Chapter 21
The Role of Imaging in Tumor Staging and Response Assessment: Envisaging an Application for the Next-Generation Trials

Antonella Messina, Giuseppina Calareso, and Alessandra Alessi

Introduction

Bladder cancer (BC) represents 4.6% of total cancer diagnoses and is more frequent in males [1]. The great majority of BC are urothelial cell carcinomas (UCC), and based on histopathology, they are defined as muscle-invasive (MIBC) and non-muscle invasive BC (NMIBC) [2]. Identification of the disease is usually made by cystoscopy after the insurgence of hematuria and/or dysuria [3]. Diagnosis is surgical with trans-ureteral resection of bladder cancer (TURBT), which is generally used as a definitive treatment in the NMIBC and for diagnosis in the MIBC [4]. A correct staging of the BC, based on the evaluation of the primitive lesion and lymph nodes involvement, is essential for prognosis and therapy. For many years, chemotherapy has been the only choice of treatment, but in recent years with the introduction of immunotherapy, a new criteria of response assessments have been developed. Imaging plays an important role in assessing the extent of BC for which ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET/CT) are used [5].

A. Messina (✉) · G. Calareso
Department of Radiology, Foundation IRCCS National Cancer Institute, Milan, Italy
e-mail: Antonella.messina@istitutotumori.mi.it

A. Alessi
Nuclear Medicine Unit, Department of Radiology, Foundation IRCCS National Cancer Institute, Milan, Italy

A. Necchi, P. E. Spiess (eds.), *Neoadjuvant Immunotherapy Treatment of Localized Genitourinary Cancers*,
https://doi.org/10.1007/978-3-030-80546-3_21

Ultrasonography

Ultrasonography (US) is a noninvasive, first-level diagnostic method used as a screening test in the presence of hematuria. It is performed with a curvilinear probe (2–5 MHz) in a patient with a well-distended bladder. By using a high-frequency probe, US can differentiate three out of four layers of the bladder wall (the muscolaris propria appears as an hypoechoic line between the superficial serous layer and the hyperechoic mucous and submucous layers) [6, 7]. Urothelial bladder carcinoma appears echographically as an irregular focal or diffuse thickening of the bladder wall or as a plaque of the wall [8]. It may appear hypoechoic, isoechoic, or hyperechoic depending on the presence of fibrosis, calcification, and hemorrhage. To stage the BC, it is necessary to assess the degree of infiltration of the bladder wall and invasion of the muscolaris layer is suggested by the disappearance of the hypoechoic intermediate layer. Although some studies report an 80% accuracy of US to detect BC [9], there is only limited experience to support the use of US for the staging of BC. In fact it plays only a limited role in the diagnosis of bladder tumor, in particular in the identification of small-size carcinomas. The use of contrast medium, however, improves the diagnostic accuracy of this technique; it is reported that accuracy of Contrast Enhanced Ultrasound (CEUS) to detect BC is 90.9%. [10, 11]Despite this evidence, US is operator dependent and the ability to identify the lesion is affected by the presence of adjacent organs and compliance of the patient.

Computed Tomography

CT scan is a second-level technique, which requires ionizing radiation. It is useful in the pre-operative staging of the tumor, in the evaluation of the response to neoadjuvant treatment, and in the follow-up after radical cystectomy. According to the latest guidelines of the National Comprehensive Cancer Network (NCCN), the presence of a solid tumor of high grade or potentially invasive solid tumor necessitates either a CT or an MR for the staging of the local lesion before TURBT [12]. CT plays an important role in evaluating macroscopical cancers invasive of the adipose tissue or the adjacent organs (T3b; 83.3% accuracy and 100% precision); however, the thickening of the adipose tissue may sometimes be related to the inflammatory reaction or post-bioptic desmoplastic reaction, thus causing false-positive results, such as loss of the clivage planes, which is not always a sign of infiltration of the adjacent organs [6, 13]. In such a case by the use of multiplanar reconstruction, it is possible to detect an involvement of the adjacent organs. Furthermore, CT does not permit the detection of infiltration of the muscolaris mucosa, even though it has been suggested that a retraction of the wall of the BC represents muscle involvement [6, 14]. However, many studies by multidetector CT show an accuracy degree between of 89% and 91% and specificity between 92% and 95%, [13, 15]. CT is useful, however, to detect distant metastases

