Experts' comments:
Immunotherapy is rapidly shifting the paradigm for urological cancer management. The seminal discoveries of CTLA-4 and PD-1 immune checkpoint receptors, recently awarded the 2018 Nobel Prize in Physiology or Medicine, led to significant improvements in the management of a range of solid tumours including RCC [1]. These immunogenic tumours are readily recognised by the immune system, and respond to the removal of immune checkpoint "breaks" which has generated a new pillar in cancer treatment and resulted in the integration of immunotherapy into routine clinical use. RCC is an immunogenic tumour and is characterised by resistance to cytotoxic chemotherapy but susceptibility to both immunotherapeutic and anti-angiogenic treatment approaches [2,3]. Guidelines for the treatment of metastatic RCC have changed dramatically to target these two major pathways. It was demonstrated that tyrosine kinase inhibitors (TKIs) with potent VEGF inhibition are superior to interferon-α, and consequently sunitinib became the new standard of care as first-line therapy [4].

However, it appears that this standard of care is about to change. Results from two large phase 3 trials comparing combinations of agents targeting immune checkpoint inhibitors and TKIs versus sunitinib have recently been reported [5,6]. The trial by Motzer et al compared the efficacy of avelumab, a PD-L1 inhibitor, plus axitinib, a small-molecule TKI, with that of sunitinib [6]. Both manuscripts were published in the same issue of the *New England Journal of Medicine*, and represent landmark papers in the field of metastatic RCC. The trial by Rini et al evaluated slightly different endpoints, and it is noteworthy that the two trials had positive outcomes and showed superiority over sunitinib in terms of PFS and the objective response rate. These new combinations are expected to become the new standard of care and be incorporated into future guidelines.

While targeted therapies can extend PFS and OS, this must be balanced against the significant rate of adverse events reported; adverse events of any cause occurred in 98.4% of the 429 patients in the pembrolizumab-axitinib group who received the assigned treatment and in 99.5% of the 425 patients in the sunitinib group who received the assigned treatment. These events were not insignificant, and led to more frequent discontinuation of any treatment because of adverse events in the pembrolizumab-axitinib than in the sunitinib group.

Nonetheless, significant progress has been made in the field of immunotherapy and targeted therapy, with practice-changing implications. Exploring the applicability of these novel treatments remains a high priority; however, longer follow-up to determine optimal combinations and monitor side effect profiles is warranted. Regardless, a new standard of care for patients with metastatic RCC is now within reach.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Lalani AA, McGregor BA, Albiges L, et al. Systemic treatment of metastatic clear cell renal cell carcinoma in 2018: current paradigms, use of immunotherapy, and future directions. Eur Urol 2019;75:100–10.
[2] Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376:354–66.
[3] Stewart GD, De Santis M, Escudier B, Powles T, Sonpavde G. Immunotherapy for renal cancer: sequencing and combinations. Eur Urol Focus 2016;2:582–8.
[4] Motzer R, Hutson T, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
[5] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27.
[6] Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103–15.

Jiasian Teh[a], Vignesh Narasimhan[a], Stephen Schultz[a], Niranjan Sathianathen[a], Declan G. Murphy[a,b,*]
[a]*Division of Cancer Surgery, Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia*
[b]*The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*

*Corresponding author. Division of Cancer Surgery, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, Victoria 3002, Australia.
E-mail address: declan.murphy@petermac.org (D.G. Murphy).

https://doi.org/10.1016/j.eururo.2019.03.002

Re: Conservative Management Following Complete Clinical Response to Neoadjuvant Chemotherapy of Muscle Invasive Bladder Cancer: Contemporary Outcomes of a Multi-institutional Cohort Study

Mazza P, Moran GW, Li G, et al

J Urol 2018;200:1005–13

Experts' summary:
This retrospective multicenter study reported long-term outcomes for 148 patients with nonmetastatic muscle-invasive bladder cancer (MIBC) who opted for bladder preservation after achieving a complete clinical response (cCR) following radical transurethral resection of bladder (TURB) followed by neoadjuvant chemotherapy (NAC). All patients refused radical cystectomy (RC) and elected for active surveillance. The median follow-up was 55 mo.

