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An Overview on Management of Muscle Invasive Bladder Cancer

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Abstract:

Muscle invasive bladder cancer (MIBC) represents an aggressive form of urothelial carcinoma characterized by a high risk of progression, metastasis, and disease-specific mortality. It accounts for approximately one-third of newly diagnosed bladder cancers and remains a major therapeutic challenge. The optimal management of MIBC requires a multidisciplinary approach integrating surgery, systemic chemotherapy, and radiotherapy. Radical cystectomy with pelvic lymph node dissection remains the gold standard for localized disease, while bladder-preserving trimodality therapy offers a potential alternative for selected patients. Recent advances in neoadjuvant chemotherapy, immunotherapy, and molecular profiling have further refined treatment strategies and improved survival outcomes.

Keywords: Muscle invasive bladder cancer; Radical cystectomy; Neoadjuvant chemotherapy; Bladder preservation; Immunotherapy; Radiotherapy; Survival outcomes.

Introduction:

Muscle-invasive bladder cancer (MIBC) is a biologically aggressive form of urothelial carcinoma characterized by tumor invasion into the detrusor muscle (stage T2 or higher). It accounts for approximately 25% of newly diagnosed bladder cancer cases and is associated with a high risk of disease progression, metastasis, and cancer-specific mortality if not adequately treated (1).

Muscle invasive bladder cancer (MIBC), which accounts for approximately 25–30% of all bladder cancer diagnoses, requires more aggressive management as compared to non-muscle invasive cancer, and radical cystectomy (RC) accompanied by pelvic lymph node dissection has been widely accepted as the standard treatment for cT2-4aN0M0 bladder cancer**. (2)**

Recent advances in molecular subtyping and the emergence of immunotherapy, particularly immune checkpoint inhibitors, are reshaping the therapeutic landscape of MIBC, offering new hope for patients with advanced or unresectable disease. Ongoing clinical trials continue to refine the role of these emerging therapies within both the neoadjuvant and adjuvant settings (3).

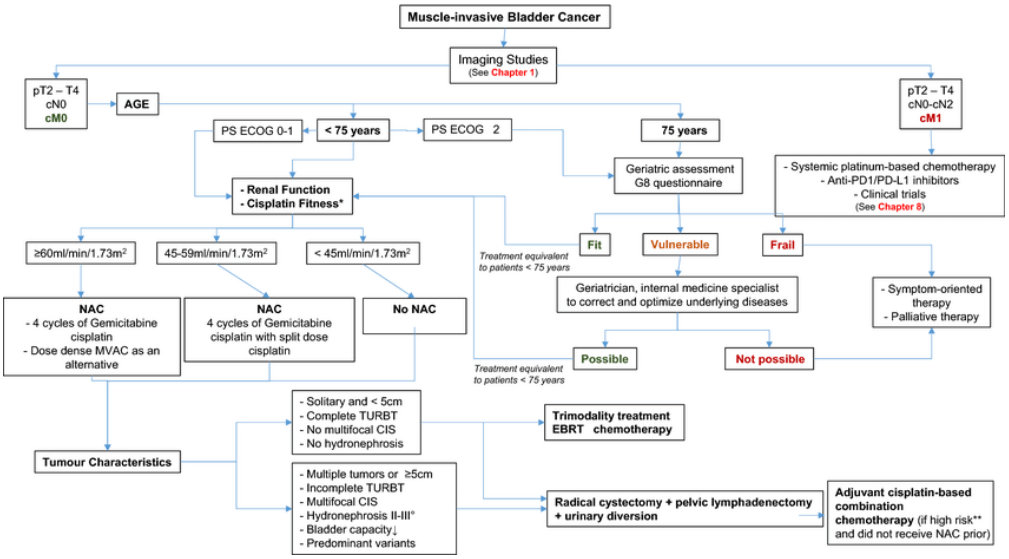

Figure 1: Suggested management algorithm for muscle-invasive bladder cancer: recommendations from joint SIU–ICUD consultation on bladder cancer. (3)

Radical cystectomy

In men, radical surgical treatment of bladder cancer involves a cystoprostatectomy; removal of the bladder, prostate (A systematic review and meta-analysis of 13,140 patients showed an incidental prostate cancer rate of 24%, seminal vesicles, distal ureters. For women, standard radical cystectomy (RC) includes removal of the bladder, the entire urethra and adjacent vagina, uterus, distal ureters, although in appropriately selected patients, approaches that preserve the uterus, vagina, fallopian tubes, and/or ovaries may be used. **(4)**

A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or para-caval nodes, yields more nodes to be examined, increases harvest of positive nodes, and may be associated with better survival and a lower pelvic recurrence rate.**(5)**

Conversely, randomized trials concluded that an extended LND did not show a significant advantage over limited LND for recurrence free survival (RFS), cancer-specific survival, or overall survival (OS) especially in the neoadjuvant therapy era.**(6)**

However, removal of the bladder requires urinary diversions that can substantially impair patients' quality of life (QOL) post-surgery. Concerns regarding urinary diversions also include possible postoperative impairment of renal function as previously reported in several studies. Furthermore, RC is associated with a significant risk of perioperative complications and mortality, which makes certain MIBC patients unfit for RC.**(7)**

Neoadjuvant systemic therapy

One of the most important concerns in the treatment of bladder cancer is the optimal use of perioperative chemotherapy for muscle invasive disease. Data support the role of neoadjuvant chemotherapy before cystectomy for stage II and IIIA lesions. Cisplatin-based neoadjuvant chemotherapy has become the standard of care in muscle-invasive bladder cancer. Giving chemotherapy prior to radical cystectomy may improve cancer-specific survival, likely by treating micrometastatic disease and pathologic downstaging**. (8)**

Early treatment intensification with neoadjuvant cisplatin-based chemotherapy has long been encouraged as means to improve survival outcomes in patients with clinically localized, muscle invasive disease undergoing definitive local therapy.**(9)** Theoretical advantages to administering early systemic therapy prior to surgical treatment, as opposed to adjuvant therapy, include:

1- Early targeting of micrometastatic disease
2- Early "litmus test" of in-vivo chemosensitivity
3- Patient performance status and ability to tolerate chemotherapy expected to be better pre-operative, with potential delays to receiving systemic therapy in post-radical cystectomy patients
4- Patients with favorable pathologic response (i.e. <ypT2 disease, ypN0) have favorable survival outcomes. **(10)**

Immune checkpoint inhibitors are increasingly being tested in the neoadjuvant setting, either as monotherapy or in combination with chemotherapy or a CTLA-4 checkpoint inhibitor. In the recently published update of the ABACUS trial assessing single-agent atezolizumab, 2-yr disease-free survival (DFS) and OS rates were 68% and 77% respectively, with a 2-yr DFS rate of 85% among patients achieving a pathological CR. A disadvantage of neoadjuvant therapy is delayed local treatment in patients who do not respond.**(11)**

Adjuvant Systemic Therapy

Data are less clear regarding the role of adjuvant systemic therapy in invasive bladder cancer. Studies have shown that adjuvant chemotherapy may delay recurrences and improve OS. A meta-analysis of 6 trials found a 25% mortality reduction with adjuvant chemotherapy, but the authors pointed out several limitations of the data and concluded that evidence is insufficient for treatment decisions. **(12)**

Adjuvant platinum-based chemotherapy for patients with high-risk disease (pT3/4 and/or LN-positive) has long been debated. A recent systematic review and meta-analysis of individual patient data from ten RCTs involving 1183 patients treated with adjuvant cisplatin-based chemotherapy for MIBC revealed an OS benefit with cisplatin-based adjuvant chemotherapy.**(13)**

Clinical trials of adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP); MVAC; and methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) regimens have each suggested a survival advantage.**(14)**

The role of adjuvant **immune checkpoint inhibitor** monotherapy has been evaluated in three phase 3 RCTs. The CheckMate 274 phase 3 RCT compared adjuvant nivolumab versus placebo in patients at high risk of recurrence with or without previous NAC.**(15)** The study demonstrated a significant improvement in median DFS. The proportion of patients who were alive and disease-free at 6 months was 74.9% with nivolumab and 60.3% with placebo, for patients with PD-L1 expression ≥1%. The FDA has approved nivolumab for adjuvant treatment in patients with high-risk disease, while the European Medicines Agency (EMA) has approved it only for patients with tumor-cell PD-L1 expression ≥1%.