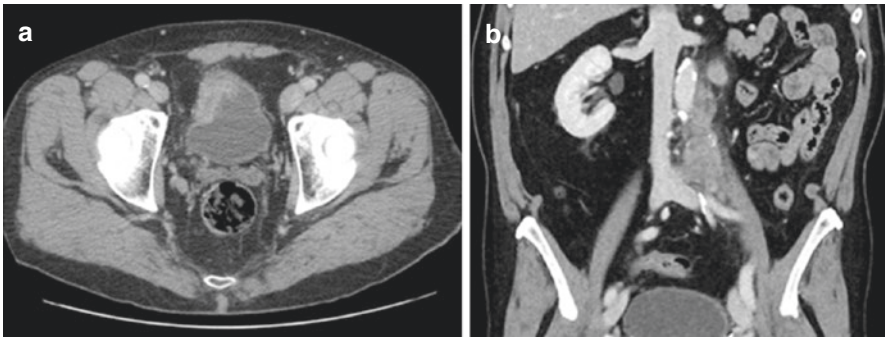

Fig. 21.1 Axial CT image of the bladder (**a**). Large lesion of the anterior right lateral wall of the bladder. Coronal CT image of the abdomen (**b**) shows paraaortic lymphadenectomy

(lymphogenous or hematogenous) and is recommended before cystectomy to exclude other different causes of hematuria (urinary stones, trauma, infection, and renal cancer). CT scan detect lymph node metastases in BCa with a sensitivity ranging between 31% and 50% and a specificity ranging between 68% and 100% [16]. CT has a limited role in the assessment of locoregional response after neoadjuvant therapies to differentiate residual tumor from inflammatory processes; to avoid this limit, some studies suggest the use of computer-aided diagnosis (CAD). Using radiogenic learning algorithms and characteristics can increase the accuracy of CT in identifying the complete response in the infiltrating muscle tumor [17].The usefulness and accuracy of CT in predicting lymph node response after adjuvant therapies are not fully shared. Recist criteria are used to evaluated the response to treatment in BC, as in other solid tumors also in BC are used the criteria RECIST 1.1 or irRECIST; among the limits of these criteria, the cutoff indicated for lymph node size must be considered. According to some studies, the reduction of the cutoff to 6 mm and assessments of morphological or contrast criteria increase the accuracy of CT in diagnosing lymph node involvement after neoadjuvant therapy [18] which, as it is known, affects the survival of BC patients after cystectomy and lymphadenectomy (Fig. 21.1).

Magnetic Resonance Imaging

The European Association of Urology (EAU) guidelines have not recommended any well-defined criteria for the diagnosis of bladder tumor, and MR is requested only when CT cannot be performed. MR, unlike CT, does not use ionizing radiation, offers superior soft tissue contrast, and provides more anatomical and functional information [19]. MR also differentiates MIBC from NMIBC and visualizes extramural invasion and T3b and T4 disease [20, 21].

Table 21.1 The 5 scores used in the VI-RADS classification system

Score	VI-RADS (Vesical Imaging-Reporting and Data System)	T2	DCE	DWI	ADC
1	Small (<1 cm) exophyitc tumor with or without peduncle with a thickend internal layer, but with an inatct muscolaris propria which appears as an uninterrupted line of low signal				
2	A larger tumor(> 1cm) exophytic with a larger base peduncle with thickening of the internal layer if present, and an uninterrpted line of the mouscolaris propria				
3	A lack of the findings of SC2 with a exophytic tumor without peduncle or sessile tumor, with wide base without thickening of the internal layer and without clear interruption of the muscolaris propria				
4	Interruption of the inferior line suggesting the invasion by the tumor of the muscolaris propria				
5	Extension of the tumor to the adipose tissue outside the bladder indicating invasion of the entire wall and other exterior bladder tissue				

Multiparametric MRI (mpMR) is the most accurate method for studying BC. The mpMR includes a morphologic study with multiplanar high definition T2 weighted sequences, a cellular density study with DWI sequences (Diffusion Weight Imaging) with b 0-800-1000 and ADC map and a Perfusional study with contrast medium intravenous (DCE) to evaluate the vascularization of the lesion. Correct bladder filling is required with or without cateheterization.

