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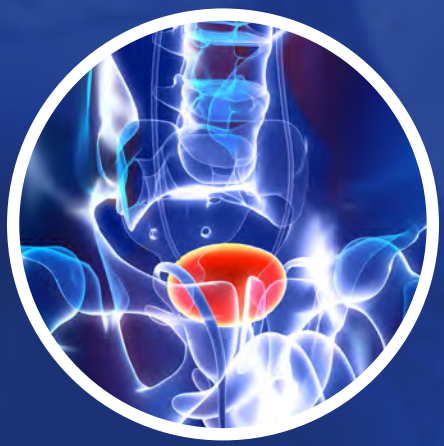

Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting

November 11, 2022

Bladder Cancer

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Featuring the B2B BENCH TO BEDSIDE URO-ONCOLOGY GU CANCERS TRIAD

5th B2B Uro–Oncology: GU Cancers Triad Meeting

In conjunction with Türk Üroloji Derneği İstanbul 1933

ABSTRACT SUBMISSION NOW OPEN

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B2B: Bladder Cancer Summary

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The 4th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 42nd Annual Congress of the Société Internationale d'Urologie, was held on November 11th, 2022, at the Palais des congrès de Montréal in Canada, and transmitted live on the *SIU@U* virtual platform. The session on bladder cancer (BCa) took place on the morning and was chaired by Dr. Alexandra Masson Lecomte, France. This session covered optimal surgical management, molecular risk stratification and precision medicine, and use of magnetic resonance imaging (MRI) for monitoring of T1 BCa. It also covered the use of circulating tumour DNA (ctDNA) and urine tumour DNA (utDNA) to monitor non–muscle-invasive BCa (NMIBC). This session included a debate on use of adjuvant chemotherapy (AC) or immuno-oncology therapy (IO) after cystectomy, a case-based discussion on bladder preservation strategies, and a state-of-the-art overview of advances in intraluminal therapy of upper tract urothelial carcinoma (UTUC).

Dr. Masson-Lecomte discussed the surgical management of T1 tumours, focusing on transurethral resection of bladder tumour (TURBT) and repeat TURBT. She pointed out that tumour stage is unknown at the time of initial TURBT; therefore, it is important to optimize the surgical setup in preparation for all possible findings, especially with respect to cystoscopy and imaging[1]. She emphasized the need for surgeons to receive feedback on the quality of their performance, as a recent report demonstrated that muscle sampling obtained on TURBT increased from 47% without feedback to 72% with feedback[2]. In addition, surgical checklists implemented by centres specialized in management of bladder tumours that address features such as tumour size and location, completeness of TURBT, and findings of clinical examination have increased the rate of recurrence-free survival (RFS) in patients with NMIBC[3]. With respect to the surgical technique, there is no evidence that en bloc or bipolar resections result in superior outcomes compared with fragmented or monopolar resections[4,5]. Thus, surgeon preference and familiarity should guide the choice of technique.

Enhanced tumour detection is essential to maximize the likelihood of complete tumour resection. The benefits of photodynamic diagnosis (PDD) in this regard have been shown both in clinical trials[6] and in real-life experience[7]. The recently completed, open-label PHOTO trial[8] found no difference in 3-year recurrence rates of NMIBC using PDD vs. white light cystoscopy. However, Dr. Masson-Lecomte feels that these findings should not discourage the use of PDD in clinical practice. She highlighted multiple caveats in the study methodology, including the fact that surgeons performing TURBT in this trial were highly experienced and, therefore, among those least likely to benefit from PDD.

B2B: Bladder Cancer Summary

The presence of detrusor muscle in biopsy samples is essential for adequate tumour staging. In fact, the presence of muscle is a good surrogate for the quality of TURBT and is predictive of risk of recurrence and progression. Obtaining muscle is not always easy, however, and it is dependent on the surgeon's experience[9]. Factors associated with the presence of detrusor muscle on a TURBT specimen include tumour size and location. Detrusor muscle is most difficult to obtain when the tumour is located in the junction between the posterior wall and the dome[10]. In the setting of T1 tumours, the rate of residual tumour on second-look resection has been consistently shown to be approximately 50%, even if detrusor muscle is evident on initial TURBT specimens[11]. The presence of residual tumour on second-look TURBT is evidence of a lower-quality initial TURBT, and improving the quality of the first TURBT reduces the likelihood of finding residual tumour[12]. Therefore, while repeated TURBT is still recommended for all patients, the goal should be to ultimately eliminate the need for it by improving initial TURBT.

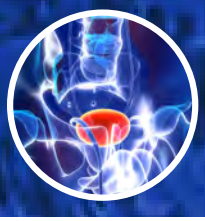
Use of multiparametric MRI (mpMRI) has been shown to improve staging accuracy[13], although this needs to be validated in real-life practice settings. Vesical Imaging-Reporting and Data System (VI-RADS) score is highly predictive both of muscle invasion on first TURBT as well as the presence of detrusor muscle on second-look TURBT in T1 tumours[13].

In a subsequent Q&A session, Dr. Masson-Lecomte specified that patients most likely to benefit from PDD are those with carcinoma in situ (CIS) or multifocal tumours, as well as those with high-grade (HG) tumours. Nevertheless, PDD offers the opportunity to perform a better resection in virtually any clinical situation. Dr. Masson-Lecomte also explained that a tumour inside a diverticulum, whether or not it reaches the bladder, likely would be best managed with radical cystectomy.

Next, Dr. Eugene Pietzak (United States) discussed the use of molecular stratification and precision therapy for HG T1 BCa. Currently, the 2 primary treatment options for this disease are intravesical bacillus Calmette-Guérin (BCG) or radical cystectomy, with tremendous variability among treatment centres and surgeons regarding which option is selected[14]. HG T1 tumours may be resistant to BCG treatment and may harbour occult muscle invasive disease, with a higher risk of progression to muscle-invasive BCa (MIBC). There is therefore a need for biomarkers to better select patients for treatment.

Patients with HG T1 tumours are underrepresented in clinical trials, indicating a need for stage-specific clinical trials in order to better characterize optimal therapy for these patients. Gene expression studies can help address this unmet need. In the UROMOL study, investigators identified class 2 luminal-like tumours that were enriched with CIS and progression signatures, with 80% of progression events occurring within this molecular subtype. The authors postulated that this tumour subtype may be a precursor to the development of secondary MIBC[15]. In a 2021 update, class 2 tumours were further subdivided into class 2a and 2b, with the class 2a tumours having a greater likelihood of progression. The authors proposed a treatment algorithm that incorporated the addition of immune checkpoint inhibitors (ICIs) for class 2 tumours[16].

Patschan et al. used an immunohistochemistry classifier to classify HG T1 tumours in a predominantly non-BCG treated population. Tumours of the genomically unstable and squamous cell–like subtypes had higher progression rates, especially if they had high T-cell infiltration[17]. More recently, Robertson et al. developed a T1-specific classifier using RNA sequencing in a cohort of 73 patients with HG T1, all of whom were treated with BCG. They identified 5 molecular subtypes of HG T1, although these were not predictive of response to BCG. Nevertheless, the T1-early and T1-MYC tumours, both of which are enriched for MYC-target genes, together appeared more likely to progress than the other subtypes[18]. Dr. Pietzak and colleagues applied the UROMOL molecular subtyping to a mixed cohort of patients and found that it was prognostic with respect to RFS but not predictive of BCG response[19]. However, a high degree of immune infiltration based on gene expression before initiation of BCG was associated with a better response in this cohort[19,20]. This finding is reflective of earlier research demonstrating that an immunosuppressive tumour microenvironment



translates into poor response to BCG[17,21–25]. Efforts to better characterize this relationship are ongoing.

It remains to be determined how the tumour immune microenvironment can best be modulated to increase treatment efficacy with BCG and other immunotherapies[26]. The BRIDGE trial will offer new insight into some of these mechanisms, as it will randomize patients with BCG-naïve HG NMIBC to either intravesical gemcitabine and docetaxel or BCG (NCT05538663). In addition, the Alliance A031803 phase 2 trial is investigating the use of intravesical gemcitabine and pembrolizumab in BCG-unresponsive patients with NMIBC (NCT04164082).

Some patients with NMIBC are likely to be good candidates for ICIs, but immune-related adverse events can be a significant problem and need to be considered in patients for whom cystectomy would be potentially curative. ICIs are most likely to be beneficial for patients with very high-risk T1 disease, since cystectomy is the only other accepted treatment option and bladder-sparing treatment is an unmet need in this setting[27].