The NCCN Guidelines suggest that adjuvant systemic therapy should be discussed with patients with high-risk pathology after cystectomy. If cisplatin-based neoadjuvant therapy was not given and the tumor is found to be pT3, pT4, or pN+ following resection, adjuvant cisplatin- based chemotherapy is the preferred approach, although adjuvant nivolumab may also be considered. If cisplatin-based neoadjuvant therapy was given and the tumor is ypT2–ypT4a or ypN+, nivolumab may be considered, although consideration of this approach should balance its effect at delaying progression of disease with the risk of side effects. A minimum of 3 cycles of a cisplatin-based combination, such as ddMVAC (preferred) or GC, may be used in patients undergoing perioperative chemotherapy. Chemotherapy regimen and dosing recommendations are mainly based on studies in advanced disease.**(16)**

Adjuvant Radiation therapy

Patients with locally advanced disease (pT3–4) have high rates of pelvic recurrence and poor OS after radical cystectomy, PLND, and perioperative chemotherapy (pelvic failure 20%–45% and survival 10%– 50% at 5 years, depending on risk factors). A 2019 systematic review evaluating the oncologic efficacy of adjuvant radiation for bladder cancer or upper tract urothelial carcinoma (UTUC) concluded that there was no clear benefit of adjuvant radiation following radical surgery (eg, cystectomy), although the combination of adjuvant radiation with chemotherapy may be beneficial in locally advanced disease. While there are no conclusive data demonstrating

improvements in OS, it is reasonable to consider adjuvant radiation in patients with pT3/pT4, positive surgical margins and/or lymph nodes identified in the pelvic dissection following radical cystectomy.**(16)**

Bladder-sparing treatments for localized disease

Over the past decade, curative oncological strategies have moved from extensive surgery to organ-preserving treatments in different cancer types, ranging from head and neck malignancies to anal cancer. Bladder preservation as an alternative to RC is generally reserved for patients with smaller solitary tumors, negative nodes, no extensive or multifocal CIS, no tumor-related hydronephrosis, and good pre-treatment bladder function **(17)**

- **Trimodality therapy**

Trimodality therapy (TMT) consists of maximal transurethral resection of bladder tumor (TURBT) (as safely as possible) followed by external beam radiotherapy (EBRT) with concurrent chemotherapy. Most TMT patients achieve a clinical complete response (cCR) (70-80%), avoiding salvage radical cystectomy, while offering long-term survival rates comparable to those in current radical cystectomy series. **(18)**

Acceptance and implementation of TMT by the urologic community has been with caution due to concerns of cancer recurrence and need for salvage RC. This is likely maintained by the lack of randomized controlled trials comparing TMT to RC, demonstrated by the Selective Bladder Preservation Against Radical Excision (SPARE) trial ending early due to a failure to accrue patients which led to small number of patients so firm conclusions about disease and toxicity outcomes following these interventions could not be drawn, although high rates of bladder preservation appeared to be achievable in chemotherapy responders without compromising OS. However, best available data from prospective TMT trials (including from NRG/RTOG in the USA and from UK-based trials), meta-analyses and multi-institutional cohorts demonstrate comparable survival. **(19)**

Barriers to TMT

To address the issue of barriers to TMT more specifically, a Canadian physician-based questionnaire sent to 34 physicians: urologists, medical oncologists, and radiation oncologists identified 4 barriers to TMT and 5 enablers of TMT. The barriers identified included: (1) Beliefs that TMT is associated with inferior survival compared to RC; (2) Lack of referral to radiation oncology; (3) Lack of "champions" to advocate for TMT; and (4) Inadequate multidisciplinary collaboration. Enablers included: (1) "Supporters" to advocate for TMT; (2) Beliefs by urologists that radiation oncologists should present TMT options to patients; (3) Institutional policy that all MIBC patients should be seen by multiple specialists; (4) System facilitators of radiation oncology referral; and (5) Patient-driven consultations seeking alternatives to RC. **(20)**

- ***TURBT***

A visibly complete resection should be attempted and achieved prior to chemoradiation. Completeness of TURBT, both microscopically and macroscopically, is associated with improved patient outcomes. Aggressive TURBT appears to improve the rates of local control by chemoradiation by as much as 20%. TURBT functions as both a diagnostic and therapeutic procedure in the management of bladder cancer. Maximal TURBT, defined as macroscopically complete resection of the bladder tumor when safely possible, is critical to successful treatment in mono- and multi-modality regimens. Guidelines for both NMIBC and MIBC emphasize conducting a maximal TURBT, with resection down to the detrusor muscle when feasible**.** Depending on the size and location of the tumor, however, maximal TUR may not be possible and requires special considerations**. (21)**

- ***Chemoradiation***

Regarding the delivery of TMT, chemoradiotherapy (CRT) can be given as a single course of chemoradiation therapy; a total dose of 64–65 Gy is directed to the whole bladder and tumor, while the nodal packets are subjected to a lower radiation dose (40–45 Gy) to potentially conserve the small bowel for future urinary diversions or as a split-course. A split-course entails induction chemoradiation therapy followed by an interval cystoscopy and biopsy and, if a satisfactory response, resume consolidative chemoradiation therapy. In cases of persistent or recurrent MIBC, salvage cystectomy (with or without perioperative chemotherapy) is recommended, unless the

patient has medical contraindications to radical surgery. Most series define complete response as the absence of visible tumor, biopsy-proven bladder cancer, and tumor cells on urine cytology. **(22)**

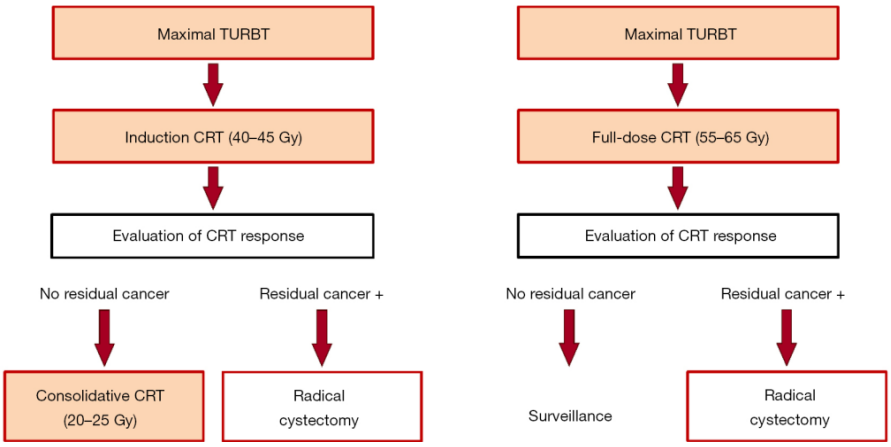

Figure 2: Therapeutic courses in two types of trimodality bladder preservation protocol: split protocol (A) and continuous protocol (B). CRT, chemoradiotherapy; TURBT, transurethral resection of bladder tumor. **(23)**

- ***Concurrent systemic therapy***

Effective chemotherapeutic agents, working locally as radio-sensitizers (and systemically by preventing metastatic growth), are fundamental for an organ-sparing approach. Cisplatin alone or in combination has been the most frequently used radiosensitizer, while paclitaxel and gemcitabine more recently have been added to the choices of chemotherapeutic agents. Chemotherapy attempts to eliminate local and systemic disease and increase radiotherapy (RT) effect on locoregional control. Chemotherapy is an integral part of TMT, due to its radiosensitizing effect and reduction of distant metastases, however, there is no consensus on the best chemotherapy scheduling. Current regimens include: cisplatin as single agent is the most common employed (with a weekly or every three-week schedule), in patient unfit for it low dose gemcitabine or carboplatin may be an alternative. A combination of fluoruracil and mitomycin C could also be adopted. **(24)**

The use of a concurrent radiosensitiser results in outcomes superior to radiotherapy alone based on the major milestone in the history of BPT which is the BC2001 study, the largest Phase III trial in this field to date. Although cisplatin has demonstrated radiosensitizing effects, its use has been limited in patients with renal dysfunction or poor performance status. The BC2001 trial revealed that the combination of fluorouracil and mitomycin C with RT could achieve effective bladder preservation, and long-term follow-up of the cohort confirmed improvements in local control rates, as well as reductions in the need for salvage cystectomy. **(25)**

Several chemotherapeutic agents including paclitaxel, cisplatin, fluorouracil, mitomycin C, trastuzumab, and gemcitabine have been evaluated in CRT regimens. Although several agents have demonstrated efficacy, no clear consensus exists regarding the optimal chemotherapy regimen. Cisplatin remains central to CRT protocols; however, dosing strategies vary widely (typically 20–40 mg/m2), and no standardized dose has been established. In cisplatin-ineligible patients, alternatives, such as fluorouracil, mitomycin C, or gemcitabine, are commonly employed**.** Ongoing randomized trials are investigating the addition of immunotherapy (for example, atezolizumab or pembrolizumab) to TMT. **(26)**

