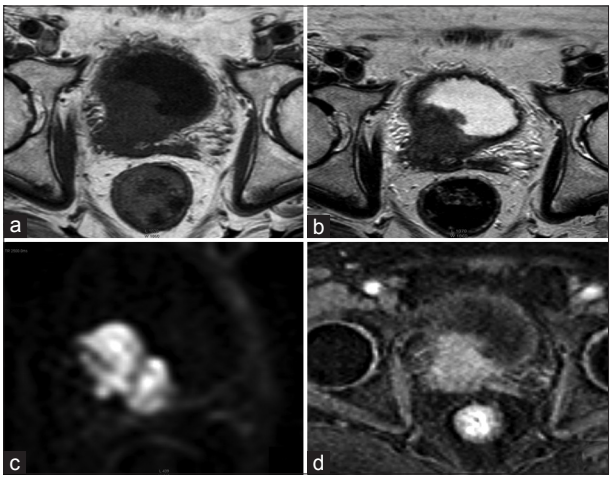

Figure 4: Stage T4a and Grade 3 transitional cell carcinoma (a and b) T1 and T2 images showing right-VesicoUreteric Junction (R-VUJ) mass with extravesical spread and seminal vesicle involvement (c) diffusion weighted images shows restricted diffusion (d) dynamic contrast-enhanced image shows rapid enhancing R-VUJ mass and involvement of prostate and seminal vesicle

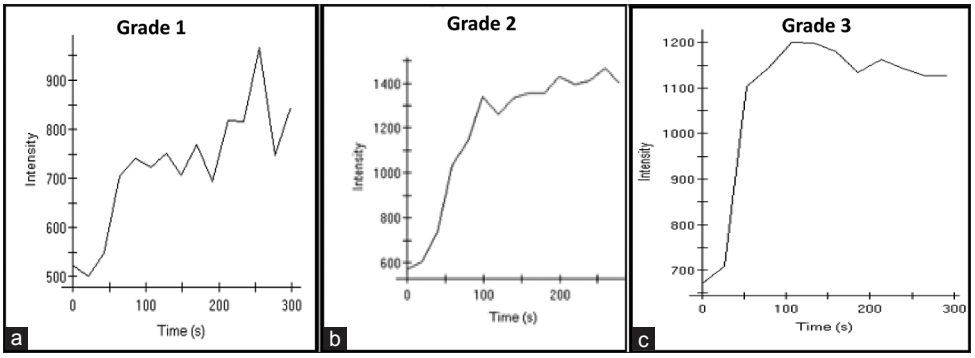

Figure 5: Time intensity curve and mean ADC values (a) Grade 1 lesion showing rapid early enhancement followed by slow increase with mean ADC value 1700 (b) Grade 2 lesion showing plateau curve with mean ADC value 1200 (c) Grade 3 lesion showing rapid enhancement followed by rapid wash out and mean ADC value 823.54

reported literature by Scattoni *et al.*,[26] who reported an accuracy of 92% using a 0.5-T magnetic resonance scanner with contrast administration. Our accuracy (86.7%) in differentiating organ confined from non-organ-confined tumors was higher than the 73% accuracy reported in a previous study in 1989 by Husband *et al.*[27] On DCE-MRI overstaging was seen in 12 (20%) patients in our study compared to study by Kim *et al.*[28] where overstaging occurred in 26% of cases. Understaging was seen in four cases. On DWI-MRI, overall agreement between DWI and HPE was observed in 23 (76.7%) cases. Diagnostic accuracy was more for Stage T4 (96.7%). For superficial versus invasive disease (<T1->T2 stage) the diagnostic accuracy was 90%. In the study, we found that although accuracy against gold standard was of relatively higher order in DWI (76.7%) when compared to DCE (73.3%) yet the difference among two methods was not significant statistically ($P = 0.655$). It was found that chances of understaging were almost equal in DCE and DWI (6.7% each). A slight difference in events of overstaging was observed between DCE (20%) and DWI (16.7%). In our study, we found that both DCE and DWI have almost equal accuracy (90%) to differentiate between superficial and invasive bladder cancer. However, DCE-MRI shows relatively lower accuracy (86.7%) as compared to the DWI-MRI which shows 90% diagnostic accuracy. Our study found no statistically significant difference in the accuracy of MRI for staging transitional and nontransitional cell carcinomas. The overall diagnostic accuracy of DCE-MRI grading for HPE grading was found to be73.3%. Maximum accuracy was observed for Grade II (90%) and minimum accuracy for Grade I (58.3%). DWI MRI provides information on perfusion and diffusion simultaneously in any organ and can be used to better differentiate normal and abnormal structures of any tissues, and it might help in the characterization of various abnormalities. DW MRI of the urinary bladder seems to be a feasible and reliable method to diagnose bladder carcinoma. Bladder carcinomas have significantly lower ADC valve when compared to surroundings such as normal bladder wall, urine, etc.

In our study, DWI (ADC criteria) shows full agreement with HPE grading in 48/60 cases, while 8 (13.3%) patients shows undergrading and 4 (6.7%) patients shows overgrading. The overall diagnostic accuracy of DWI (ADC criteria) for HPE grading was found to be 80%. Maximum accuracy was observed for Grade I (91.7%) and minimum accuracy for Grade II (60%). Statistically, the extent of agreement between DWI (ADC criteria) and HPE was substantial (κ =0.693) and significant too ($P < 0.001$).

CONCLUSIONS

MRI is a single comprehensive modality of choice for preoperative (T) staging as well as grading of the bladder cancer especially in a patient with deranged KFT and in patients with allergy to iodinated contrast agents. MRI scores over the other technique in being a radiation free modality. It can preoperatively assist in accurate staging and grading along with invasive techniques like cystoscopy and cystoscopic biopsy. Newer advances like dynamic and diffusion weighted MRI can add onto more information in evaluation of bladder cancer. DCE-MRI and DWI-MRI are comparable in staging and grading and thus combination of DCE-MRI and DWI-MRI should be advocated whenever differentiation has to be made out between superficial and muscle invasive disease during preoperative workup.

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