ICIs may improve response to BCG when the two are used in combination because the interaction between programmed cell death 1 (PD-1) and programmed death-ligand 1 (PD-L1) is a potential mechanism of resistance to BCG, particularly in T1 tumours and CIS[28–31]. ICI monotherapy after BCG has modest efficacy, but the combination of ICIs and BCG may be synergistic[32]; this approach is being evaluated in multiple clinical trials, such as ALBAN (NCT03799835), CREST (NCT04165317), POTOMAC (NCT03528694), and KEYNOTE-676 (NCT03711032). In addition, Dr. Pietzak is co-primary investigator on a phase 2 clinical trial of BCG plus pembrolizumab as a first-line therapy for patients with BCG-naïve very high-risk T1 NMIBC (NCT03504163).

Regarding the genomic landscape of HG T1 tumours, previous research has demonstrated that these tumours are characterized by fewer *FGFR* mutations and increased *ERBB2/HER* alterations. These 2 patterns are mutually exclusive. HG T1 tumours also present with an increased rate of *TP53/MDM2* alterations and cell cycle dysregulation as well as a higher tumour mutational burden, with more DNA damage repair gene alterations, compared with low-grade (LG) tumours[33]. Such genomic alterations are similar to those found in MIBC. Bellmunt et al. performed whole exome sequencing on 62 HG T1 patients treated with BCG who had a good outcome, defined as no recurrence > 4 years from last BCG exposure. They found that a high tumour mutational burden as well as DNA damage mutation alterations were associated with good outcomes[34]. Other studies have also revealed similar findings[20,35,36].

ARID1A mutations are associated with an increased risk of recurrence following treatment with BCG[33,34], and the mechanism behind this association is being actively investigated. In addition, *TP53* alterations may be associated with progression after BCG treatment[34,36]. When comparing patients who are genomically very high risk with those who are just high risk, the very high-risk patients have a genomic profile similar to that of MIBC and are enriched in *ERBB2/HER2* alterations[20,37–39]. This provides potential targets for future therapies, including antibody-drug conjugates.

During his Q&A session, Dr. Pietzak confirmed that *HER2* gene amplification is consistently found to be more common in T1 micropapillary tumours and represents a high-risk feature. He also noted that delivering ICIs within the bladder rather than intravenously does not reduce the risk of immune-related toxicity[40]. Finally, he clarified that bladder tumours are not as enriched in smoking-related mutational signatures compared to other tobacco-related cancers; however, *ERCC2* altered tumours may be enriched in smokers, which could suggest better response to BCG and ICIs in these patients, although the immunosuppressive effects of smoking may limit this.

The next presentation was by Dr. Karin Birkenkamp-Demtröder (Denmark), who discussed whether ctDNA and utDNA can be used to monitor NMIBC. She explained that cancer patients may have ctDNA in their bloodstream that is derived from tumour cells and is highly fragmented and protected by nucleosomes. It has a half-life of < 2.5 hours in the plasma, allowing for real-time monitoring[41]. Also, tumour utDNA may be shed from the urothelium in the bladder and

can be found in the urine supernatant, but it contains different DNA fragment sizes, making it difficult to discriminate between DNA derived from plasma or the bladder lining.

Both ctDNA and utDNA contain tumour-relevant information, including single nucleotide variants and insertion or deletion mutations, which can be assessed via droplet digital polymerase chain reaction or next-generation sequencing. These approaches can be performed in a tumour-agnostic or tumour-informed manner, with the latter being more sensitive[42].

Indeed, ctDNA traces in the plasma can be used to predict recurrence and progression to MIBC in NMIBC[43]. In addition, the presence of ctDNA in the plasma at the time of cystectomy is a predictor of progression in localized MIBC and is associated with a lower RFS[44]. The time to progression or relapse after detection of ctDNA in these patients can be months or years, offering a large window of opportunity to intervene. In a study of 82 patients with Ta or T1 tumours treated with TURBT followed by BCG immunotherapy, panel sequencing of 861 genes revealed ctDNA in about 66% of patients, which was more likely to be detected in patients who were stage T1 or who had tumours > 3 cm. A higher molecular tumour burden index was associated with a shorter disease-free survival (DFS)[45].

To date, no ctDNA or utDNA markers found in the urine have made their way to the clinical setting. One promising approach, however, is UroMark, which is an analysis of a methylation signature in urine pellet DNA that was demonstrated to have a sensitivity of 89% and specificity of 97% for detection of BCa[46]. In addition, Dudley et al. looked at 460 genes detected by deep panel sequencing and demonstrated that utDNA is associated with clinical risk parameters. Patients with CIS as well as those with pT1-4 tumours vs. Ta tumours and HG vs. LG tumours were more likely to have detectable utDNA. Using utDNA, they detected BCa with a sensitivity of 83% in a tumour-agnostic approach and 93% with a tumour-informed approach. The presence of utDNA was associated with reduced RFS. In addition, using a tumour-agnostic approach, they detected 84% of recurrences, which compared favourably to the 53% detection rate using cytology and cystoscopy[47].

There is also a role for utDNA in surveillance on or after treatment. In a study of 156 patients who received ≥ 5 cycles of BCG where utDNA was assessed by deep panel sequencing, higher utDNA was associated with a greater risk of HG recurrence, failure of BCG therapy, and higher T-cell exhaustion both before and after BCG treatment. In addition, clearance of utDNA after BCG treatment was associated with an improved RFS[48].

During her Q&A session, Dr. Birkenkamp-Demtröder recommended that ctDNA and utDNA should be used in combination with cystoscopy rather than replacing this testing modality. For the near future, plasma ctDNA will likely be particularly useful for the management of high-risk tumours, especially if detected after cystectomy, as presence of ctDNA after cystectomy is an indication of metastasis.

In the next session, Dr. Andrea Kokorovic (Canada) discussed the use of MRI for optimal assessment of T1 NMIBC. She pointed out that the depth of tumour invasion is a key determinant in BCa, influencing both prognosis and management approach. Both cystoscopy and imaging play key roles in diagnosis and staging. Among imaging options, ultrasound has low sensitivity. The most commonly used modality is triphasic computed tomography (CT) urography, but mpMRI is emerging as novel technology for use in this setting.

The main goals of imaging are to detect lesions in the upper and lower urinary tract, determine if the tumour is locally advanced, and detect the presence of metastases. The addition of mpMRI allows for differentiation between NMIBC and MIBC as an alternative to a histologic diagnosis. Compared with CT, mpMRI is superior for detecting flat and small (< 1 cm) lesions and is better for differentiation of tissue planes and local tumour description. Currently, the European Association of Urology (EAU) recommends use of MRI for local staging of BCa[49], but access to MRI may be a limiting factor.

Key advantages to use of mpMRI include provision of detailed tumour morphology (ie, distinguishing among exophytic, endophytic, sessile, papillary, and

pedunculated lesions), as well as accurate detection of tumour size and location. Its primary advantage, however, lies in the ability to offer accurate staging[50]. VI-RADS is a 5-point scale based on findings obtained via mpMRI to describe the depth of invasion and probability of muscle invasion, which has demonstrated excellent performance in distinguishing NMIBC from MIBC in multiple studies[51]. The sensitivity of detecting muscle invasion is usually 90% or higher, with a specificity of 85% to 88%[52–54].

One potential use of mpMRI is to determine which patients with NMIBC need a repeat TURBT. In one study, patients with suspected BCa underwent mpMRI before primary resection of their tumour, and those with a VI-RADS > 2 were assumed to have MIBC. Patients with high-risk NMIBC, based on initial histology, went on to receive re-TURBT. The TURBT reports were compared with preoperative VI-RADS findings, and VI-RADS score was a good predictor of outcomes on re-TURBT (ie, detecting absence of cancer/persistent NMIBC vs. upstaging to MICB), with a sensitivity of 85% and specificity of 94%[13]. These findings, said Dr. Kokorovic, suggest that patients with a VI-RADS score of 1 to 2 could go on to receive intravesical therapy, avoiding a re-TURBT, while re-TURBT would be recommended in those with lesions with VI-RADS score 3 to 5, to rule out the potential of muscle invasion. There is some speculation that patients with VI-RADS score 5 lesions could immediately receive radical treatment preceded by neoadjuvant chemotherapy (NAC) or upfront radical cystectomy. This hypothesis is currently under investigation in the BladderPath trial[55].

Another potential use of mpMRI is as a biomarker for detecting NMIBC with aggressive histology. Certain MRI parameters, such as molecular diffusion coefficient and apparent diffusion coefficient, have been shown to correlate with Ki-67 labelling index, which may be predictive of recurrence, progression, aggressiveness, and survival of patients with BCa[56]. This was a small study, however, and is thus not ready for clinical application.