Initial efforts to integrate ICI (immune ckeckpoint inhibitors) into TMT included a Phase 1 trial that combined radiation therapy (50 Gy in 20 fractions), gemcitabine, and atezolizumab**.** Although the primary endpoints focused on safety and toxicity, the study was discontinued because of the high incidence of grade three gastrointestinal toxicities (three of eight patients), highlighting the challenges of combining pelvic irradiation with this regimen. Alternative combinations were then investigated. A Phase 1b trial evaluated the combination of mitomycin C and capecitabine with nivolumab (an anti-PD-1 antibody) and ipilimumab (an anti- CTLA- 4 antibody). Although dose-limiting toxicities were observed in the group receiving ipilimumab 3 mg/kg plus nivolumab 1 mg/kg,

acceptable toxicity profiles were reported in other cohorts including nivolumab monotherapy (480 mg) and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. A follow-up Phase 2 study combining conventional CRT with pembrolizumab demonstrated promising efficacy and tolerability. One of the most significant ongoing investigations is the KEYNOTE-992 trial, an international, multicenter, Phase 3, double-blind, randomized trial comparing standard CRT with and without pembrolizumab. This trial aims to determine whether the addition of an ICI improves outcomes in TMTfor MIBC. **(27)**

- ***Radiotherapy***

A different range of dose of irradiation, fractionation schedules, sequences of treatment and volumes delineation have been applied. The standard fractionation usually is of 1.8–2 Gy/fraction with the total irradiation dose to the whole bladder being approximately 55–66 Gy and 45–50 Gy to the pelvic lymph nodes. Several studies demonstrated that a total dose >55–60 Gy was associated with increasing local control suggesting the importance of dose escalation on the outcome for bladder cancer**.** Conventionally, radical radiotherapy is delivered with an empty bladder and the target volume includes the entire bladder and any extra-vesicle tumor extension with a margin of around 1.5–2 cm for organ motion and set-up errors. Since the bladder is a mobile and deformable structure, its volume can vary markedly during a course of radiotherapy. One study reported that more of half of all treatment may be delivered with some element of "geometric miss" despite employing safety margins of 1.5 cm around an empty bladder**.** The incorporation of cone beam computed tomography imaging (CBCT) to radiotherapy delivery has enabled the direct visualization of bladder position and target volumes in the treatment room, resulting in the era of image guided radiotherapy (IGRT) and adaptive radiotherapy. **(28)**

The radiation treatment volume should include the whole bladder and the pelvic lymph nodes. Support for nodal irradiation comes from surgical studies demonstrating that the extent of lymph node dissection improves survival rates, even in node-negative patients, related probably to the high rate of occult pelvic micrometastases. The rationale for irradiating pelvic lymph nodes is supported by data from surgical series' which suggest that micro-metastases could be demonstrated in nearly one third of cases with clinically and radiologically negative nodes. However, **Tunio et al. (29) and Petal et al. (30)** found no difference in bladder preservation, disease-free survival, and OS rates between patients randomized to receive whole-pelvis or bladder- only RT.

Evidence from cystectomy series shows that pathologically detected micro metastasis in clinically and radiologically negative pelvic nodes ranges from 25% to 44%. The regional lymph nodes most at risk are those in the true pelvis, below the bifurcation of common iliac arteries, and include internal iliac, external iliac, obturator, perivesical, and presacral nodes. Extended pelvic nodal dissection with higher lymph nodal yield has shown improved outcomes. However, for bladder conservation, there is variability in practice worldwide in terms of elective nodal irradiation. In a series of Radiation Therapy Oncology Group (RTOG) trials, the radiation fields included a limited pelvic portal treated to 40 to 45 Gy followed by a boost to the bladder, the rationale being that regional nodal involvement is not uncommon in MIBC. Among others, the UK-based BC 2001 trial comparing radiation with CRT did not use elective nodal radiotherapy (RT) and reported a nodal relapse rate of under 5% which is similar to the patterns of failure reported in the studies in which pelvic RT has been used. **(31)**

This discordance between biological rationale and an apparent lack of clinical benefit with prophylactic pelvic irradiation could possibly be explained by the incidental dose received by the pelvic nodal regions, particularly the nodes lying along the external iliac, obturator, and internal iliac vessels and the increasing integration of systemic chemotherapy into radiation protocols may be adequate to treat micro metastatic disease in pelvic lymph nodes and neutralize any potential benefit of elective pelvic nodal irradiation. So, the Radiation Therapy Oncology Group (RTOG) guidelines recommend considering the treatment of pelvic lymph nodes. The decision to include or exclude the pelvic lymph nodes in bladder cancer radiotherapy varies according to clinical protocols and remains controversial. The National Comprehensive Cancer Network (NCCN) guidelines state that including the pelvic field should be optional and determined based on the patient's comorbidities and the risk of radiation-related toxicity. **(16)**

- **Neoadjuvant or adjuvant chemotherapy along with trimodality therapy**

Chemotherapy plays a crucial role not only in controlling systemic micrometastases, but also in improving local control, and enhancing overall survival (OS) rates. Analogous to the well-established use of neoadjuvant chemotherapy (NAC) before radical cystectomy, its potential role prior to TMT in BPT has also been investigated. **(7)**

While the positive impact of neoadjuvant chemotherapy prior to RC on oncologic outcomes in MIBC patients is widely accredited, there has been no definitive evidence regarding its utility in bladder preserving therapy (BPT). In the single institutional large series (n=348), the Massachusetts General Hospital team analyzed MIBC patients who underwent TMT with or without neoadjuvant chemotherapy (methotrexate, cisplatin, and vinblastine), and showed that there was no significant association between the use of neoadjuvant chemotherapy and survival outcomes. In contrast, a separate study in 104 MIBC patients, who underwent neoadjuvant therapy with gemcitabine and cisplatin followed by CRT (60–65 Gy), showed favorable local cancer control and survival outcomes with complete response, five-year cancer-specific survival and five-year overall survival rates of 79%, 76%, and 68%, respectively. Most recently, Jiang *et al.* retrospectively analyzed 57 MIBC patients treated neoadjuvant chemotherapy (gemcitabine and cisplatin) followed by CRT (60–66 Gy), and demonstrated encouraging outcomes and tolerability with overall survival rate of 74% and disease-specific survival of 88% at two years **(32)**. Several phase 1-2 trials in MIBC patients receiving adjuvant chemotherapy post CRT demonstrated five-year overall survival rate to be 56–73%. The contribution of neoadjuvant or adjuvant chemotherapy in the TMT regimen has not been demonstrated. **(33)** So, further studies are warranted to define the potential role of neoadjuvant or adjuvant chemotherapy in BPT.

Combination of immunotherapy and bladder preservation therapy

The combination of immune checkpoint inhibitors with CRT-based BPT could be a promising approach in achieving a synergistic anti-tumor activity between radiation and immunotherapy. There are several ongoing clinical trials of BPT comprising immune checkpoint inhibitors. NCT02621151 and NCT02622262 are single-arm phase II trials evaluating the combination of pembrolizumab with CRT using gemcitabine (NCT02621151) or cisplatin (NCT02662062). NCT02891161 is a phase 1-2 study evaluating the safety and efficacy of the combination of durvalumab and radiation therapy. NCT03993249 is a randomized phase II study comparing the combination of standard CRT and nivolumab. Additionally, SWOG trial (NCT03775265)—a randomized phase III study—plans to enroll 475 patients and evaluate CRT-based BPT with and without atezolizumab. The treatment regimen will include radiation therapy, chemotherapy based on physician's choice and anti-PD-L1 monoclonal antibody atezolizumab (or placebo). This study will show more definitive evidence whether the addition of immunotherapy to CRT will increase the chance of successful bladder preservation in MIBC patients **(23)**.