In 2018, Panebianco and colleagues introduced a new way to diagnose and stage primary BC with the development of an mpMR imaging protocol called "VI-RADS" (Vesical Imaging-Reporting and Data System), consisting of a 5-score tool as indicated in Table 21.1 (modified from Panebianco et al. [26]).Today, this system has been endorsed by the guidelines of the European Association of Urology (EAU). This protocol provides higher level of accuracy in the staging and diagnosis of BC, in particular in the differentiation of superficial from muscle-invasive tumor, thus requiring less-invasive methods for diagnosis and staging, particularly useful in patients with severe comorbidities. There are however some drawbacks in VI-RADS protocol regarding the staging of the primary lesion (30% are multifocal) and the fact that the upper urinary tract cannot be reliably assessed. According to the available data, VI-RADS criteria cannot be also applied to images from patients undergoing treatment, and it is not validated as a method to assess tumor response to treatment. Based on experiences reported by other authors, mpMR images could also represent a further aid to physicians in response assessment to neoadjuvant therapies. It is important to have baseline and post treatment MR exame to evaluate tumore response (complete response or partial response) (Figs. 21.1, 21.2, and 21.3) or disease progression is considered (Fig. 21.4). Treatment for BC may currently include chemotherapy (CT) and immunotherapy. Regardless of the

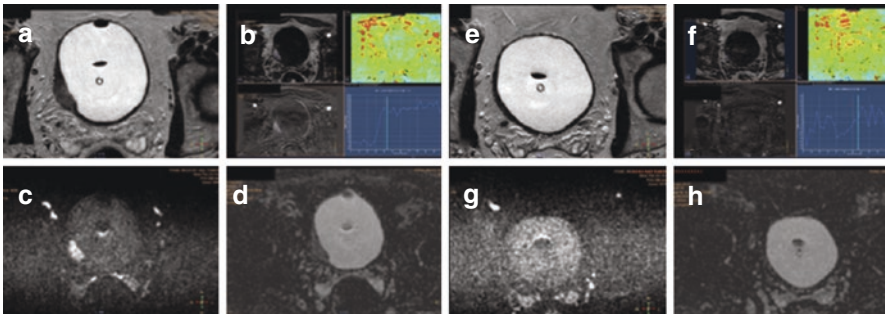

Fig. 21.2 Pre-treatment images (**a**–**d**) and post-treatment images (**e**–**h**) . In the pre-treatment images, a large muscle-infiltrating lesion of the right lateral wall of the bladder is observed: hypointense in T2 (**a**), with enhancement after contrast medium with a type 2 contrast intensity-time curve (**b**); hyperintense in native DWI (**c**), and hypointense in ADC maps (**d**). The post-treatment images show the disappearance of the lesion with bladder wall returning within normal limits. In this case, there was a complete response