Finally, mpMRI may have a role to play in patient surveillance. In one study of 47 patients with history of NMIBC undergoing surveillance cystoscopy, MRI was performed prior to cystoscopy. Two radiologists blinded to results of cystoscopy interpreted the MRI. There were 34 recurrent bladder tumours detected by cystoscopy in 24 patients. Of these 34 recurrences, 32 were detected by MRI. Among 23 patients without bladder tumour on cystoscopy, MRI detected 2 lesions. This translated to a sensitivity of 91.6% and specificity of 91.5%. Notably, the study authors did not report histology, and this level of accuracy may not be adequate for higher-risk lesions[57].

Potential advantages of MRI surveillance include patient comfort, decreased need for resources, and cost savings. Important limitations, however, are that MRI is unable to detect CIS, and it may have decreased sensitivity/specificity in patients who have undergone treatment. Finally, some physicians may be unwilling to offer or may withhold radical treatment based on imaging without histologic confirmation.

The added value of MRI in BCa management is under evaluation in the BladderPath study. Patients suspected of having BCa were randomized to the standard management pathway that included TURBT or to a pathway that included mpMRI prior to TURBT, with the imaging findings used to help determine treatment. Preliminary findings revealed that patients in the mpMRI-containing pathway had a reduction in time to correct treatment of 30 days[58].

During the Q&A, Dr. Kokorovic said that standard practices for when to use mpMRI have not yet been established. In the meantime, she suggested using it in patients who have been diagnosed with BCa if the results are likely to change the treatment approach, in patients for whom an examination under anesthesia is challenging, and in patients with high-risk or variant histology. Dr. Kokorovic highlighted that, ideally, in the future, magnetic resonance (MR) urograms could be conducted at the same time as mpMRI of the bladder to combine upper tract evaluation and bladder staging into one study and eliminate the need for a CT urogram.

Dr. Kokorovic's presentation was followed by a debate on the use of AC vs. adjuvant IO after radical cystectomy in MIBC, with Dr. Evanguelos Xylinas (France) presenting the pro-chemotherapy side and Dr. Srikala Sridhar (Canada) presenting the pro-IO side.

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Dr. Xylinas pointed out that there is an unmet need in the adjuvant setting for BCa because of high rates of disease recurrence and cancer-specific mortality. Over the last 40 to 50 years, trends in outcomes of patients treated with radical cystectomy include an increased use of NAC and a decreased use of AC. An increase in overall survival (OS) has been observed, but Dr. Xylinas attributed this to better patient selection for radical cystectomy and better management of comorbidities rather than better treatment, as RFS has not changed[59]. The features associated with recurrence in the 1980s are similar to those associated with recurrence today. These include locally advanced disease and lymph node involvement[59].

To date, studies on the use of AC in MIBC have largely included a high-risk patient population, although represented by small samples sizes. Results have been equivocal due to low power to show benefit. In a meta-analysis of 9 of these trials, patients were shown to benefit from adjuvant cisplatin-based chemotherapy[60]. Indeed, EAU guidelines strongly recommend cisplatin-based chemotherapy for patients with pT3/4 and/or pN+ disease if no NAC has been given[61]. There is consensus in the field that there is no benefit to AC following NAC and cystectomy, but there is no level 1 evidence to guide this practice.

Recently, new systemic therapies have been approved for metastatic BCa, and these are now under investigation in the adjuvant setting for MIBC. This includes adjuvant IO such as adjuvant nivolumab, which was compared to placebo in the phase 3 CheckMate 274 trial[62]. Dr. Xylinas pointed out that the improvement in DFS with nivolumab in the PD-L1 > 1% population in this trial is similar to the progression-free survival (PFS) outcomes with AC of a 2015 study that compared AC with deferred treatment[63]. Ultimately, Dr. Xylinas concluded that the question is not whether AC or IO is universally superior, but rather how to select the appropriate approach for individual patients. One tool for helping to answer this question might be ctDNA[64].

To advocate in favour of adjuvant IO, Dr. Sridhar focused on 3 key messages: 1) there is Level 1 evidence for the use of cisplatin-based NAC[65,66] but not AC; 2) pathological complete response (pCR) is predictive of OS[67]; and 3) chemotherapy is better tolerated in the neoadjuvant setting.

The primary goals in the adjuvant setting are to eliminate residual cells, reduce risk of relapse, and improve OS. In metastatic disease, IO has shown efficacy in both platinum-refractory patients and in the first-line switch maintenance settings, which suggests a potential for sequential efficacy after prior chemotherapy[68]. An important role for IO may be in patients with residual disease post-NAC or in patients who are ineligible to receive cisplatin-based chemotherapy.

There are three key phase 3 trials of adjuvant IO in the MIBC setting. CheckMate 274 compared nivolumab with placebo in a high-risk population. In the overall population, DFS was superior with nivolumab, with a hazard ratio (HR) = 0.70. In the PD-L1 ≥ 1% population, the HR = 0.53. Benefits were observed across most subgroups and were even more pronounced among patients who received NAC. Other benefits associated with nivolumab were improvements in non-urothelial tract RFS and distant metastasis-free survival, with a consistent safety profile[62]. The OS data for this trial are not yet available.

IMvigor010 compared atezolizumab with observation and was a negative trial. Nevertheless, the duration of DFS in the atezolizumab arm was 19.4 months[69], which is similar, cross-trial comparisons notwithstanding, to the 20.4 months observed in CheckMate 274[62]. Dr. Sridhar suggested, therefore, that atezolizumab may have activity in this setting and negative findings may be in part due to trial design. In IMvigor010, there was a high rate of treatment discontinuation in the observation arm[69], which was not seen in CheckMate 274 due to the use of a placebo[62].

Finally, the ongoing phase 3 AMBASSADOR trial is comparing pembrolizumab with observation[70], and findings have not yet been published.

Dr. Sridhar agreed that ctDNA is likely important for adequate patient selection for adjuvant IO. In IMvigor010, patients with detectable ctDNA had a worse prognosis compared to patients with no detectable ctDNA, and they appeared to have a benefit from adjuvant atezolizumab. These post hoc results served as the premise for the ongoing phase 3

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IMvigor011 trial, in which patients with high-risk MIBC who are ctDNA positive after cystectomy are being randomized to atezolizumab or placebo[71]. Results are not yet available.

For patients who are not eligible for cisplatin-based NAC or AC, IO has been shown to offer improved DFS in CheckMate 274[62]. It is also likely better tolerated than AC in some patients. Thus, IO represents an important option for patients who are ineligible for or who cannot tolerate AC.

For patients with invasive UTUC, the POUT trial demonstrated a DFS benefit with the addition of AC but no OS advantage[72]. Notably, loss of renal function postoperatively limits cisplatin use, which was shown in POUT to be superior to carboplatin. Thus, many patients simply do not receive AC because of loss of renal function. An alternative option is therefore NAC followed by possible adjuvant IO, although adjuvant nivolumab seemed less effective in UTUC than in CheckMate 274[62].

For cisplatin-eligible patients with MIBC who go straight to radical cystectomy, AC has been shown to offer an improved DFS with a nonsignificant improvement in OS, but trials in this setting have largely been small and underpowered, often closing prematurely prior to reaching enrollment goals. CheckMate 274 did not have these limitations. It may be important to focus more on trial conduct and design rather than the agents themselves.

Dr. Sridhar concluded that, in select populations of patients with MIBC, such as those who are PD-L1-positive or ctDNA-positive, there may be a role for adjuvant IO; however AC remains the standard of care among eligible patients who did not receive NAC.

A case-based panel discussion on bladder preservation followed, moderated by Dr. Masson-Lecomte. On the panel were Drs. Pietzak, Kokorovic, Xylinas, and Sridhar. The first case was that of a 79-year-old male who was self-sufficient and lived alone with his wife. He had been recently diagnosed with Parkinson disease but had few symptoms. He also had a 44-mm aneurysm of the abdominal aorta under simple monitoring, as well as hypertension and chronic obstructive pulmonary disease treated with short-acting bronchodilator inhalers. In July 2021, hematuria and lower urinary tract symptoms (LUTS) led to cystoscopy and detection of a 25-mm tumour located on the left ureteric orifice, which was completely resected with JJ stenting a month later. Glomerular filtration rate (GFR) with the stent was 60 mL/min. Pathology indicated pure urothelial carcinoma T2 G3/HG with lymphovascular invasion (LVI) and CIS around the tumour. The patient was re-resected 4 weeks later to remove the JJ stent because it was poorly tolerated. At this time, there was no residual tumour.