- **Tetramodality therapy**

TURBT with induction chemoradiotherapy followed by consolidative partial cystectomy (PC) which allows for pathological confirmation of CRT response (pathological CRT response), sometimes referred to as **tetramodal therapy** is gaining popularity for its multimodal approach in a highly selected patient population. In one bladder-sparing protocol consisted of debulking TUR and low dose chemoradiotherapy followed by partial cystectomy with PLND in 46 highly selected patients, five-year cancer specific survival and recurrence-free survivals were 93% and 97% respectively, although histologic examination of PC specimens revealed residual MIBC in (10%) of specimens. **(34)**

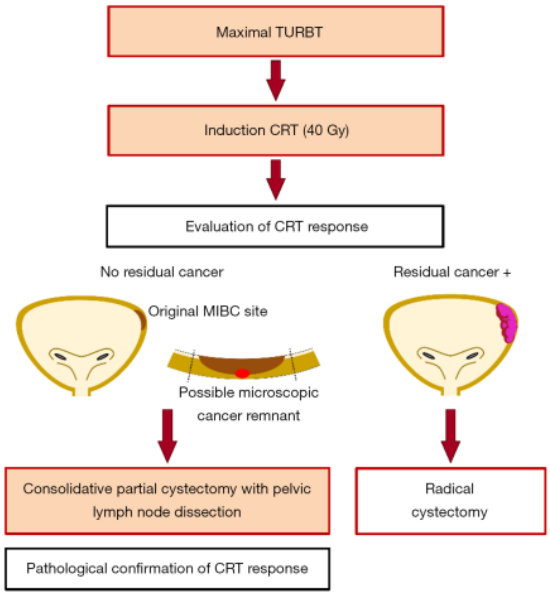

Figure 3: Schematic of tetramodality bladder preservation protocol incorporating maximal TURBT and induction CRT followed by consolidative partial cystectomy with pelvic lymph node dissection. Consolidative partial cystectomy is offered to patients who were clinically evaluated to have a complete response after induction CRT, which enables pathological confirmation of CRT response and may contribute to surgical removal of possible microscopic cancer remnant. (23)

Molecular biomarkers should be considered in addition to standard clincopathologic criteria to determine the best candidates for TMT. Bladder tumors often have alterations in DNA repair pathways, like MRE11 and ERCC1/2, that are linked to sensitivity chemotherapy and radiation, which may improve response to TMT. Choudhury *et al*. showed that low MRE11 expression is predictive of worse cancer specific survival (CSS) in patients undergoing radiotherapy, but not predictive for patients undergoing cystectomy. Others found that high expression of ERCC1/2 protein was associated with improved cancer-specific survival outcomes and recurrence rates.**(35)**

Metastatic bladder cancer

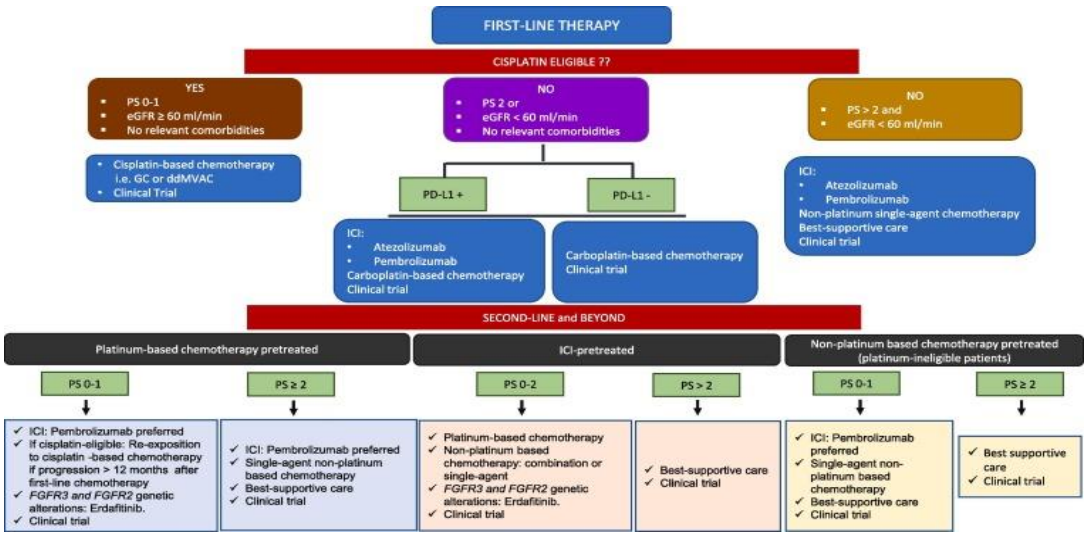

Figure 4: Management of metastatic bladder cancer (36)

Metastatic urothelial cancer generally has a good response rate to chemotherapy (about 70%), but the overall prognosis is still poor as the duration of the benefit is short. Potential options for first-line treatment of patients

with advanced UC depend on whether patients are eligible for cisplatin-based chemotherapy (good performance status PS of 0–1, and adequate renal function ;glomerular filtration rate [GFR] of 50–60 mL/min)**,** unsuitable for cisplatin (PS of 2 and/or impaired renal function [GFR of >30 but <60 mL/min]) but eligible for carboplatin-based chemotherapy, or unsuitable for any platinum-based chemotherapy (≈10% of patients). For cisplatin eligible patients, MVAC given in a dose-dense manner has been the most studied, but cisplatin and gemcitabine offer similar results with greater safety and less morbidity**. (37)**

Cisplatin-based combination chemotherapy became a standard treatment for metastatic bladder cancer in the early 1990s after a randomized clinical trial demonstrated a survival benefit with MVAC versus cisplatin alone. A series of subsequent randomized trials found that administration of MVAC in a dose-dense fashion with granulocyte colony-stimulating factor support was associated with less toxicity and possibly enhanced efficacy and that the combination of gemcitabine plus cisplatin yielded similar efficacy but less toxicity than MVAC. Although cisplatin-based chemotherapy became a standard of care for patients with metastatic urothelial cancer, many patients with bladder cancer are of advanced age and many are ineligible for cisplatin. For these patients, gemcitabine plus carboplatin is generally substituted. **(38)**

Recently, a substudy of the CheckMate-901 Phase 3 trial that enrolled cisplatin-eligible patients showed that treatment with nivolumab + cisplatin-based chemotherapy followed by nivolumab monotherapy resulted in significantly longer OS and PFS than cisplatin-based chemotherapy alone.**(39)**

Pembrolizumab (anti–PD-1) and atezolizumab have been approved by the European Medicines Agency for patients with advanced UC with PD-L1–positive tumors who are ineligible for cisplatin. Atezolizumab (but not pembrolizumab) is recommended by NICE for first line therapy in patients with PD-L1–positive tumors (≥5% expression on tumor-infiltrating immune cells. In the United States, the combination of enfortumab vedotin (EV; an antibody drug conjugate targeted to the cell surface protein nectin-4) + pembrolizumab received accelerated approval as first line treatment for cisplatin-ineligible patients. **(40).**

Avelumab (anti–PD-L1) maintenance is standard of care for patients who have had an objective response (complete or partial) or stable disease after completing first line platinum-based chemotherapy. Immune checkpoint inhibitors ICI are approved for patients who have had disease progression during or after platinum-based chemotherapy but remain ICI naive. Recently updated ESMO and European Association of Urology (EAU) guidelines recommend second-line ICI treatment in patients who have disease progression with first line chemotherapy and therefore are not eligible to receive avelumab maintenance.**(38)**

Although requiring thorough validation in larger series, if the early data showing that LOY tumors (Y chromosome loss in cancer drives growth by evasion of adaptive immunity demonstrating that cancer cells with LOY mutations alter T cell function, promoting T cell exhaustion and sensitizing them to PD-1-targeted immunotherapy) are more vulnerable to ICIs holds, this would be a potentially valuable marker to stratify patients to this approach. **(41)**

Recently, cohort 1 of the randomised Phase 3 THOR trial showed significantly improved OS and PFS with erdafitinib, a small-molecule FGFR inhibitor, vs chemotherapy (docetaxel or vinflunine) in patients with FGFR2/3 molecular alterations who had prior ICI treatment.**(42)**

In contrast, cohort 2 of the THOR trial showed no statistically significant difference in OS between erdafitinib vs pembrolizumab in pretreated patients with FGFR2/3 molecular alterations without prior ICI treatment. **(43)**

Drug	Mechanism of action	Evidence	Select adverse events
Erdafitinib	Small-molecule inhibitor of fibroblast growth factor receptor 3	In a phase II study of patients with *FGFR3*-mutated metastatic urothelial cancer progressing despite prior platinum-based chemotherapy, erdafitinib demonstrated an objective response rate of 42%[320]	Hyperphosphataemia, stomatitis, hand–foot syndrome as well as ocular disorders such as central serous retinopathy
Enfortumab vedotin	Antibody–drug conjugate comprised of a monoclonal antibody directed against nectin 4 linked to a monomethyl auristatin E payload	The phase III EV-301 trial[321] randomized patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy and PD1 or PDL1 blockade to treatment with enfortumab vedotin versus standard chemotherapy (docetaxel, paclitaxel or vinflunine); the trial demonstrated an improvement in overall survival with enfortumab vedotin versus chemotherapy (HR 0.70, 95% CI 0.56–0.89; *P* = 0.001); the combination of enfortumab vedotin plus pembrolizumab has been explored as first-line treatment in cisplatin-ineligible patients with metastatic urothelial cancer[322], yielding a 73% response rate	Peripheral neuropathy, hyperglycaemia, rash
Sacituzumab govitecan	Antibody–drug conjugate comprising a monoclonal antibody directed against TROP2 linked to the topoisomerase I inhibitor SN-38 payload	A large phase II trial demonstrated an objective response rate of 27% with sacituzumab govitecan in patients with metastatic urothelial cancer progressing despite prior platinum-based chemotherapy and PD1 or PDL1 immune-checkpoint inhibition[323]	Diarrhoea, neutropenia

