BJU Int 2025; **135:** 364–365 doi:10.1111/bju.16672

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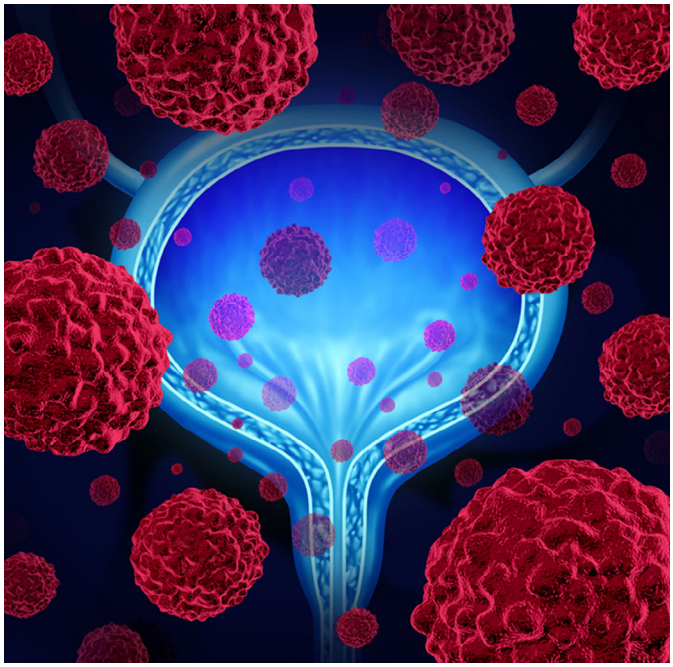
Research Highlights

Advances in the management of high-risk localised muscle invasive bladder cancer

This month's column focuses on several advances in the management of high-risk localised muscle invasive bladder cancer. Lerner et al. evaluated the role of an extended lymphadenectomy in the management of patients undergoing radical cystectomy with clinical stage T2 (confined to muscle) to T4a (invading adjacent organs) with two or fewer positive nodes. They randomly assigned 592 patients to either a bilateral standard lymphadenectomy that included lymph nodes on both sides of the pelvis or and an extended lymphadenectomy that involved the removal of the common iliac, pre-sciatic, and pre-sacral lymph nodes. Randomisation occurred during surgery and was stratified according to the receipt and type of neo-adjuvant chemotherapy, tumour stage and patient performance. The primary outcome was disease-free survival. The trial involved 36 surgeons operating at 27 sites in the US and Canada. Just over half the patients received neo-adjuvant therapy. After median 6.1 years of follow up, disease recurrence or death had occurred in 130 patients (45%) who underwent an extended lymphadenectomy and in 127 (42%) who underwent standard lymphadenectomy. Overall survival at 5 years was 59% in the extended-lymphadenectomy group and 63% in the standard-lymphadenectomy group (HR 1.13; 95% CI 0.88–1.45). Adverse events of grade 3 to 5 occurred in 157 patients (54%) in the extended-lymphadenectomy group and 132 (44%) in the standard-lymphadenectomy group. Nineteen patients undergoing extended lymphadenectomy died within 90 days of surgery compared with only seven patients undergoing standard lymphadenectomy. The authors concluded that an extended lymphadenectomy yielded no increase in disease-free or overall survival and was associated with higher peri-operative morbidity and mortality.



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Lerner SP, Tangen C, Svalek RS et al. Standard or extended lymphadenectomy for muscle-invasive bladder cancer. *N Eng J Med* 2024; 391: 1206–16.

Standard therapy for the treatment of patients with muscle invasive bladder cancer involves the use of cisplatin-based chemotherapy followed by radical cystectomy and pelvic node dissection. Recent studies have explored the safety and efficacy of adding immunotherapy to cisplatin-based therapies. Powles et. el. recently evaluated the impact of durvalumab, a selective high-affinity human IgG1 kappa monoclonal antibody that binds to programmed death ligand 1 and blocks the interaction of PD-L1 with programmed death 1 and CD80. They conducted a phase 3 open-label randomised trial among patients with muscle-invasive bladder cancer receiving gemcitabine-cisplatin every 3 weeks for four cycles followed by radical cystectomy. Half of the patients (n = 553) received neoadjuvant durvalumab every 3 weeks for 4 cycles prior to surgery followed by adjuvant durvalumab every four weeks for eight cycles after surgery. The other half (n = 530) received gemcitabine and cisplatin alone. The estimated event free survival was 67.8% at 24 months for the group receiving durvalumab and 59.8% for the comparison group. The estimated overall survival was 82.2% at 24 months among those patients receiving durvalumab and 75.2% in the comparison group (HR 0.75; P = 0.01). Treatment related adverse events Grade 3 or 4 occurred

in 41% of patients in both groups of which 0.6% lead to death. The authors concluded that durvalumab led to an improved event-free survival and overall survival among patients with muscle invasive bladder cancer when compared to using gemcitabine and cis-platin alone.

> *"Durvalumab led to an improved event-free survival and overall survival among patients with muscle invasive bladder cancer"*

Powles T, Catto JWF, Galsky MD et al. Perioperative Durvalumb with Neoadjuvant Chemotherapy in Operable Bladder Cancer. *N Eng J Med* 2024; 391: 1773–86.

Apolo et al. explored the role of another check point inhibitor, pembrolizumab, in the treatment of high-risk muscle-invasive urothelial carcinoma after radical surgery. They randomised 702 patients 1:1 in a phase 3 trial comparing simple observation against pembrolizumab at a dose of 200 mg every 3 weeks for a one year. Patients were stratified by pathological stage, the presence of programmed death ligand 1 and previous neoadjuvant therapy. After a median follow up of 44.8 months patients receiving pembrolizumab had a median disease-free survival 0f 29.6 months compared to 14.2 months for patients who were observed (HR = 0.73; P = 0.003). Half the patients receiving pembrolizumab had grade 3 or higher adverse events compared with only one third of the patients who were observed. The authors concluded that patients with high-risk muscle invasive transitional cell carcinoma benefit from pembrolizumab administered after surgery.

Finally, Groakre et al. conducted a phase 2 randomised trial exploring the efficacy of Ponsegromab, a humanised monoclonal antibody that inhibits growth differentiation factor 15 (GDF-15). GDF-15 is a stress-induced cytokine that binds to the glial cell-derived neutrotrophic factor family receptor alpha-like protein in the hindbrain. This pathway appears to be the primary modulator of anorexia and likely induces cachexia in patients suffering from advanced cancers. They randomised 187 patients with advanced lung, pancreatic and colon cancers and elevated GDF-15 levels 1:1:1:1 in a study comparing placebo with ponsegromab given subcutaneously every 4 weeks for three doses of 100 mg, 200 mg or 400 mg. Patients receiving ponsegromab had improved weight gain, appetite and physical activity when compared to patients receiving placebo. Adverse events were comparable in both groups. The authors concluded that GDF-15 is a driver of cancer induced cachexia.

Apolo AB, Ballman KV, Sonpavde G et al. Aduvant Pembrolizumab versus observation in muscle invasive urothelial carcinoma. *N Eng J Med* 2025; 392: 45–55.

Groarke JD, Crawford J, Collins SM, Lubaczewski S et al. Ponsegromab for the treatment of cancer cachexia. *N Eng J Med* 2024; 391: 2291–303.

Research Highlights is written by Peter Albertsen.