For this patient, the panel was asked whether they would consider trimodal therapy (TMT), radical cystectomy, or NAC. Dr. Kokorovic responded that TMT can be limited by imperfect clinical staging, namely the possibility that undetected residual cancer is present. The patient's comorbidities were fairly typical of BCa patients, so she would refer this patient to medical oncology for consideration for NAC with possible consolidative radical cystectomy. Dr. Sridhar would consider cisplatin-based chemotherapy, as there are supportive treatments to help manage patients with a lower GFR. She would also consider splitting the cisplatin dose over days 1 and 8 to optimize tolerability and scan after 2 cycles to ensure no disease progression. This patient would likely also be evaluated by a multidisciplinary team to determine if he would be a candidate for subsequent TMT or radical cystectomy. Dr. Xylinas agreed that the patient could be offered any of the 3 treatment options under discussion. He and Dr. Pietzak would not exclude TMT based on the pathological findings, especially since the patient underwent a second resection.

Dr. Masson-Lecomte reported that the patient was treated with NAC, primarily because of the LVI, which is highly correlated with poor prognosis and metastasis. The patient was administered 3 cycles of gemcitabine and cisplatin (GC) chemotherapy, then stopped due to renal toxicity, with a GFR 46 mL/min. A second cystoscopy revealed no signs of residual tumour. The patient was offered radical cystectomy with lymph node dissection or TMT, and the patient chose the latter. He received 2 cycles of radiosensitizing 5 fluorouracil (5FU), which was well-tolerated, and he has no signs of residual disease to date.

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Dr. Sridhar explained the rationale for giving NAC in detail. She noted that patients being offered TMT are no longer the older, frail patients of the recent past. Young, fit, healthy patients are highly motivated to keep their bladder and are typically cisplatin-eligible. A propensity analysis demonstrated that, in MIBC patients who are candidates for both radical cystectomy and TMT, outcomes are fairly similar[73]. In MIBC, NAC eliminates micrometastatic disease and improves OS. The RTOG 89-03 trial failed to demonstrate benefits of methotrexate, cisplatin, and vinblastine (MCV) chemotherapy prior to selective bladder preservation but was underpowered. In addition, patients received only 2 cycles of NAC, which was poorly tolerated without the supportive measures used today[74]. Thus, it is difficult to interpret the findings.

In a review of 57 patients treated at Dr. Sridhar's institution, 65% were stage II, 25% were stage III, and 11% had regional nodal metastases. All completed external beam radiotherapy, and 95% completed NAC, with 84% completing ≥ 64% of their concurrent chemotherapy doses. After a median follow-up of 19.3 months, median OS was not reached, 2-year OS was 74%, disease-specific survival was 88%, and 2 year bladder intact DFS was 64%. The salvage cystectomy rate was 14%, distant relapse occurred in 11%, and 9% ultimately died of metastatic disease[75].

Dr. Masson-Lecomte then presented the second case, this one of a 62-year-old female heavy smoker who was divorced, had a new partner, and was highly motivated to retain an active sex life. She had 3 children and had received a hysterectomy in 2010 for uterine fibroids. She had stage A chronic lymphocytic leukemia that was completely stable for 4 years and that was presently not treated. Hematuria in May 2020 led to an ultrasound, which revealed a 30-mm tumour of the left lateral wall, away from the ureteric orifice. Her GFR was 75 mL/min. She underwent complete TURBT, and pathology revealed T2 HG/G3 urothelial carcinoma with squamous differentiation, no CIS, and no LVI. A thoraco-abdominal CT revealed no sign of metastasis.

For this patient, Dr. Masson-Lecomte asked whether she was a good candidate for TMT, NAC, or radical cystectomy with neobladder. Dr. Pietzak would consider TMT and bladder preserving options and would do his own examination under anesthesia and TURBT for risk stratification. Risk of recurrence is an important consideration, given the patient is relatively young. Radical cystectomy with a neobladder could be a good option, if the vagina was preserved and pelvic support could be provided, but it would be important to tell the patient that functional outcomes for females are suboptimal. Drs. Xylinas and Sridhar would also recommend upfront TMT as a bladder preservation strategy, given that the patient is young and sexually active, and has a small tumour. Dr. Sridhar added that she would also offer upfront NAC, likely GC chemotherapy, given the high GFR. Dr. Kokorovic agreed that TMT is a good option but was concerned about the squamous differentiation because she was unaware of how well these tumours respond to radiation; this histology responds well to chemotherapy. Dr. Masson-Lecomte pointed out that in the VESPER trial, treatment outcomes with either GC or dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) chemotherapy were unaffected by histologic subtype[76].

Dr. Masson-Lecomte explained that this patient was determined not to be a good candidate for a neobladder because of her previous hysterectomy, which left no posterior hammock. She was treated with upfront TMT and was included in the Bladder Sparing/GETUG-AFU 35 clinical trial, in which patients receive extensive TURBT and TMT with radiosensitizing chemotherapy, followed by adjuvant immunotherapy. This patient received 60 Gy on the bladder and pelvis, as well as 5FU-cisplatin chemotherapy for 2 cycles. IO consisted of 12 months of atezolizumab. At 30 months of follow-up, there is no sign of residual disease or LUTS.

Dr. Sridhar discussed upfront TMT that incorporates IO. Several trials are ongoing in this setting. For instance, SWOG/NRG1806 is a phase 3 trial comparing concurrent chemoradiation with or without atezolizumab for localized MIBC[77]. EA8185 (INSPIRE) is a phase 2 trial exploring the role of durvalumab ± chemoradiotherapy[78], and KEYNOTE-992 is examining pembrolizumab with or without concurrent chemotherapy for bladder preservation in localized MIBC[79]. The CCTG BL13 study is exploring TMT with or without adjuvant durvalumab in MIBC. In this trial, upfront

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NAC is permitted. Important endpoints in these trials include bladder intact DFS, OS, and tolerability[80]. As IO therapies are relatively well-tolerated, a broader scope of patients may be eligible to receive them. Importantly, many studies that evaluate new agents in the neoadjuvant setting mandate cystectomy, and it is important to have data on patients who opt for bladder-sparing approaches. Younger, fitter patients who are eligible for cisplatin and who would like to spare their bladders should be considered for NAC, Dr. Sridhar said, because pCR is predictive of OS; therefore, pCR should be the key goal in these patients.

During the discussion, the issue of how to evaluate response to TMT was raised. Without cystectomy, there is no tissue available for pathological analysis unless a biopsy is obtained. Many of the clinical trials evaluating TMT include biopsy-based outcomes. Determining how to assess these patients in the clinical setting will be an important future challenge. Bladder intact DFS is a logical endpoint, since keeping the bladder is a primary goal of the bladder-sparing approach.

The third case was that of a 77-year-old female smoker referred in 2018. She was completely independent and married, with 2 children. In 2017, she had a left microsatellite instability-positive colon cancer, which was treated surgically, and was left with bowel dysfunction. Comorbidities included hypertension and type 2 diabetes. Hematuria in June 2018 led to a CT scan, which revealed a 15-mm anterior wall bladder tumour, with no signs of metastases. GFR was 67 mL/min. The patient underwent complete TURBT, and pathology revealed T2 HG/G3 urothelial carcinoma with 60% micropapillary components. There was no evidence of CIS, but LVI was present. Positron emission tomography (PET)/CT ordered for the colon cancer suggested the presence of metastases to the pubic branch. Biopsy revealed no tumour cells, but some doubt about the potential for metastasis remained. Dr. Masson-Lecomte asked how important systemic therapy was for this patient and what the best local treatment option would be.

Dr. Kokorovic felt that radical cystectomy would be the appropriate next step in this patient, and she would refer to medical oncology for consideration of chemotherapy. She would not consider TMT because micropapillary tumours are very aggressive. Dr. Sridhar agreed, adding that she would offer NAC before cystectomy. This case also highlighted a potential role for PET in correctly staging patients with variant histologies, although it is not routinely used. Drs. Xylinas and Pietzak would similarly start with systemic therapy because of the variant histology and uncertain presence of metastasis, then re-evaluate. Dr. Pietzak added that the micropapillary component would lead him to perform an even more extended lymph node dissection than usual, given the high rates of nodal involvement for this tumour type.

The patient was treated with NAC consisting of 6 cycles of dd-MVAC, which was well-tolerated. A second TURBT revealed a normal bladder, with no residual tumour at pathology. MRI revealed a completely normal bladder wall. PET/CT revealed no sign of metastasis, and the lesion on the pubis disappeared with chemotherapy. The patient refused any further local treatment and opted for simple surveillance with cystoscopy and CT scan. After 4 years, she is in complete remission. While this is not a routine approach, the panelists acknowledged that it does occur in clinical practice, sometimes with good outcomes. Dr. Kokorovic said the case highlights the need for better biomarkers to identify who requires more aggressive treatment, and Dr. Pietzak highlighted that he would encourage patients declining cystectomy to at least receive TMT.