Figure 5: New systemic therapies that have received regulatory approval. (26)

Radiotherapy

➢ Radiobiology

A reliable estimation of the alpha/ beta ratio for bladder cancer is not feasible. It is possible that no single alpha/ beta ratio for bladder cancer exists, as has been suggested for malignant melanomas. However considering bladder cancer as a rapidly proliferating cancer, it is reasonable to deal with a high α/β ratio of 10 Gy (and thus low fractionation sensitivity) **(44)**

Overall Treatment Time

Accelerated tumor cell proliferation during RT has been described for several tumor types. The overall duration of the course of fractionated RT (overall treatment time OTT) has been shown to be an important factor in local control for such fast-repopulating tumors.**(45)**

Clinical data on the influence of overall treatment time OTT on treatment of bladder cancer outcome is scarce and not conclusive. In a retrospective analysis, it was suggested that tumor (clonogenic) cell repopulation in transitional cell carcinoma of the bladder accelerates after a lag period of 5 to 6 weeks after start of treatment and that a dose increment of 0.36 Gy/d is required to compensate for this repopulation. However, it was concluded that the OTT did not significantly influence the treatment outcome. Altogether, there is insufficient evidence to support the importance of OTT on the treatment outcome in bladder cancer. Therefore, it was decided not to include the OTT in the radiobiologic model calculations. **(46)**

Total Dose

Differences in local control between different schedules were more related to the total dose than to the fractionation schedules used indicating that a dose escalation could significantly increase local control. The total dose generally applied for bladder cancer is relatively low when compared with other solid tumors. In addition, dose escalation has been proven valuable for many solid tumor types, such as lung cancer and prostate cancer, and there are no reasons to assume bladder cancer to behave differently**. (47)**

The standard radiotherapy regimen for invasive bladder cancer is a dose of 60–66 Gy. The reported local control rates after external beam RT for bladder cancer are generally disappointing and vary between 25% and 65%. Owing to the limited radiation tolerance of the normal bladder and bowel, the total dose used in bladder cancer is relatively low compared with doses used in other cancers, such as prostate cancer, lung cancer, and head and neck cancers. There are some reports suggesting the importance of total dose on the outcome for bladder cancer. **(48)**

Organs at Risk

When irradiating bladder tumors, the organs at risk are normal bladder tissue, bowel, and the rectum. For acute toxicity, these tissues behave like most acute-responding tissues and are not sensitive to fractionation and are characterized by a high alpha/ beta ratio (10 Gy). To keep acute toxicity acceptable, the OTT should not be too short because of the increased risk for acute reactions. Late-responding bowel, rectum, and bladder tissues are sensitive to large fraction sizes; the reported alpha/ beta ratios vary between 3 Gy and 6 Gy. **(49)** Therefore, to keep both acute and late toxicity acceptable, short OTTs and high fraction sizes should be avoided.

A method to improve treatment outcome is to combine RT with concurrent chemotherapy. This approach has been shown to be effective in many cancer types, such as lung cancer, cervical cancer, head-and-neck cancers and esophageal cancer. For bladder cancer, more evidence becomes available suggesting that the combination of RT with chemotherapy will increase treatment efficacy. The combination of RT with chemotherapy (mostly cisplatin based) will increase acute toxicity and be another reason to avoid short OTTs and large fraction sizes in RT for bladder cancer. **(50)**

- **Technique of Radiotherapy (51)**

Positioning and simulation

When standard planning is performed:

- If single-dose level; whole bladder radiotherapy, is planned, patients have to stop any absorption of fluids within 30 minutes before the planning CT and to void bladder immediately before planning CT.
- when index tumor irradiation (i.e. irradiation of tumor bed and/or gross residual tumor, either for partial bladder radiotherapy or when a two-dose level approach is considered sequentially or concomitantly) is planned, full bladder protocols should be used to move healthy tissues away from the irradiated volume; patients have to void bladder then drink 250– 500 ml of water approximately 30 minutes before the planning CT.
- Ideally, rectum should be empty as well, with the same local practices as those used for prostate planning.
- Patients must be supine in comfortable position with adequate immobilization devices (knee and/or ankle supports).
- CT scan thickness should be 3 mm; the superior limit must be at the L3/L4 level (to encompass common iliac vessels), and the inferior limit must be 2 cm below ischial tuberosities.
- CT should be contrast-enhanced if renal function allows it, only in cases of: extravesicular extension at diagnosis, incomplete TURBT, delay of more than 6 weeks between the TURBT and the planning CT with no second look feasible before starting, or in case of pelvic lymph nodes (PLN) irradiation

Delineation of the target volumes

Gross tumor volume (GTV)

The GTV refers to any residual gross disease following TURBT, visualized on cystoscopy or on a contrast-enhanced CT or MRI scan.

Clinical tumor volumes (CTV)

The tumor CTV is usually the whole bladder contoured as a solid organ, with inclusion of any extravesical tumor spread. The rationale for including the whole bladder is the multifocality of lesions both at presentation and at recurrence.

Inclusion of proximal urethra/prostate/vagina anterior wall. Among males with MIBC, occult pathological prostatic involvement has been found in 24–43% of cystoprostatectomy specimen. **(52)**

Three main risk factors of prostatic involvement have been identified: presence of CIS, multifocal disease and trigone/ bladder neck involvement. In these cases, the inclusion of the whole prostate (with no additional margin) in the CTV can be discussed.

Among females, proximal urethral involvement occurs in approximately 12% of patients, the only risk factor being bladder neck or anterior vaginal wall invasion. Microscopic vaginal and cervical involvement remain rare (around 5%), and in most cases are associated with urethral involvement. Therefore, in case of bladder neck

involvement and/or anterior vaginal wall involvement, the inclusion of proximal urethra (until pelvic floor) can be discussed in the CTV, with no additional margin. To delineate proximal urethra, an MRI is recommended.

Pelvic lymph node clinical tumor volume CTVN: Pelvic lymph node (PLN) CTV include external iliac, internal iliac, obturator and sacral lymph nodes. The delineation of pelvic lymphatic stations was retrospectively conducted based on CT-sim images of patients initially treated with bladder-only irradiation, following international consensus guidelines. **(53)**

Planning target volume (PTV)

CTV to PTV margins take into account set-up margins as well as internal motions relating to changes of position, volume and shape of the organ, both between each fraction (inter-fraction) and within a fraction (intra-fraction). CTV to PTV margins should be chosen to ensure that the CTV is covered in most of the fractions and ideally by the 95% isodose line. Within a non-adaptive strategy, when bony alignment only is used, CTV-to-PTV margins should be of 1.5 to 2 cm in all directions except for superior and anterior directions where margins of 2 to 2.5 cm should be used. When a daily soft-tissue imaging realignment IGRT (such as cone beam CT) is used, it is reasonable to reduce these anisotropic margins to 1 to 1.5 cm and 1.5 to 2 cm, respectively. Margins should not differ between empty bladder and full bladder protocols. When PTV margins are applied on the index tumor CTV, daily soft tissue imaging should be systematically performed, and margins should take into account the localization of the tumor within the bladder: we recommend at least 1.5–2 cm in all directions for tumor of the superior wall or the anterior wall, and 1–1.5 cm in all directions in the other cases. **(54)**

Organs at risk

The delineation of organs at risk should follow standard practices, for bowel bag, rectum, anal canal and femoral heads. **(55)**

- **Rectum**

The circumference of the rectum should be outlined in its entirety, to include the faecal contents. Outlining should extend from the anus (usually at level of the ischial tuberosities or 1cm below the lower margin of the PTV – whichever is more inferior) to the rectosigmoid junction. The rectosigmoid junction can usually be identified on the CT slice where the bowel turns anteriorly and to the left. The overall length of the rectum is typically 10-12cm.

- **Bowel**

The entire bowel visible on relevant levels of the planning scan will be outlined and included in the analysis. The outlining will include the small bowel, the large bowel and the sigmoid colon, down to the level of the rectosigmoid junction. The superior extent of outlining should be 2cm beyond the superior extent of the PTV2.

