EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer

Disease management I

DISEASE MANAGEMENT:

1. Neoadjuvant Chemotherapy (NAC)

The standard treatment for patients with urothelial muscle invasive bladder cancer (MIBC) is radical cystectomy (RC). However, RC only provides 5-year survival in about 50% of patients. To improve these results in patients with cN0M0 disease, cisplatin-based NAC has been used.

Role of cisplatin-based chemotherapy:

- **Neoadjuvant cisplatin-containing combination chemotherapy improves overall survival (OS) (5–8% at five years).**
- **Neoadjuvant treatment may have a major impact on OS in patients who achieve ypT0 or < ypT2.**

The role of imaging and predictive biomarkers:

- **There are still no tools available to select patients who have a higher probability of benefitting from NAC.**
- **In the future, genetic markers might facilitate the selection of patients for NAC and differentiate responders from non-responders.**

Role of neoadjuvant immunotherapy:

- **Currently immunotherapy with checkpoint inhibitors as monotherapy, or in different combinations, is being tested in phase II and III trials. Initial results are promising.**

Recommendations	Strength rating
If eligible for cisplatin-based chemotherapy, offer neoadjuvant cisplatin-based combination chemotherapy to patients with muscle-invasive bladder cancer (T2-T4a, cN0 M0).	Strong
Do not offer NAC to patients who are ineligible for cisplatin-based combination chemotherapy.	Strong
Only offer neoadjuvant immunotherapy to patients within a clinical trial setting.	Strong

2. Pre- and post-operative radiotherapy in muscle-invasive bladder cancer

Pre-operative radiotherapy:

- **No contemporary data exists to support that pre-operative RT for operable MIBC increases survival.**
- **Using a dose of 45–50 Gy in fractions of 1.8–2 Gy, results in down-staging after 4 to 6 weeks.**
- **Limited high-quality evidence supports the use of pre-operative RT to decrease local recurrence of MIBC after RC.**
- **Addition of adjuvant RT to chemotherapy is associated with an improvement in local relapse-free survival for locally-advanced bladder cancer (pT3b–4, or node-positive).**

Recommendations	Strength rating
Do not offer pre-operative radiotherapy (RT) for operable muscle-invasive bladder cancer since it will only result in down-staging, but will not improve survival.	Strong
Do not offer pre-operative RT when subsequent radical cystectomy (RC) with urinary diversion is planned.	Strong
Consider offering adjuvant radiation in addition to chemotherapy following RC, based on pathologic risk (pT3b–4 or positive nodes or positive margins).	Weak

Post-operative radiotherapy:

- **Consider adjuvant radiation in patients with pT3/pT4 pN0–2 urothelial BC following RC, although this approach has been evaluated in only a limited number of studies. No conclusive data demonstrating improvements in OS.**
- **Radiation fields should encompass areas at risk for harbouring residual microscopic disease based on pathologic findings at surgery and may include cystectomy bed and pelvic LNs. Doses in the range of 45 to 50.4 Gy may be considered.**

3. Radical cystectomy

RC is the standard treatment for localised MIBC. Performance status (PS) and life expectancy influence the choice of primary management as well as the type of urinary diversion.

Timing: Do not delay radical cystectomy (RC) for > 3 months as it increases the risk of progression and cancer-specific mortality, unless the patient receives neoadjuvant chemotherapy.

Indications: Patients with T2–T4a, N0–Nx, M0 disease.

- **BCG-refractory, BCG-relapsing and BCG-unresponsive NMIBC , extensive papillary disease that cannot be controlled with TURB and intravesical chemotherapy alone.**
- **Salvage cystectomy: non-responders to conservative therapy, recurrence after bladder-sparing treatment, and non-UC.**
- **Palliative cystectomy: fistula, pain, recurrent visible haematuria.**

Radical cystectomy: technique and extent

Sexual function-preserving cystectomy (SPC) in males: Prostate sparing, Capsule sparing, Seminal sparing and Nerve-sparing cystectomy.

No consensus exists regarding which approach preserves function best.

Concern regarding the impact of 'sparing-techniques' on oncological outcomes.

Organ-preserving RC for female: Data remain immature.

Recommendations	Strength rating
Do not offer sexual-preserving radical cystectomy to men as standard therapy for muscle-invasive bladder cancer.	Strong
Offer sexual-preserving techniques to men motivated to preserve their sexual function since the majority will benefit.	Strong
Select patients based on: • organ-confined disease; • absence of any kind of tumour at the level of the prostate, prostatic urethra or bladder neck.	Strong
Women: Select patients based on: • absence of tumour in the area to be preserved to avoid positive soft tissue margins; • absence of pT4 urothelial carcinoma.	Strong

Lymphadenectomy, role and extent:

Radical cystectomy includes removal of regional LNs.

There are data to support that extended LND (vs. standard or limited LND) improves survival after RC.

Perform a lymph node dissection as an integral part of RC.	Strong

Laparoscopic/robotic-assisted laparoscopic cystectomy:

Robot-assisted RC has longer operative time (1–1.5 hours) and major costs, but shorter length of hospital stay (1–1.5 days) and less blood loss compared to open RC. Similar rates of (major) complications. Similar oncological endpoint and QoL

Surgeons experience and institutional volume are considered the key factor for outcome of both RARC and ORC, not the technique.

Recommendations	Strength rating
Inform the patient of the advantages and disadvantages of open radical cystectomy (ORC) and robot-assisted radical cystectomy (RARC) to allow selection of the proper procedure.	Strong
Select experienced centres, not specific techniques, both for RARC and ORC.	Strong