The last case was a 68-year-old single, isolated active smoker male referred in 2017. He had a myocardial infarction in 2013 with some peripheral arterial obstructive disease. Severe LUTS resistant to medical treatment led to a CT scan, which revealed a large right lateral wall tumour with multiple bladder diverticula. There was no hydronephrosis and no signs of metastasis. GFR was 85 mL/min, and left ventricular ejection fraction was 55%. The first TURBT was incomplete because of the size of the tumour and the presence of diverticula. Pathology revealed T2 HG/G3 pure urothelial carcinoma with CIS around the tumour.

Dr. Masson-Lecomte asked the panelists if they would consider upfront bladder preservation in this patient. They agreed that the bladder was probably not worth saving, and quality of life would likely be better

with cystectomy. This patient received NAC in the form of 6 cycles of dd-MVAC and had an extraordinary response, with a clear CT and normal-looking bladder on cystoscopy. A second TURBT with deep resection revealed no residual tumour, which was confirmed on MRI. LUTS was much improved. Given this response, Dr. Masson-Lecomte asked whether the panel would now consider a bladder-sparing approach, and they agreed they would, although radical cystectomy would still be seriously considered. This patient did not want radical cystectomy and so underwent 2 cycles of radiochemotherapy instead, which was well-tolerated. Cystoscopy yielded normal findings in September 2022, but a CT scan revealed suspicious lesions in the pelvic bones, which was confirmed on MRI. It remains uncertain if metastasis would have occurred even if radical cystectomy was performed.

The last presentation in the BCa session was by Dr. Seth P. Lerner (United States), who discussed advances in intraluminal therapy for UTUC, which can be delivered via percutaneous nephrostomy or ureteral catheter. A variety of drugs, both chemotherapy and IO with BCG, can be used, although the level of evidence for the latter is modest[81]. Importantly, one cannot rely on reflux via a JJ stent to treat the urinary tract because this approach often does not reach the renal pelvis.

Studies indicate that intraluminal therapy using BCG appears to be most effective in cases of CIS[82]. While a meta-analysis showed no difference in outcomes with or without treatment regardless of drug used, disease stage/grade, or delivery modality[83], Dr. Lerner pointed out that this is likely due to small cohorts and a lack of high-level evidence across the disease spectrum for Ta/T1 or CIS.

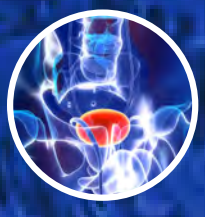
Given the complex nature of delivering intraluminal therapy, he recommended reserving it for patients with LG UTUC who are most likely to benefit, particularly when it can be used as an alternative to nephroureterectomy. The EAU[81] and the National Comprehensive Cancer Network®[84] guidelines for treatment of UTUC now address use of intracavitary kidney-sparing surgery, although the American Urological Association has yet to do so.

UGN-101 is a reverse thermal gel that is liquid at low temperatures and semi-solid at body temperature and that contains mitomycin at a concentration of 4 mg/1 mL. It can be injected via a ureteral catheter at cold temperatures, where it fills the entire collecting system proximal to the ureteral-pelvic junction. When it warms to body temperature, it becomes semi-solid and is water soluble. As the kidney produces urine, the gel dissolves over 4 to 6 hours, solving the problem of dwell time within the collecting system[85,86]. The gel injector functions via the same principles as a balloon dilator for treatment of ureteral stricture or percutaneous access.

Data from the OLYMPUS trial demonstrated that LG UTUC can be chemically ablated using UGN-101[87]. For this open-label, phase 3 trial, 74 patients with biopsy- and cytology-confirmed LG UTUC with a measurable 5- to 15-mm tumour located above the ureteropelvic junction received intracavitary UGN-101 in 6 once-weekly installations. The primary disease evaluation occurred within 4 to 6 weeks after treatment completion. Those with a complete response (CR) were given the option to go to monthly maintenance therapy for up to 12 months[87].

The CR was 59%, and this was identical whether tumours were considered resectable or unresectable. For patients who achieved a CR, estimated durability was 82% at 12 months[88]. The primary adverse event of concern with UGN-101 is ureteral stenosis or stricture. In this trial, the ureteral stenosis rate was 43.7%, but most of these were all easily managed, said Dr. Lerner. Two patients ultimately required a nephrectomy due to stenosis. There were 3 deaths, but these were deemed unrelated to treatment[87].

FGFR3 alterations are the most common mutation in UTUC, with observed rates of 54% to 74%. These are particularly common in LG disease[89,90]. This provides an important target for future therapies. Unfortunately, a recent phase 3 adjuvant trial exploring the role of infigratinib for UTUC has recently been discontinued. Nevertheless, unpublished data by Dr. Surena Matin, of the MD Anderson Cancer Center, demonstrate an increased response rate among *FGFR3*-positive patients.



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Another potential future approach is padeliporfin, a form of vascular targeted photodynamic therapy. In phase 1 research that included 22 patients with UTUC who recurred after prior endoscopic treatment, 9 of 18 patients who were eligible for efficacy assessment had a CR by 30 days post-treatment[91]. The ongoing single-arm, open-label, phase 3 ENLIGHTENED trial (NCT04620239) is further exploring this approach.

During the Q&A session, Dr. Lerner clarified that the best candidates for UGN-101 are likely to be patients with larger volume tumours that cannot be completely ablated or resected and those with lower pole tumours that can be difficult to access

Abbreviations Used in the Text

5FU	5 fluorouracil
AC	adjuvant chemotherapy
BCa	bladder cancer
BCG	bacillus Calmette-Guérin
CIS	carcinoma in situ
CR	complete response
CT	computed tomography
ctDNA	circulating tumour DNA
dd-MVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DFS	disease-free survival
EAU	European Association of Urology
GC	gemcitabine and cisplatin
GFR	glomerular filtration rate
HG	high grade
HR	hazard ratio
ICI	immune checkpoint inhibitor
IO	immuno-oncology therapy
LG	low grade
LUTS	lower urinary tract symptom
LVI	lymphovascular invasion
MCV	methotrexate, cisplatin, and vinblastine
MIBC	muscle-invasive bladder cancer
mpMRI	multiparametric magnetic resonance imaging
MR	magnetic resonance
MRI	magnetic resonance imaging
NAC	neoadjuvant chemotherapy
NMIBC	non–muscle-invasive bladder cancer
OS	overall survival
pCR	pathological complete response
PD-1	programmed cell death 1
PDD	photodynamic diagnosis
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
RFS	recurrence-free survival
TMT	trimodal therapy
TURBT	transurethral resection of bladder tumour
utDNA	urine tumour DNA
UTUC	upper tract urothelial carcinoma
VI-RADS	Vesical Imaging-Reporting and Data System