- **Right and left femoral heads**

The femoral heads are outlined to the bottom of the curvature of their heads.

Dose and fractionation (56)

Muscle invasive bladder cancer (node negative)

Preferred:

• 55Gy in 20 fractions over 4 weeks
• 60-64Gy in 30-32 fractions over 6-6.5 weeks

Node positive bladder cancer

Preferred:

• 64Gy in 32 fractions over 6.5 weeks with 48-53Gy in 32 to the elective pelvic LN groups
• Boost to involved LN 57-64Gy in 32 fractions as per OAR tolerance

Alternative:

• 55Gy in 20fractions over 4 weeks with 42-44 Gy in 20 fractions to the elective LN groups.
• Boost to involved LNs per 50-55Gy in 20 fractions as per OAR tolerance

Palliative treatment for symptomatic control

Indications

• T4 or node positive
• Metastatic disease

Dose Schedules

- 30-36Gy in 5-6 fractions treated weekly
- 21Gy in 3 fractions alternate days
- 30Gy in 10 daily fractions
- 20Gy in 5 daily fractions daily
- 8Gy single fraction

➢ **Altered fractionation**

When delivering radiotherapy, fractionation refers to two linked parameters, the dose per fraction and the OTT; altered fractionation therefore implies modification of one or of these two parameters, as compared to the conventional fractionation. A decrease of OTT (less than 6 weeks) typically aims to avoid clonogenic tumor repopulation (for tumors with high a/b ratio), with potential benefits on quality of life and cost-effectiveness, at the cost of increased acute toxicity; while a decrease of dose per fraction aims at reducing late toxicity. OTT for the bladder has been suggested to have an impact on outcome as tumor clonogenic repopulation in urothelial carcinoma of the bladder was shown to accelerate after a lag period of about 5–6 weeks following the start of treatment. It was thus concluded that a dose increment of 0.36 Gy per day was required to compensate for this repopulation. Similarly, the a/b ratio higher than 10 Gy **(44)** suggests a low sensitivity to fractionation for urothelial bladder cancer cells.

Pure hyperfractionated radiotherapy (without acceleration). Pure hyperfractionated radiotherapy refers to a regimen with OTT of at least 6 weeks, and dose per fraction <1.8 Gy. Several bladder-sparing prospective trials can be considered as pure hyperfractionated regimens. Indeed, they included bi-fractionated regimens (2 fractions per day), with dose per fraction of around 1.5 Gy, and OTT of 8–9 weeks due to a split course schedule. Zapatero et al. used the same schedule. In these trials total dose to the bladder ranged from 45.6 Gy to 52.3 Gy and total dose to the index tumor was 64.3–64.8 Gy. **Hafeez et al. (57)** reported results of a dose-escalation regimen using pure hyperfractionated radiotherapy on the whole bladder and moderate accelerated boost on the index tumor with acceptable oncological outcomes and tolerance.

Pure hypofractionated radiotherapy (without acceleration). Two trials report on the outcome of a bifractionated (BID) hypofractionated protracted regimen (OTT = 11.5 weeks) with split course among patients with localized operable MIBC: 3 Gy b.i.d at days 1, 3, 15, 17 on the whole pelvis followed by reevaluation, then, in case of complete response, 2.5 Gy b.i.d at days 64, 66, 78, 80, to a total dose of 44 Gy on the whole bladder. Complete response was obtained in 67 to 74%, and 3-year OS was 59% to 83%. **(58)**

Hyperfractionated accelerated radiotherapy. The phase II EORTC 22971 trial is the only prospective trimodal therapy assessing hyperfractionated accelerated radiotherapy (2 daily fractions of 1.2 Gy up to 60 Gy on the whole bladder over 5 weeks). **(59)**

Hypofractionated accelerated radiotherapy. Moderate hypofractionated accelerated radiotherapy has been assessed in five trimodal therapy trials (including one trial using non-chemotherapy based radiosensitizers). Radiotherapy was delivered continuously over 4 weeks on the whole bladder to a total dose of 52.5–55 Gy. No direct comparison of hypofractionated versus conventional fractionated radiotherapy for trimodal therapy exists to date; however, an individual patient-data meta-analysis of two phase III randomized trials was recently published comparing two schedules widely used in the UK: 64 Gy in 32 fractions and 55 Gy in 20 fractions among 782 patients. While the toxicity profile was similar between the two regimens, the hypofractionated schedule was non-inferior to conventionally fractionated schedule in terms of invasive locoregional recurrence (ILRC) and OS, and superiority of the hypofractionated schedule was demonstrated for ILRC. **(60)**

➢ **Treatment delivery**

Due to variations in shape and position throughout a radiation course, bladder radiotherapy is technically difficult and necessitates wide margins of a 1.5 cm PTV to achieve target coverage in >90% of fractions around the tumor target, which increases toxicity above what is necessary while not consistently eliminating geographical misses. Enhancing targeting might increase toxicity. **(61)**

Conformal 3D radiotherapy

Traditional 3D conformal radiotherapy (3D CRT) planning techniques generated a three-field plan (anterior and two wedged lateral/posterior oblique fields) or four-field plan to treat the bladder PTV. Multi-leaf collimators

MLCs were used to minimize the dose to normal tissue, with high energy photons (10–15 MV) depending on patient size. **(62)**

Intensity modulated radiotherapy IMRT

Several retrospective studies have compared IMRT versus 3D conformal radiotherapy: overall, IMRT dose delivery was associated with improvement of rectum and bowel sparing, translating into less toxicity. The other advantage of IMRT over 3D CRT could be the feasibility of simultaneous concomitant boost on the bladder or on the tumor, which is particularly useful with continuous radiation schedules.**(63)**

Image-guided radiotherapy (IGRT)

Image-guided radiotherapy (IGRT) allows soft tissue visualization, improving accuracy. IGRT led to adaptive radiotherapy strategies that aim to minimize treatment volume whilst maintaining target coverage. **(64)**

Adaptive Radiotherapy

Library of Plans (Online Solution)

One adaptive radiotherapy solution developed to accommodate the inter-fraction target variation is to generate a library of patient-specific treatment plans from varying PTV sizes, which captures the spectrum of likely target volume change. Cone beam computed tomography acquired before each fraction means the most appropriate PTV and corresponding plan can be selected that covers the target appropriately with minimal normal tissue exposure. This is often referred to as 'plan of the day'(PoD). In bladder cancer radiotherapy, selection of the best-fit plan improves bladder coverage while reducing the PTV by about 40% compared with a single plan based on the standard 1.5 cm PTV. PoD radiotherapy is complex, and requires clear guidelines and on-going quality assurance at the time of its introduction. **(61)**

Composite Volume (Offline Solution)

The composite volume as applied to bladder radiotherapy was first described by Pos *et al***. (65)** Daily imaging was acquired for the first 5 days of treatment in order to define a patient-specific volume that aims to capture the maximal excursions of the target (internal target volume)

References:

1. Alfred Witjes, J., Max Bruins, H., Carrión, A., Cathomas, R., Compérat, E., Efstathiou, J. A., et al. (2024). European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2023 Guidelines. Eur Urol, 85(1), 17-31. doi:10.1016/j.eururo.2023.08.016
2. Aminoltejari, K., & Black, P. C. (2020). Radical cystectomy: a review of techniques, developments and controversies. Transl Androl Urol, 9(6), 3073-3081. doi:10.21037/tau.2020.03.23
3. Leow, J., Bedke, J., Chamie, K., Collins, J., Daneshmand, S., Grivas, P., et al. (2019). SIU–ICUD consultation on bladder cancer: treatment of muscle-invasive bladder cancer. World J Urol, 37. doi:10.1007/s00345-018-2606-y
4. Koie, T., Hatakeyama, S., Yoneyama, T., Hashimoto, Y., Kamimura, N., & Ohyama, C. (2010). Uterus-, fallopian tube-, ovary-, and vagina-sparing cystectomy followed by U-shaped ileal neobladder construction for female bladder cancer patients: oncological and functional outcomes. Urology, 75(6), 1499-1503. doi:10.1016/j.urology.2009.08.083
5. Wright, J. L., Lin, D. W., & Porter, M. P. (2008). The association between extent of lymphadenectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer, 112(11), 2401-2408.
6. Sasaki, Y., Izumi, K., Fukuta, K., Kadoriku, F., Atagi, Y., Daizumoto, K., et al. (2024). Impact of lymph node dissection on surgical and oncological outcomes in patients undergoing robot-assisted radical cystectomy for bladder cancer: a multicenter retrospective study. J Robot Surg, 18(1), 141. doi:10.1007/s11701-024-01893-y
7. Ghandour, R., Singla, N., & Lotan, Y. (2019). Treatment Options and Outcomes in Nonmetastatic Muscle Invasive Bladder Cancer. Trends Cancer, 5(7), 426-439. doi:10.1016/j.trecan.2019.05.011