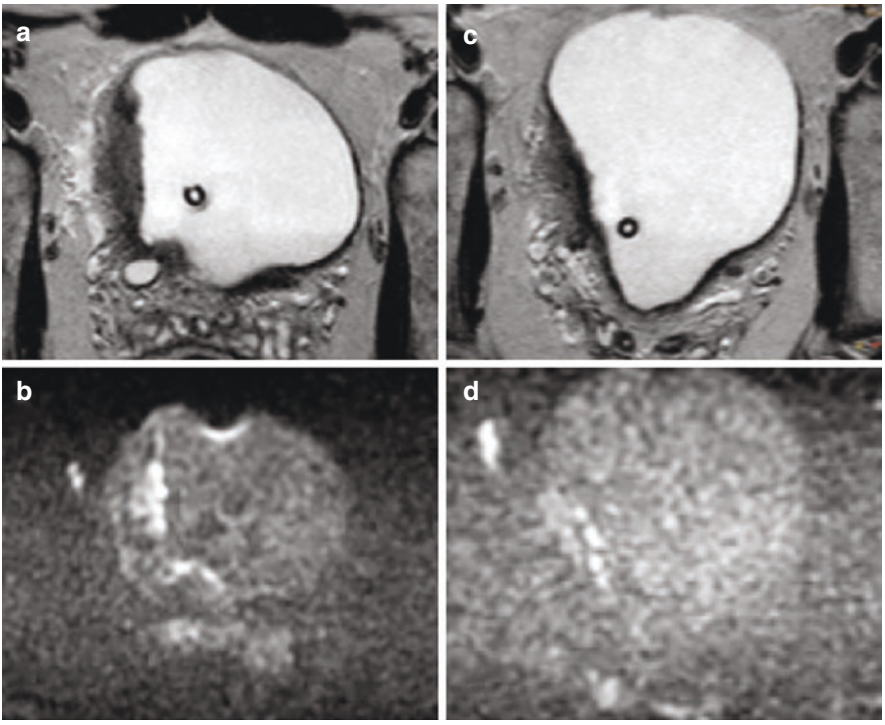

Fig. 21.3 In baseline MR images (**a**–**b**), there is a plurinodular lesion, hypointense in T2 (**a**) and hyperintense in DWI in sequences with a high b-value. After treatment (**c**, **d**), there is a moderate size reduction of the lesions. Most visible micronodularities persist in DWI (**d**) sequences with high b-value. Thsee features indicate a partial response to treatment

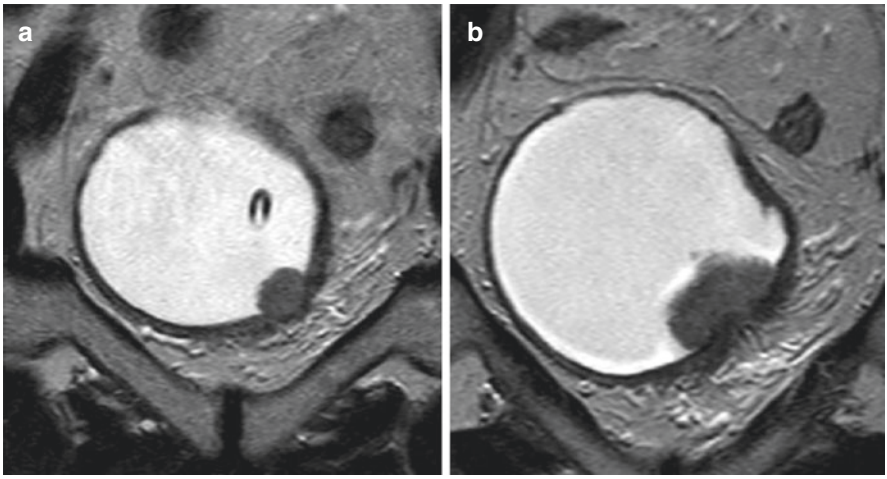

Fig. 21.4 T2- weighted coronal image pre treatment (**a**) and T2 weighted coronal image post tretment (**b**) These images show an increas in size of the lesion of the left lateral bladder wall (progression desease)

therapeutic option, patients are always subjected to cystoscopy and endoscopic resection of the existing lesions, including those with thickening of the bladder walls due to inflammation. Therefore, the baseline MRI images may be difficult to interpret due to the persistence of disease in the context of an inflamed thickening of the bladder wall. In this case, the T2 and DWI sequences are more reliable if they are jointly assessed. While the evaluation of response to standard chemotherapy may be easier, in patients treated with immunotherapy, the post-therapy stromal tissue is generally more complex than after chemotherapy, as it is usually characterized by a significant recruitment of T-cells that surround the residual disease resulting in a major inflammation in the bladder wall [14]. All these features can make hardly detect any micronodular disease (Fig. 21.2). DWI sequences seemed to be the most reliable sequences in association with T2 sequences. In the near future, a biparametric MR study of the bladder could be performed without using contrast medium. This feature might in part explain the discordance between the mean values of ADC after neoadjuvant chemotherapy and the hystopathological response which can result in unreliable quantitative post-immunotherapy evaluation. On the contrary, the changes in the mean ADC values after neoajuvant chemotherapy or chemoradiotherapy have been reported to be the first markers of response in bladder tumors [22, 23]. The finding that 20% of patients who are thought to have had a total tumor eradication, although in agreement with some published data, should be taken with extreme caution, because it might be inconsistent with the hystopathological final results. Such limitations are entirely consistent with previous studies, which show that there is no advantage in staging the tumor by MR (including mpMR) with a total accuracy ranging from 56% to 62% and with an overestimate