References

1. Mariappan P. Attention to detail and a permissive set-up: crucial for an effective TURBT. *Nat Rev Urol.*2021;18(5):253–254. doi: 10.1038/s41585-021-00441-9
2. Das A, Cohen JE, Ko OS, Jordan BJ, Glaser AP, Auffenberg GB, et al. Surgeon scorecards improve muscle sampling on transurethral resection of bladder tumor and recurrence outcomes in patients with nonmuscle invasive bladder cancer. *J Urol.*2021;205(3):693–700. doi: 10.1097/ju.0000000000001372
3. Suarez-Ibarrola R, Soria F, Abufaraj M, D'Andrea D, Preto M, Gust KM, et al. Surgical checklist impact on recurrence-free survival of patients with non-muscle-invasive bladder cancer undergoing transurethral resection of bladder tumour. *BJU Int.*2019;123(4):646–650. doi: 10.1111/BJU.14557
4. Teoh JYC, MacLennan S, Chan VWS, Miki J, Lee HY, Chiong E, et al. An international collaborative consensus statement on en bloc resection of bladder tumour incorporating two systematic reviews, a two-round Delphi survey, and a consensus meeting. *Eur Urol.*2020;78(4):546–569. doi: 10.1016/J.EURURO.2020.04.059
5. Murugavaithianathan P, Devana SK, Mavuduru R, Kumar S, Singh SK, Mandal AK, et al. Bipolar transurethral resection of bladder tumor provides better tissue for histopathology but has no superior efficacy and safety: a randomized controlled trial. *J Endourol.*2018;32(12):1125–1130. doi: 10.1089/END.2017.0328
6. Burger M, Grossman HB, Droller M, Schmidbauer J, Hermann G, Dragoescu O, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. *Eur Urol.*2013;64(5):846–854. doi: 10.1016/J.EURURO.2013.03.059
7. Gallagher KM, Gray K, Anderson CH, Lee H, Stewart S, Donat R, et al. "Real-life experience": recurrence rate at 3 years with Hexvix® photodynamic diagnosis-assisted TURBT compared with good quality white light TURBT in new NMIBC-a prospective controlled study. *World J Urol.*2017;35(12):1871–1877. doi: 10.1007/S00345-017-2077-6
8. Heer R, Lewis R, Vadiveloo T, Yu G, Mariappan P, Cresswell J, et al. A randomized trial of PHOTOdynamic surgery in non–muscle-invasive bladder cancer. *NEJM Evid.*2022;1(10). doi: 10.1056/EVIDOA2200092
9. Mariappan P, Zachou A, Grigor KM. Detrusor muscle in the first, apparently complete transurethral resection of bladder tumour specimen is a surrogate marker of resection quality, predicts risk of early recurrence, and is dependent on operator experience. *Eur Urol.*2010;57(5):843–849. doi: 10.1016/J.EURURO.2009.05.047
10. Bebane S, Denize J, Goujon A, Meria P, Verine J, Mongiat-Artus P, et al. Perioperative outcomes of transurethral resection for T1 bladder tumors: quality evaluation based on patient, tumor and surgeon criteria. *World J Urol.*2021;39(11):4159–4165. doi: 10.1007/S00345-021-03765-8
11. Naselli A, Hurle R, Paparella S, Buffi NM, Lughezzani G, Lista G, et al. Role of restaging transurethral resection for T1 non-muscle invasive bladder cancer: a systematic review and meta-analysis. *Eur Urol Focus.*2018;4(4):558–567. doi: 10.1016/J.EUF.2016.12.011
12. Mariappan P, Johnston A, Padovani L, Clark E, Trail M, Hamid S, et al. Enhanced quality and effectiveness of transurethral resection of bladder tumour in non–muscle-invasive bladder cancer: a multicentre real-world experience from Scotland's Quality Performance Indicators Programme. *Eur Urol.*2020;78(4):520–530. doi: 10.1016/J.EURURO.2020.06.051
13. Del Giudice F, Barchetti G, De Berardinis E, Pecoraro M, Salvo V, Simone G, et al. Prospective assessment of Vesical Imaging Reporting and Data System (VI-RADS) and its clinical impact on the management of high-risk non-muscle-invasive bladder cancer patients candidate for repeated transurethral resection. *Eur Urol.*2020;77(1):101–109. doi: 10.1016/J.EURURO.2019.09.029
14. Martin-Doyle W, Leow JJ, Orsola A, Chang SL, Bellmunt J. Improving selection criteria for early cystectomy in high-grade T1 bladder cancer: a meta-analysis of 15,215 patients. *J Clin Oncol.*2015;33(6):643–650. doi: 10.1200/JCO.2014.57.6967
15. HedegaardJ, Lamy P, Nordentoft I, Algaba F, Høyer S, Ulhøi BP, et al. Comprehensive transcriptional analysis of early-stage urothelial carcinoma. *Cancer Cell.*2016;30(1):27–42. doi: 10.1016/J.CCELL.2016.05.004
16. Lindskrog SV, Prip F, Lamy P, Taber A, Groeneveld CS, Birkenkamp-Demtröder K, et al. An integrated multi-omics analysis identifies prognostic molecular subtypes of non-muscle-invasive bladder cancer. *Nat Commun.*2021;12(1):1–18. doi: 10.1038/s41467-021-22465-w

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17. Patschan O, Sjödahl G, Chebil G, Lövgren K, Lauss M, Gudjonsson S, et al. A molecular pathologic framework for risk stratification of stage T1 urothelial carcinoma. *Eur Urol.*2015;68(5):824–832. doi: 10.1016/J.EURURO.2015.02.021

18. Robertson AG, Groeneveld CS, Jordan B, Lin X, McLaughlin KA, Das A, et al. Identification of differential tumor subtypes of T1 bladder cancer. *Eur Urol.*2020;78(4):533–537. doi: 10.1016/j.eururo.2020.06.048

19. Damrauer JS, Roell KR, Smith MA, Sun X, Kirk EL, Hoadley KA, et al. Identification of a novel inflamed tumor microenvironment signature as a predictive biomarker of bacillus Calmette-Guérin immunotherapy in non-muscle-invasive bladder cancer. *Clin Cancer Res.*2021;27(16):4599–4609. doi: 10.1158/1078-0432.CCR-21-0205/672180

20. Goel A, Ward DG, Noyvert B, Yu M, Gordon NS, Abbotts B, et al. Combined exome and transcriptome sequencing of non-muscle-invasive bladder cancer: associations between genomic changes, expression subtypes, and clinical outcomes. *Genome Med.*2022;14(1):1–16. doi: 10.1186/S13073-022-01056-4

21. Miyake M, Tatsumi Y, Gotoh D, Ohnishi S, Owari T, Iida K, et al. Regulatory T cells and tumor-associated macrophages in the tumor microenvironment in non-muscle invasive bladder cancer treated with intravesical bacille Calmette-Guérin: a long-term follow-up study of a Japanese cohort. *Int J Mol Sci.*2017;18(10):2186. doi: 10.3390/IJMS18102186

22. Takayama H, Nishimura K, Tsujimura A, Nakai Y, Nakayama M, Aozasa K, et al. Increased infiltration of tumor associated macrophages is associated with poor prognosis of bladder carcinoma in situ after intravesical bacillus Calmette-Guerin instillation. *J Urol.*2009;181(4):1894–1900. doi: 10.1016/J.JURO.2008.11.090

23. Ajili F, Kourda N, Darouiche A, Chebil M, Boubaker S. Prognostic value of tumor-associated macrophages count in human non-muscle-invasive bladder cancer treated by BCG immunotherapy. Ultrastruct. *Pathol.*2013;37(1):56–61. doi: 10.3109/01913123.2012.728688

24. Pichler R, Fritz J, Zavadil C, Schäfer G, Culig Z, Brunner A. Tumor-infiltrating immune cell subpopulations influence the oncologic outcome after intravesical bacillus Calmette-Guérin therapy in bladder cancer. *Oncotarget.*2016;7(26):39916–39930. doi: 10.18632/ONCOTARGET.9537

25. Chevalier MF, Trabanelli S, Racle J, Salomé B, Cesson V, Gharbi D, et al. ILC2-modulated T cell–to-MDSC balance is associated with bladder cancer recurrence. J Clin Invest.2017;127(8):2916–2929. doi: 10.1172/JCI89717

26. Chu C, Pietzak E. Immune mechanisms and molecular therapeutic strategies to enhance immunotherapy in non-muscle invasive bladder cancer. *Urol Oncol.*2022; Epub ahead of print. doi: 10.1016/J.UROLONC.2022.05.013

27. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. *J Urol.*2016;196(4):1021–1029. doi: 10.1016/J.JURO.2016.06.049

28. Kates M, Matoso A, Choi W, Baras AS, Daniels MJ, Lombardo K, et al. Adaptive immune resistance to intravesical BCG in non-muscle invasive bladder cancer: implications for prospective BCG-unresponsive trials. *Clin Cancer Res.*2020;26(4):882–891. doi: 10.1158/1078-0432.CCR-19-1920

29. Hashizume A, Umemoto S, Yokose T, Nakamura Y, Yoshihara M, Shoji K, et al. Enhanced expression of PD-L1 in non-muscle-invasive bladder cancer after treatment with bacillus Calmette-Guerin. *Oncotarget.*2018;9(75):34066–34078. doi: 10.18632/ONCOTARGET.26122

30. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer.*2007;109(8):1499–1505. doi: 10.1002/CNCR.22588

31. Rouanne M, Betari R, Radulescu C, Goubar A, Signolle N, Neuzillet Y, et al. Stromal lymphocyte infiltration is associated with tumour invasion depth but is not prognostic in high-grade T1 bladder cancer. *Eur J Cancer.*2019;108:111–119. doi: 10.1016/J.EJCA.2018.12.010

32. Copland A, Sparrow A, Hart P, Diogo GR, Paul M, Azuma M, et al. Bacillus Calmette-Guérin induces PD-L1 expression on antigen-presenting cells via autocrine and paracrine interleukin-STAT3 circuits. *Sci Reps.*2019;9(1):1–10. doi: 10.1038/s41598-019-40145-0