8. Kimura, Tomokazu, Inoue, S., Sano, T., Zennami, K., & Akamatsu, S. (2025). Recent Advances and Future Directions in Bladder Preservation Therapy for Muscle-Invasive Bladder Cancer. International Journal of Urology, 32(10), 1334-1341. doi:https://doi.org/10.1111/iju.70164

9. Yin, M., Joshi, M., Meijer, R. P., Glantz, M., Holder, S., Harvey, H. A., et al. (2016). Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. Oncologist, 21(6), 708-715. doi:10.1634/theoncologist.2015-0440

10. Ravi, P., Pond, G. R., Diamantopoulos, L. N., Su, C., Alva, A., Jain, R. K., et al. (2021). Optimal pathological response after neoadjuvant chemotherapy for muscle-invasive bladder cancer: results from a global, multicentre collaboration. BJU Int, 128(5), 607-614. doi:10.1111/bju.15434

11. Boeri, L., Soligo, M., Frank, I., Boorjian, S. A., Thompson, R. H., Tollefson, M., et al. (2019). Delaying Radical Cystectomy After Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer is Associated with Adverse Survival Outcomes. Eur Urol Oncol, 2(4), 390-396. doi:10.1016/j.euo.2018.09.004

12. Krajewski, W., Nowak, Ł., Moschini, M., Poletajew, S., Chorbińska, J., Necchi, A., et al. (2021). Impact of Adjuvant Chemotherapy on Survival of Patients with Advanced Residual Disease at Radical Cystectomy following Neoadjuvant Chemotherapy: Systematic Review and Meta-Analysis. J Clin Med, 10(4). doi:10.3390/jcm10040651

13. Nadal, R., & Apolo, A. B. (2018). Overview of Current and Future Adjuvant Therapy for Muscle-Invasive Urothelial Carcinoma. Curr Treat Options Oncol, 19(7), 36. doi:10.1007/s11864-018-0551-z

14. Lehmann, J., Franzaring, L., Thüroff, J., Wellek, S., & Stöckle, M. (2006). Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int, 97(1), 42-47. doi:10.1111/j.1464-410X.2006.05859.x

15. Bajorin, D. F., Witjes, J. A., Gschwend, J. E., Schenker, M., Valderrama, B. P., Tomita, Y., et al. (2021). Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med, 384(22), 2102-2114. doi:10.1056/NEJMoa2034442

16. Flaig, T. W., Spiess, P. E., Abern, M., Agarwal, N., Bangs, R., Boorjian, S. A., et al. (2022). NCCN Guidelines(R) Insights: Bladder Cancer, Version 2.2022. J Natl Compr Canc Netw, 20(8), 866-878. doi:10.6004/jnccn.2022.0041

17. Jiang, D. M., Chung, P., Kulkarni, G. S., & Sridhar, S. S. (2020). Trimodality therapy for muscle-invasive bladder cancer: recent advances and unanswered questions. Current Oncology Reports, 22(2), 14.

18. Pakmanesh, H., Khajehsalimi, A., Hesamarefi, M., Ebadzadeh, M. R., Bazrafshan, A., Malekpourafshar, R., et al. (2024). Comparison of the overall survival of different treatment methods in patients with Muscle-invasive bladder cancer: A retrospective study. Urologia, 91(4), 687-694. doi:10.1177/03915603241256009

19. Zlotta, A. R., Ballas, L. K., Niemierko, A., Lajkosz, K., Kuk, C., Miranda, G., et al. (2023). Radical cystectomy versus trimodality therapy for muscle-invasive bladder cancer: a multi-institutional propensity score matched and weighted analysis. Lancet Oncol, 24(6), 669-681. doi:10.1016/s1470-2045(23)00170-5

20. Walker, M., French, S. D., Doiron, R. C., Brennan, K., Feldman-Stewart, D., Siemens, D. R., et al. (2017). Bladder-sparing radiotherapy for muscle-invasive bladder cancer: A survey of providers to determine barriers and enablers. Radiother Oncol, 125(2), 351-356. doi:10.1016/j.radonc.2017.08.036

21. Russell, C. M., Lebastchi, A. H., Borza, T., Spratt, D. E., & Morgan, T. M. (2016). The Role of Transurethral Resection in Trimodal Therapy for Muscle-Invasive Bladder Cancer. Bladder Cancer, 2(4), 381-394. doi:10.3233/blc-160076

22. Hamad, J., McCloskey, H., Milowsky, M. I., Royce, T., & Smith, A. (2020). Bladder preservation in muscle-invasive bladder cancer: a comprehensive review. Int Braz J Urol, 46(2), 169-184. doi:10.1590/S1677-5538.IBJU.2020.99.01

23. Tanaka, H., Kijima, T., & Fujii, Y. (2020). Bladder preservation therapy in muscle-invasive bladder cancer: Current evidence and future perspectives. AME Medical Journal, 5.

24. Biagioli, M. C., Fernandez, D. C., Spiess, P. E., & Wilder, R. B. (2013). Primary bladder preservation treatment for urothelial bladder cancer. Cancer Control, 20(3), 188-199. doi:10.1177/107327481302000307

25. Hall, E., Hussain, S. A., Porta, N., Lewis, R., Crundwell, M., Jenkins, P., et al. (2022). Chemoradiotherapy in Muscle-invasive Bladder Cancer: 10-yr Follow-up of the Phase 3 Randomised Controlled BC2001 Trial. Eur Urol, 82(3), 273-279. doi:https://doi.org/10.1016/j.eururo.2022.04.017

26. Dyrskjøt, L., Hansel, D. E., Efstathiou, J. A., Knowles, M. A., Galsky, M. D., Teoh, J., et al. (2023). Bladder cancer. Nature Reviews Disease Primers, 9(1), 58. doi:10.1038/s41572-023-00468-9

27. Weickhardt, A., Foroudi, F., Lawrentschuk, N., Xie, J., Sidhom, M., Pal, A., et al. (2024). Pembrolizumab with Chemoradiation as Treatment for Muscle-invasive Bladder Cancer: Analysis of Safety and Efficacy of the PCR-MIB Phase 2 Clinical Trial (ANZUP 1502). Eur Urol Oncol, 7(3), 469-477. doi:10.1016/j.euo.2023.09.011

28. Lalondrelle S, H. R., Warren-Oseni K, et al. (2011). Adaptive-predictive organ localization using cone beam computed tomography for improved accuracy in external beam radiotherapy for bladder cancer. Int J Radiat Oncol Biol Phys.79:705–12.

29. Tunio, M. A., Hashmi, A., Qayyum, A., Mohsin, R., & Zaeem, A. (2012). Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. Int J Radiat Oncol Biol Phys, 82(3), e457-462. doi:10.1016/j.ijrobp.2011.05.051

30. Patel, S. A., Liu, Y., Solanki, A. A., Baumann, B. C., Efstathiou, J. A., Jani, A. B., et al. (2023). Bladder only versus bladder plus pelvic lymph node chemoradiation for muscle-invasive bladder cancer. Urol Oncol, 41(7), 325.e315-325.e323.

31. James, N. D., Hussain, S. A., Hall, E., Jenkins, P., Tremlett, J., Rawlings, C., et al. (2012). Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med, 366(16), 1477-1488.

32. Jiang, D. M., Jiang, H., Chung, P. W. M., Zlotta, A. R., Fleshner, N. E., Bristow, R. G., et al. (2019). Neoadjuvant Chemotherapy Before Bladder-Sparing Chemoradiotherapy in Patients With Nonmetastatic Muscle-Invasive Bladder Cancer. Clin Genitourin Cancer, 17(1), 38-45. doi:10.1016/j.clgc.2018.09.021

33. Akay, S. U., Seyyar, M., Kılıçoğlu, G. S., & Kesen, O. (2025). Definitive Radiotherapy in Bladder Cancer. The Bulletin of Urooncology, 24(2), 25-33. doi:10.4274/uob.galenos.2025.2024.12.2

34. Kijima, T., & Tanaka, H. (2019). Selective tetramodal bladder-preservation therapy, incorporating induction chemoradiotherapy and consolidative partial cystectomy with pelvic lymph node dissection for muscle-invasive bladder cancer: oncological and functional outcomes of 107 patients. 124(2), 242-250. doi:10.1111/bju.14736

35. Choi, W., Ochoa, A., McConkey, D. J., Aine, M., Höglund, M., Kim, W. Y., et al. (2017). Genetic Alterations in the Molecular Subtypes of Bladder Cancer: Illustration in the Cancer Genome Atlas Dataset. Eur Urol, 72(3), 354-365. doi:10.1016/j.eururo.2017.03.010

36. Nadal, R., & Bellmunt, J. (2019). Management of metastatic bladder cancer. Cancer Treatment Reviews, 76, 10-21. doi:https://doi.org/10.1016/j.ctrv.2019.04.002

37. von der Maase, H., Hansen, S. W., Roberts, J. T., Dogliotti, L., Oliver, T., Moore, M. J., et al. (2023). Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomized, Multinational, Multicenter, Phase III Study. J Clin Oncol, 41(23), 3881-3890.