ranging from of 32% to 38% [24, 25]. The findings obtained with mpMRI are interesting and could be used in the future to evaluate the individual role of each parameter of the pathological response [26]. Nonetheless, it is evident that the morphological response of the tumor alone is insufficient to evaluate the total response and, in a substantial percentage of reports, difficult to interpret because they are either mixed or incomplete, or there have been tissue changes in the lesion after treatment. Such a method to evaluate the pathological response to neoadjuvant treatment in a noninvasive way may have important implications in clinical practice and in the design of future studies on neoadjuvant approaches [27]. In particular, the use of equipment which may lead to identification of patients who might obtain either a complete or major pathological response could be relevant to identify those patients who are suitable for bladder conservation strategies, thus avoiding cystectomy after an immunotherapy-induced response. In the future, particular attention will be likely attributed to radiomics which, when routinely available, might help radiologists in disease staging and in evaluating the response to treatment of the bladder wall.

Positron Emission Tomography/Computed Tomography

Over the last decade, positron emission tomography in combination with computed tomography (PET/CT) has become an important tool in the oncology field, covering a major role in staging, response assessment, early response monitoring, and the prognosis of many types of tumors. 18Fluorine-2-deoxy-2-fluorodeoxyglucose (^{18}F-FDG) is the most commonly used radiopharmaceutical in PET/CT imaging, which is excreted through the kidney. Therefore, differentiation of bladder pathology or pelvic lymph node involvement from physiological 18F-FDG activities is difficult [28]; to overcome these limitations, several strategies can be applied such as bladder catheterization and forced diuresis, but they are rarely used in clinical practice. Many authors also evaluated the use of alternative tracers such as 11C-choline, 11C-acetate, and 11C-methionine, which have a lower urinary excretion, but these radiopharmaceuticals are not always available [29]. PET/CT may be helpful in the detection of disease outside the bladder at nodal or more distant sites and in the assessment of recurrent disease. The European Urology Guidelines (EAU) do not recommend the routine use of PET/CT in the staging or in the follow-up of BC; therefore, CT and MR remain the first choice. The NCCN guidelines suggest the possible use of PET/CT with FDG for the staging of selected patients (>cT2 stage), to establish the presence of locoregional or distant lymph nodal involvement, and to evaluate suspicious relapses and/or metastasis [12]. According to some studies, FDG PET/CT has a sensibility of 56% and a specificity of 98% in revealing lymph nodal metastases of BC, thus demonstrating major diagnostic accuracy in staging with regard to the exclusive use of CT [30, 31]. Meta-analysis aimed at comparing imaging methods to assess pelvic lymph nodes involvement in patients with BC showed a slightly

reduced percentage (22%) in recognizing metastases by MRI (22%) compared to CT and PET/CT (both 29%). However, the values showed great variability. The accuracy of CT imaging ranges between 56% and 60%, MR between 67% and 95%, and PET/CT between 64% and 94%. An accurate clinical staging of pelvic lymph nodes is still an open challenge in the field of diagnostic imaging. The use of hybrid methods such as PET/MRI might increase accuracy and resolution in the pelvic disease. The diagnostic performance of MRI has been compared to that of PET/MRI in a study conducted in 22 patients with BC. PET/MRI showed greater accuracy in detecting the primary lesion (86% vs 77%), the pathological pelvic lymph nodes (95% vs 76%), and extranodal disease (100% vs 91%) [32]; its use is still controversial. For several decades chemotherapy has been the only therapeutic alternative in BC: either as neoadjuvant therapy for muscle-invasive tumors localized to the bladder, or as first-line treatment of locally-advanced or metastatic tumors, or for post-surgical adjuvant purposes [33]. The recent approval of anti-PD-1/PD-L1 treatment in urothelial cancer has expanded the therapeutic approach. The different mechanisms of therapeutic action led to unusual pictures of treatment response, with the recognition of phenomena of "flare" or response patterns that simulate a "pseudo-progression" mistakenly interpreted as progression of disease [34]. The consequence of this phenomenon led to the proposal of new criteria of response assessment by PET/CT. Among the major changes proposed by this new approach, we find the concept of "total burden of disease," according to which the tumor extension must be evaluated as a whole and not as appearance/remission of single lesions. Currently, preliminary clinical data, PURE-01 trial (NCT02736266), which proposed the use of pembrolizumab as neoadjuvant, before radical cystectomy in patients with MIBC, does not justify the use of FDG PET/CT in clinical practice [35]. In treatment with immune checkpoint inhibitors, PET/CT may be helpful in the early detection of immuno-related adverse events (irAE), whose long-term impact has yet to be defined. The opportunity to radiolabel monoclonal antibodies PD-1 and PD-L1 [36], in order to recognize and trace the distribution of the drug "cold," assess the extent of tumor collection, as well as its variations over time, and identify the subjects that would benefit from treatment, could give PET/CT an important role in this scenario.