33. Pietzak EJ, Bagrodia A, Cha EK, Drill EN, Iyer G, Isharwal S, et al. Next-generation sequencing of nonmuscle invasive bladder cancer reveals potential biomarkers and rational therapeutic targets. *Eur Urol.*2017;72(6):952–959. doi: 10.1016/J.EURURO.2017.05.032

34. Bellmunt J, Kim J, Reardon B, Perera-Bel J, Orsola A, Rodriguez-Vida A, et al. Genomic predictors of good outcome, recurrence, or progression in high-grade T1 non-muscle-invasive bladder cancer. *Cancer Res.*2021;80(20):4476–4486. doi: 10.1158/0008-5472.CAN-20-0977/654203

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35. Bastos DA, Mattedi RL, Barreiro R, Dos Santos FF, Buzatto V, Masotti C, et al. Genomic biomarkers and underlying mechanism of benefit from BCG immunotherapy in non-muscle invasive bladder cancer. *Bladder Cancer.*2020;6(2):171–186. doi: 10.3233/BLC-200289

36. Hurst CD, Cheng G, Platt FM, Castro MAA, Marzouka NADS, Eriksson P, et al. Stage-stratified molecular profiling of non-muscle-invasive bladder cancer enhances biological, clinical, and therapeutic insight. *Cell Rep Med.*2021;2(12):100472. doi: 10.1016/j.xcrm.2021.100472

37. Ding W, Tong S, Gou Y, Sun C, Wang H, Chen Z, et al. Human epidermal growth factor receptor 2: a significant indicator for predicting progression in non-muscle-invasive bladder cancer especially in high-risk groups. *World J Urol.*2015;33(12):1951–1957. doi: 10.1007/S00345-015-1557-9

38. Kocsmár I, Kocsmár É, Pajor G, Kulka J, Székely E, Kristiansen G, et al. Addition of chromosome 17 polysomy and her2 amplification status improves the accuracy of clinicopathological factor-based progression risk stratification and tumor grading of non-muscle-invasive bladder cancer. *Cancers (Basel).*2022;14(19):4570. doi: 10.3390/CANCERS14194570/S1

39. Patelli G, Zeppellini A, Spina F, Righetti E, Stabile S, Amatu A, et al. The evolving panorama of HER2-targeted treatments in metastatic urothelial cancer: a systematic review and future perspectives. *Cancer Treat Rev.*2022;104:102351. doi: 10.1016/j.ctrv.2022.102351

40. Meghani K, Cooley LF, Choy B, Kocherginsky M, Swaminathan S, Munir SS, et al. First-in-human intravesical delivery of pembrolizumab identifies immune activation in bladder cancer unresponsive to bacillus Calmette-Guérin. *Eur Urol.*2022;82(6):602–610. doi: 10.1016/j.eururo.2022.08.004

41. Elazezy M, Joosse SA. Techniques of using circulating tumor DNA as a liquid biopsy component in cancer management. *Comput Struct Biotechnol J.* 2018;16:370–378. doi: 10.1016/j.csbj.2018.10.002

42. Keller L, Belloum Y, Wikman H, Pantel K. Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. *Br J Cancer.*2020;124(2):345–358. doi: 10.1038/s41416-020-01047-5

43. Birkenkamp-Demtröder K, Nordentoft I, Christensen E, Høyer S, Reinert T, Vang S, et al. Genomic alterations in liquid biopsies from patients with bladder cancer. *Eur Urol.*2016;70(1):75–82. doi: 10.1016/J.EURURO.2016.01.007

44. Christensen E, Birkenkamp-Demtröder K, Sethi H, Shchegrova S, Salari R, Nordentoft I, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma. *J Clin Oncol.*2019;37(18):1547–1557. doi: 10.1200/JCO.18.02052

45. Zhang J, Dai D, Tian J, Li L, Bai J, Xu Y, et al. Circulating tumor DNA analyses predict disease recurrence in non-muscle-invasive bladder cancer. *Front Oncol.* 2021;11:657483. doi: 10.3389/FONC.2021.657483/PDF

46. Feber A, Dhami P, Dong L, de Winter P, Tan WS, Martínez-Fernández M, et al. UroMark—a urinary biomarker assay for the detection of bladder cancer. *Clin Epigenetics.*2017;9(1):1–10. doi: 10.1186/S13148-016-0303-5/TABLES/3

47. Dudley JC, Schroers-Martin J, Lazzareschi DV, Shi WY, Chen SB, Esfahani MS, et al. Detection and surveillance of bladder cancer using urine tumor DNA. *Cancer Discov.*2019;9(4):500–509. doi: 10.1158/2159-8290.CD-18-0825

48. Strandgaard T, Lindskrog V, Nordentoft I, Christensen E, Birkenkamp-Demtröder K, Andreasen TG, et al. Elevated T-cell exhaustion and urinary tumor DNA levels are associated with bacillus Calmette-Guérin failure in patients with non–muscle-invasive bladder cancer. *Eur Urol.*2022;82(6):646–656. doi: 10.1016/J.EURURO.2022.09.008

49. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). *Eur Urol.*2022;81(1):75–94. doi: 10.1016/J.EURURO.2021.08.010

50. Panebianco V, de Berardinis E, Barchetti G, Simone G, Leonardo C, Grompone MD, et al. An evaluation of morphological and functional multi-parametric MRI sequences in classifying non-muscle and muscle invasive bladder cancer. *Eur Radiol.*2017;27(9):3759–3766. doi: 10.1007/s00330-017-4758-3

51. Panebianco V, Narumi Y, Altun E, Bochner BH, Efstathiou JA, Hafeez S, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (Vesical Imaging-Reporting And Data System). *Eur Urol.*2018;74(3):294–306. doi: 10.1016/J.EURURO.2018.04.029

52. 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(2):502–511. doi: 10.1148/RADIOL.2017171028

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53. Cornelissen SWE, Veenboer PW, Wessels FJ, Meijer RP. Diagnostic accuracy of multiparametric MRI for local staging of bladder cancer: a systematic review and meta-analysis. *Urology.*2020;145:22–29. doi: 10.1016/J.UROLOGY.2020.07.021

54. Del Giudice F, Flammia RS, Pecoraro M, Moschini M, D'Andrea D, Messina E, et al. The accuracy of Vesical Imaging-Reporting and Data System (VI-RADS): an updated comprehensive multi-institutional, multi-readers systematic review and meta-analysis from diagnostic evidence into future clinical recommendations. *World J Urol.*2022;40(7):1617–1628. doi: 10.1007/S00345-022-03969-6

55. Bryan RT, Liu W, Pirrie SJ, Amir R, Gallagher J, Hughes AI, et al. Comparing an imaging-guided pathway with the standard pathway for staging muscle-invasive bladder cancer: preliminary data from the BladderPath study. *Eur Urol.*2021;80(1):12–15. doi: 10.1016/j.eururo.2021.02.021

56. Wang F, Wu LM, Hua XL, Zhao ZZ, Chen XX, Xu JR. Intravoxel incoherent motion diffusion-weighted imaging in assessing bladder cancer invasiveness and cell proliferation. *J Magn Reson Imaging.*2018;47(4):1054–1060. doi: 10.1002/JMRI.25839

57. El-Assmy A, Abou-El-Ghar ME, Refaie HF, Mosbah A, El-Diasty T. Diffusion-weighted magnetic resonance imaging in follow-up of superficial urinary bladder carcinoma after transurethral resection: initial experience. *BJU Int.*2012;110(11b):E622–E627. doi: 10.1111/J.1464-410X.2012.11345.X

58. James N. 1733MO - First results from BladderPath: a randomised trial of MRI versus cystoscopic staging for newly diagnosed bladder cancer. *Ann Oncol.*2022;33(Suppl_7):S785–S807. doi: 10.1016/annonc/annonc1080

59. Mitra AP, Cai J, Miranda G, Bhanvadia S, Quinn DI, Schuckman AK, et al. Management trends and outcomes of patients undergoing radical cystectomy for urothelial carcinoma of the bladder: evolution of the University of Southern California experience over 3,347 cases. *J Urol.*2022;207(2):302–313. doi: 10.1097/JU.0000000000002242

60. Leow JJ, Martin-Doyle W, Rajagopal PS, Patel CG, Anderson EM, Rothman AT, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. *Eur Urol.*2014;66(1):42–54. doi: 10.1016/J.EURURO.2013.08.033

61. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, et al. European Association of Urology guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2020 guidelines. *Eur Urol.*2021;79(1):82–104. doi: 10.1016/J.EURURO.2020.03.055

62. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med.*2021;384(22):2102–2114. doi: 10.1056/NEJMOA2034442