38. Cathomas, R., Lorch, A., Bruins, H. M., Compérat, E. M., Cowan, N. C., Efstathiou, J. A., et al. (2022). The 2021 Updated European Association of Urology Guidelines on Metastatic Urothelial Carcinoma. Eur Urol, 81(1), 95-103. doi:10.1016/j.eururo.2021.09.026

39. van der Heijden, M. S., Sonpavde, G., Powles, T., Necchi, A., Burotto, M., Schenker, M., et al. (2023). Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. N Engl J Med, 389(19), 1778-1789. doi:10.1056/NEJMoa2309863

40. Balar, A. V., Galsky, M. D., Rosenberg, J. E., Powles, T., Petrylak, D. P., Bellmunt, J., et al. (2017). Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet, 389(10064), 67-76. doi:10.1016/s0140-6736(16)32455-2

41. Abdel-Hafiz, H. A., Schafer, J. M., Chen, X., Xiao, T., Gauntner, T. D., Li, Z., et al. (2023). Y chromosome loss in cancer drives growth by evasion of adaptive immunity. Nature, 619(7970), 624-631. doi:10.1038/s41586-023-06234-x

42. Loriot, Y., Matsubara, N., Park, S. H., Huddart, R. A., Burgess, E. F., Houede, N., et al. (2023). Phase 3 THOR study: Results of erdafitinib (erda) versus chemotherapy (chemo) in patients (pts) with advanced or metastatic urothelial cancer (mUC) with select fibroblast growth factor receptor alterations (FGFRalt). Journal of Clinical Oncology.

43. Siefker-Radtke AO, M. N., Park SH, Huddart RA, Burgess EF, Ozguroglu M, et al. . (2023). Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select FGFR alterations: cohort 2 of the randomized phase III THOR trial. Ann Oncol. doi:https://doi.org/10.1016/j.annonc.2023.10.003

44. van Leeuwen, C. M., Oei, A. L., Crezee, J., Bel, A., Franken, N. A. P., Stalpers, L. J. A., et al. (2018). The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. Radiat Oncol, 13(1), 96. doi:10.1186/s13014-018-1040-z

45. Fowler JF, L. M. (1992). Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys, 23(457-467).

46. Sminia., F. J. P. G. H. C. S. P. (2006). Radical radiotherapy for invasive bladder cancer: What dose and fractionation schedule to choose?. Int. J. Radiation Oncology Biol. Phys., 64((4)), 1168–1173. doi:doi:10.1016/j.ijrobp.2005.09.023

47. Pollack A, Z. G., Starkschall G, et al. (2002). Prostate cancer radiation dose response: Results of the M. D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys, 53, 1097–1105.

48. Majewski, W., Maciejewski, B., Majewski, S., Suwinski, R., Miszczyk, L., & Tarnawski, R. (2004). Clinical radiobiology of stage T2-T3 bladder cancer. International Journal of Radiation Oncology*Biology*Physics, 60(1), 60-70. doi:https://doi.org/10.1016/j.ijrobp.2004.02.056

49. Bentzen SM, B. M. (2002). Basic clinical radiobiology (3rd ed.). London: Arnold.

50. Shipley WU, Z. A., Kaufman DS, et al. (2005). Selective bladder preservation by trimodality therapy for patients with muscularis propria-invasive bladder cancer and who are cystectomy candidates—the Massachusetts General Hospital and Radiation Therapy Oncology Group experiences. Semin Radiat Oncol, 15, 36 – 41.

51. Khalifa, J., Supiot, S., Pignot, G., Hennequin, C., Blanchard, P., Pasquier, D., … Sargos, P. . (2021). Recommendations for planning and delivery of radical radiotherapy for localized urothelial carcinoma of the bladder. . Radiotherapy and Oncology, 161, 95–114. . doi:doi:10.1016/j.radonc.2021.06.011

52. Moschini, M., Shariat, S. F., Freschi, M., Soria, F., Abufaraj, M., Gandaglia, G., et al. (2017). Impact of Prostate Involvement on Outcomes in Patients Treated with Radical Cystoprostatectomy for Bladder Cancer. Urologia Internationalis, 98(3), 290-297. doi:10.1159/000454736

53. Verghote, F., Sargos, P., Christodouleas, J. P., Murthy, V., Baumann, B. C., Dirix, P., et al. (2022). International Consensus Guidelines for Adjuvant Radiation Therapy for Bladder Cancer After Radical Cystectomy: Update From an IBIS Workgroup. Pract Radiat Oncol, 12(6), 524-532. doi:10.1016/j.prro.2022.05.014

54. Foroudi, F., Pham, D., Bressel, M., Wong, J., Rolfo, A., Roxby, P., et al. (2012). Bladder cancer radiotherapy margins: a comparison of daily alignment using skin, bone or soft tissue. Clin Oncol (R Coll Radiol), 24(10), 673-681. doi:10.1016/j.clon.2012.06.012

55. Gay, H. A., Barthold, H. J., O'Meara, E., Bosch, W. R., El Naqa, I., Al-Lozi, R., et al. (2012). Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group consensus panel atlas. Int J Radiat Oncol Biol Phys, 83(3), e353-362. doi:10.1016/j.ijrobp.2012.01.023

56. John McGrane, D. C. C. (2023). Regional Clinical Guidelines –Bladder

57. Hafeez, S., Warren-Oseni, K., McNair, H. A., Hansen, V. N., Jones, K., Tan, M., et al. (2016). Prospective study delivering simultaneous integrated high-dose tumor boost (≤ 70 Gy) with image guided adaptive radiation therapy for radical treatment of localized muscle-invasive bladder cancer. International Journal of Radiation Oncology* Biology* Physics, 94(5), 1022-1030.

58. Housset, M., Maulard, C., Chretien, Y., Dufour, B., Delanian, S., Huart, J., et al. (1993). Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. Journal of Clinical Oncology, 11(11), 2150-2157.

59. Poortmans, P. M., Richaud, P., Collette, L., Ho Goey, S., Pierart, M., Van Der Hulst, M., et al. (2008). Results of the phase II EORTC 22971 trial evaluating combined accelerated external radiation and chemotherapy with 5FU and cisplatin in patients with muscle invasive transitional cell carcinoma of the bladder. Acta Oncologica, 47(5), 937-940.

60. Choudhury, A., Porta, N., Hall, E., Song, Y. P., Owen, R., MacKay, R., et al. (2021). Hypofractionated radiotherapy in locally advanced bladder cancer: an individual patient data meta-analysis of the BC2001 and BCON trials. Lancet Oncol, 22(2), 246-255. doi:10.1016/s1470-2045(20)30607-0

61. Huddart, R., Hafeez, S., Griffin, C., Choudhury, A., Foroudi, F., Syndikus, I., et al. (2024). Dose-escalated Adaptive Radiotherapy for Bladder Cancer: Results of the Phase 2 RAIDER Randomised Controlled Trial. Eur Urol. doi:https://doi.org/10.1016/j.eururo.2024.09.006

62. Morris, S., Roques, T., Ahmad, S., & Loo, S. . (2023). Practical Radiotherapy Planning (5th ed.): CRC Press.

63. Murthy V, G. P., Baruah K, Krishnatry R, Joshi A, Prabhash K, et al. . (2019). Adaptiveradiotherapy for carcinoma of the urinary bladder: long-term outcomes with dose escalation. Clin Oncol (R Coll Radiol), 31, 646–652. . doi:10.1016/j.clon.2019.06.005.

64. Kong, V., Hansen, V., & Hafeez, S. (2021). Image-guided adaptive radiotherapy for bladder cancer. Clinical Oncology, 33(6), 350-368.

65. Pos, F. J., Hulshof, M., Lebesque, J., Lotz, H., Van Tienhoven, G., Moonen, L., et al. (2006). Adaptive radiotherapy for invasive bladder cancer: a feasibility study. International Journal of Radiation Oncology* Biology* Physics, 64(3), 862-868.