References

1. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. SEER stat fact sheets: bladder cancer.
2. Soukup V, Capoun O, Cohen D, et al. Prognostic performance and reproducibility of the 1973 and 2004/2016 World Health Organization Grading classification systems in non-muscle-invasive bladder cancer: a European Association of Urology non-muscle invasive bladder cancer guidelines panel systematic review. Eur Urol. 2017;72:801–13.
3. Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol. 2017;71:447–61.

4. Sylvester RJ, van der Meijden GP, Sylvester R, Pisano F, et al. Prognostic factors and risk treated with Bacillus Calmette-Guerin: results of a retrospective multicenter study of 2451 patients. Eur Urol. 2015;67:74–82.
5. National Collaborating Center for Cancer. Accessed 1 Nov 2017. Bladder cancer: diagnosis and management. https://www.ncbi.nlm.nih.gov/books/NBK305022/pdf/Bookshelf_NBK305022.pdf.
6. Lee CH, Tan CH, de Castro Faria S, Kundra V. Role of imaging in the local staging of urothelial carcinoma of the bladder. AJR. 2017;208:1193–205.
7. McAchran SE, Hartke DM, Nakamoto DA, Resnick MI. Sonography of the urinary bladder. Ultrasound Clin. 2007;2:17–26.
8. MacVicar D, Husband JE. Radiology in the staging of bladder cancer. Br J Hosp Med. 1994;51:454–8.
9. Denkhaus H, Crone-Munzebrock W, Huland H. Non invasive ultrasound in detecting and staging bladder carcinoma. Urol Radiol. 1985;7:121–31.
10. Nicolau C, Bunesch L, Peri L, et al. Accuracy of contrast-enhanced ultrasound in the detection of bladder cancer. Br J Radiol. 2011;84:1091–9.
11. Caruso G, Salvaggio G, Campisi A, Melloni D, Midiri M, Bertolotto M, et al. Bladder tumor staging: comparison of contrast-enhanced and gray-scale ultrasound. AJR Am J Roentgenol. 2010;194:151–6.
12. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Bladder cancer v5. 2017.
13. Kim B, Semelka RC, Ascher SM, Chalpin DB, Carroll PR, Hricak H. Bladder tumor staging: comparison of contrast-enhanced CT, T1- and T2-weighted MR imaging, dynamic gadolinium enhanced imaging, and late gadolinium-enhanced imaging. Radiology. 1994;193:239–45.
14. Ng CS. Radiologic diagnosis and staging of renal and bladder cancer. Semin Roentgenol. 2006;41:121–38.
15. Kamat AM, Hegarty PK, Gee JR, et al. ICUD-EAU International Consultation on Bladder Cancer 2012: screening, diagnosis, and molecular markers. Eur Urol. 2013;63(1):4–15.
16. Maxine Sun, PhDa, Quoc-Dien Trinh, MDb Diagnosis and staging of bladder cancer.
17. Cha KH, et al. Diagnostic accuracy of CT for prediction of bladder cancer treatment response with and without computerized decision support. Acad Radiol. 2019;26:1137–45.
18. Ghodoussipou S, et al. Preoperative chemotherapy in clinically node positive muscle invasive bladder cancer: radiologic variables can predict response. Urol Oncol 2020;S1078–1439(20)30386–0. https://doi.org/10.1016/j.urolonc.2020.08.020.
19. McKibben MJ, Woods ME. Preoperative imaging for staging bladder cancer. Curr Urol Rep. 2015;16:22. https://doi.org/10.1007/s11934-015-0496-8.
20. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of MRI for prediction of muscle-invasiveness of bladder cancer: a systematic review and meta-analysis. Eur J Radiol. 2017;95:46–55.
21. Huang L, Kong Q, Liu Z, Wang J, Kang Z, Zhu Y. The diagnostic value of MR imaging in differentiating T staging of bladder cancer: a meta-analysis. Radiology. 2018;286:502–11.
22. Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol. In press. https://doi.org/10.1200/JCO.18.01148.
23. Pearson RA, Thelwall PE, Snell J, et al. Evaluationo fearly response to neoadjuvant chemotherapy in muscle-invasive bladder cancer using dynamic contrast-enhanced MRI and diffusion weighted MRI: MARBLE study. J Clin Oncol. 2016;34:403.
24. Saito W, Amanuma M, Tanaka J, et al. Histopathological analysis of bladder cancer stalk observed on MRI. Magn Reson Imaging. 2000;18:11–5.
25. Tekes A, Kamel I, Imam K, et al. Dynamic MRI of bladder cancer: evaluation of staging accuracy. Am J Roentgenol. 2005;184:121–7. [16] Vargas HA, Akin O, Schoder H, et al.