63. Sternberg CN, Skoneczna I, Kerst JM, Albers P, Fossa SD, Agerbaek M, et al. Immediate versus deferred chemotherapy after radical cystectomy in patients with pT3-pT4 or N+ M0 urothelial carcinoma of the bladder (EORTC 30994): an intergroup, open-label, randomised phase 3 trial. *Lancet Oncol.*2015;16(1):76–86. doi: 10.1016/S1470-2045(14)71160-X

64. Powles T, Assaf ZJ, Davarpanah N, Banchereau R, Szabados BE, Yuen KC, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. *Nature.*2021;595(7867):432–437. doi: 10.1038/s41586-021-03642-9

65. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.*2003;349(9):859–866. doi: 10.1056/NEJMOA022148

66. Vale CL. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol.*2005;48(2):202–206. doi: 10.1016/J.EURURO.2005.04.006

67. Sonpavde G, Goldman BH, Speights VO, Lerner SP, Wood DP, Vogelzang NJ, et al. Quality of pathologic response and surgery correlate with survival for patients with completely resected bladder cancer after neoadjuvant chemotherapy. *Cancer.*2009;115(18):4104–4109. doi: 10.1002/cncr.24466

68. Parikh M, Powles T. Immune checkpoint inhibition in advanced bladder and kidney cancer: responses and further management. *Am Soc Clin Oncol Educ Book.*2021;41(41):e182–e189. doi: 10.1200/EDBK_323835

69. Bellmunt J, Hussain M, Gschwend JE, Albers P, Oudard S, Castellano D, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.*2021;22(4):525–537. doi: 10.1016/S1470-2045(21)00004-8

B2B: Bladder Cancer Summary

70. Apolo AB, Rosenberg JE, Kim WY, Chen RC, Sonpavde G, Srinivas S, et al. Alliance A031501: phase III randomized adjuvant study of MK-3475 (pembrolizumab) in muscle-invasive and locally advanced urothelial carcinoma (MIBC) (AMBASSADOR) versus observation. *J Clin Oncol.*2019;37(7_suppl):TPS504–TPS504. doi: 10.1200/jco.2019.37.7_suppl.tps504

71. Grunewald CM, Niegisch G, Albers P. Using circulating tumor DNA to guide adjuvant therapy in bladder cancer: IMvigor010 and IMvigor011. *Eur Urol Focus.*2022;8(3):646–647. doi: 10.1016/J.EUF.2022.04.001

72. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. The *Lancet.*2020;395(10232):1268–1277. doi: 10.1016/S0140-6736(20)30415-3

73. Kulkarni GS, Hermanns T, Wei Y, Bhindi B, Satkunasivam R, Athanasopoulos P, et al. Propensity score analysis of radical cystectomy versus bladder-sparing trimodal therapy in the setting of a multidisciplinary bladder cancer clinic. *J Clin Oncol.*2017;35(20):2299–2305. doi: 10.1200/JCO.2016.69.2327

74. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, et al. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol.*1998;16(11):3576–3583. doi: 10.1200/JCO.1998.16.11.3576

75. 7Jiang DM, Jiang H, Chung PWM, Zlotta AR, Fleshner NE, Bristow RG, et al. Neoadjuvant chemotherapy before bladder-sparing chemoradiotherapy in patients with nonmetastatic muscle-invasive bladder cancer. *Clin Genitourin Cancer.*2019;17(1):38–45. doi: 10.1016/J.CLGC.2018.09.021

76. Pfister C, Gravis G, Fléchon A, Chevreau C, Mahammedi H, Laguerre B, et al. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: results of the GETUG-AFU V05 VESPER Trial. *J Clin Oncol.*2022;40(18):2013–2022. doi: 10.1200/JCO.21.02051

77. Singh P, Tangen C, Efstathiou JA, Lerner SP, Jhavar SG, Hahn NM, et al. INTACT: phase III randomized trial of concurrent chemoradiotherapy with or without atezolizumab in localized muscle invasive bladder cancer–SWOG/NRG1806. *J Clin Oncol.*2020;38(6_suppl):TPS586–TPS586. doi: 10.1200/JCO.2020.38.6_SUPPL.TPS586

78. Joshi M, Kim SE, Solanki AA, Miyamoto DT, Degraff D, Zou JW, et al. EA8185: phase II study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node-positive urothelial carcinoma (INSPIRE), ECOG-ACRIN/nrg collaboration. *J Clin Oncol.*2021;39(6_suppl):TPS500–TPS500. doi: 10.1200/JCO.2021.39.6_SUPPL.TPS500

79. Shore ND, James ND, van der Heijden MS, Balar AV, Fang X, Kapadia E, et al. Abstract CT564: KEYNOTE-992: a randomized phase 3 trial of pembrolizumab versus placebo in patients with muscle-invasive bladder cancer receiving concurrent chemoradiotherapy. *Cancer Res.*2022;82(12_Supplement):CT564–CT564. doi: 10.1158/1538-7445.AM2022-CT564

80. Kassouf W, Crabb SJ, Duran I, Brundage MD, Reaume MN, Dragomir A, et al. CCTG BL13 a randomized phase II trial assessing trimodality therapy with or without adjuvant durvalumab to treat patients with muscle-invasive bladder cancer (NCT03768570). *J Clin Oncol.*2022;40(16_suppl):TPS4619–TPS4619. doi: 10.1200/JCO.2022.40.16_suppl.TPS4619

81. Rouprêt M, Babjuk M, Burger M, Compérat E, Gontero P, Liedberg F, et al. EAU guidelines on upper urinary tract urothelial cell carcinoma - 2022 limited update. European Association of Urology. Published 2022. Accessed November 14, 2022. https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma

82. Giannarini G, Kessler TM, Birkhäuser FD, Thalmann GN, Studer UE. Antegrade perfusion with bacillus Calmette-Guérin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? *Eur Urol.*2011;60(5):955–960. doi: 10.1016/J.EURURO.2011.07.051

83. Foerster B, D'Andrea D, Abufaraj M, Broenimann S, Karakiewicz PI, Rouprêt M, et al. Endocavitary treatment for upper tract urothelial carcinoma: a meta-analysis of the current literature. *Urol Oncol.*2019;37(7):430–436. doi: 10.1016/J.UROLONC.2019.02.004

B2B: Bladder Cancer Summary

84. Flaig TW, Spiess PE, Abern M, Agarwal N, Bangs R, Boorjian SA, et al. NCCN Guidelines® insights: bladder cancer, version 2.2022. *J Natl Compr Canc Netw.*2022;20(8):866–878. doi: 10.6004/JNCCN.2022.0041

85. Kleinmann N, Wirth G, Lin JS, Matin SF, Nativ O, Mayer G, et al. Thermo reversible hydrogel based delivery of mitomycin C (UGN-101) for treatment of upper tract urothelial carcinoma (UTUC). *Bladder Cancer.*2019;5(1):21–29. doi: 10.3233/BLC-180182

86. Meiron M, Chamie K, Lerner SP, Jeshurun M, Hakim G, Schoenberg MP, et al. MP77-08 MITOGEL: optimizing drug delivery to the upper urinary tract—a preclinical evaluation. *J Urol.*2014;191(4S):e914. doi: 10.1016/j.juro.2014.02.2471

87. Kleinmann N, Matin SF, Pierorazio PM, Gore JL, Shabsigh A, Hu B, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. *Lancet Oncol.*2020;21(6):776–785. doi: 10.1016/S1470-2045(20)30147-9

88. Matin SF, Pierorazio PM, Kleinmann N, Gore JL, Shabsigh A, Hu B, et al. Durability of response to primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel: OLYMPUS trial final report. *J Urol.*2022;207(4):779–788. doi: 10.1097/JU.0000000000002350

89. Sfakianos JP, Cha EK, Iyer G, Scott SN, Zabor EC, Shah RH, et al. Genomic characterization of upper tract urothelial carcinoma. *Eur Urol.*2015;68(6):970–977. doi: 10.1016/J.EURURO.2015.07.039

90. Moss TJ, Qi Y, Xi L, Peng B, Kim TB, Ezzedine NE, et al. Comprehensive genomic characterization of upper tract urothelial carcinoma. *Eur Urol.*2017;72(4):641–649. doi: 10.1016/J.EURURO.2017.05.048

91. Nogueira L, Tracey A, Alvim R, Reisz P, Sjoberg D, Demac Q, et al. PD43-01 updated treatment results from a phase I study of WST11 phototherapy (VTP) for upper tract urothelial carcinoma. *J Urol.*2021;206(Supplement 3):e730–e730. doi: 10.1097/JU.0000000000002057.01

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