Prospective evaluation of MRI, C-acetate PET/CT and contrast-enhanced CT for staging of bladder cancer. Eur J Radiol. 2012;81:4131–7.
26. Panebianco V, Narumi Y, Altun E, et al. Multiparametric magnetic resonance imaging f or bladder cancer: development of VI-RADS (Vesical Imaging-Reporting and Data System). Eur Urol. 2018;74:294–306.
27. Necchi A, Bandini M, et al. Multiparametric magnetic resonance imaging as a non invasive assessment of tumor response to neoadjuvant pembrolizumab in muscle-invasive bladder cancer: preliminary findings from the Pure-01 study. Eur Urol. 2020;77:636–43.
28. Lakhani A, Khan SR, Bharwani N, Stewart V, Rockall AG, Khan S, Barwick TD. FDG PET/CT pitfalls in gynecologic and genitourinary oncologic imaging. Radiographics. 2017;37(2):577–94.
29. Salmanoglu E, Halpern E, Trabulsi EJ, Kim S, Thakur ML. A glance at imaging bladder cancer. Clin Transl Imaging. 2018;6(4):257–69.
30. Crozier J, Papa N, Perera M, et al. Comparative sensitivity and specificity of imaging modalities in staging bladder cancer prior to radical cystectomy: a systematic review and meta-analysis. World J Urol. 2011;37:667–90.
31. Zehnder P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol. 2011;186:1261–8.
32. Rosenkrantz AB, Friedman KP, Ponzo F, et al. Prospective pilot study to evaluate the incremental value of PET information in patients with bladder cancer undergoing 18F-FDG simultaneous PET/MRI. Clin Nucl Med. 2017;42:e8–e15.
33. Waite K, Youssef H. The role of neoadjuvant and adjuvant systemic chemotherapy with cytoreductive surgery and heated intraperitoneal chemotherapy for colorectal peritoneal metastases: a systematic review. Ann Surg Oncol. 2017;24(3):705–20.
34. Nobashi T, Baratto L, Reddy SA, et al. Predicting response to immunotherapy by evaluating tumors, lymphoid cell-rich organs, and immune-related adverse events using FDG-PET/CT. Clin Nucl Med. 2019;44:e272–9.
35. Marandino L, Capozza A, Bandini M, Raggi D, et al. [18]Fluoro-depxy-glucose positron emission tomography to evaluate lymph node involvement in patients with muscle-invasive bladder cancer receiving neoadjuvant pembrolizumab. Urol Oncol. Seminars and original investigations. 2020:1–7. https://doi.org/10.1016/j.urolonc.2020.09.035.
36. Bensch F, van der Veen EL, Lub-de Hooge MN, et al. 89Zr-atezolizumab imaging as a non-invasive approach to assess clinical response to PD-L1 blockade in cancer. Nat Med. 2018;24:1852–8. https://doi.org/10.1038/s41591-018-0255-8.