Intravesical recurrence was observed in 48% of patients; MIBC recurrences (23%) occurred earlier than noninvasive recurrences (77%) with a median time to recurrence of 33 versus 17 mo. Patients with MIBC relapse had significantly worse survival ($p < 0.015$). The 5-yr recurrence-free survival rate in the entire cohort was 64%. Of note, the

presence of carcinoma in situ (CIS) at diagnosis was the only significant predictor of intravesical recurrence on multivariable analysis (hazard ratio 3.36, 95% confidence interval 1.98–5.70; $p < 0.001$).

Salvage RC was performed in 18% of patients, of which 44% was for MIBC relapse. RC salvaged 75% of MIBC recurrences and 93% of noninvasive recurrences. Among patients with non-muscle-invasive relapse who did not undergo salvage RC, 15% died of bladder cancer. Of note, 3% of patients died of bladder cancer after developing systemic disease without intravesical or pelvic lymph node recurrence. In the entire cohort, 75% of patients survived for a mean of 110 mo (5-yr overall survival of 86%), with 82% of survivors retaining their bladder. Of the 37 deaths reported in the study, 40% were due to bladder cancer (5-yr disease-specific survival of 90%).

Experts' comments:

Bladder cancer is a major health problem worldwide. Approximately 25% of patients have MIBC at diagnosis. To date, the gold standard treatment for patients with clinically localized MIBC is neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) [1]. Of note, multimodal bladder preservation therapy may be offered to appropriately selected, well-informed, compliant patients (especially if RC is not an option).

To date, TURB alone, chemotherapy alone, and radiotherapy alone are not recommended as primary treatments for MIBC, while RC is associated with significant morbidity and may seriously alter patient quality of life. Thus, as our ultimate aim is to deliver the right treatment to the right patient at the right time following the paradigm of precision medicine, the question is whether MIBC can be cured with radical TURB plus systemic chemotherapy. According to the available evidence, the current answer is no. However, outcomes in bladder cancer have not improved over the last 25 yr and the urology community is rather conservative when challenging dogmas and introducing novel treatment paradigms. Therefore, we believe that the time has come to look at bladder cancer from a different perspective.

Avoiding RC with potential salvage RC for patients who achieve cCR following TURB and NAC is emerging as a new treatment concept [2], although it is highly controversial among bladder cancer experts. Mazza et al. should be commended for providing evidence that a selected proportion of patients who achieve cCR after TURB plus NAC can achieve long-term survival. Interestingly, these findings are in line with previous evidence of the feasibility and safety of this strategy in highly selected patients with MIBC who refuse RC [3].

The main take home message from all these studies is that few patients may not benefit from immediate RC. Unfortunately, in current clinical practice it is still impossible to select these patients after NAC. In addition, there is still a lack of reliable triggers to define the appropriate timing for deferred RC (which might be of more value than salvage RC). Thus, focusing on patients who survive after bladder-sparing treatment with TURB plus chemotherapy means that we might forget about those patients for whom this approach fails and who die of bladder cancer. This potential survivorship bias forces us to be aware of the key challenges in active surveillance for MIBC.

Patients included in the study by Mazza et al. were indeed very highly selected and had distinct disease characteristics. In particular: (1) the vast majority of patients had a solitary, low-to-moderate volume, cT2 pure urothelial cell MIBC before NAC; (2) 89% of patients underwent repeat TURB before NAC; (3) CIS was present in only 29% of cases (of note, CIS the only significant predictor of intravesical recurrence); and (4) MIBC was associated with hydronephrosis in only 8% of patients (of note, this feature was significantly associated with cancer-specific death). Taken together, these data highlight that avoiding RC is safe only in a specific subset of patients.

Moreover, cCR was defined as the absence of bladder wall disease at post-NAC TURB according to negative urine cytology and normal imaging. This definition of cCR is suboptimal and carries a non-negligible risk of underestimating the systemic spread of the disease (occult lymph node metastases or micrometastases). Bladder cancer is not only an endoluminal disease but also a bladder wall disease and potentially a micrometastatic disease; thus, RC may represent overtreatment for certain pT0 cases, but bladder preservation strategies may undertreat a different subset of patients. Notably, while NAC may theoretically impact on the micrometastatic burden of the disease, recent evidence showed poor survival outcomes for patients with MIBC and occult lymph node metastases treated with NAC and RC [4]. Finally, in spite of cCR after NAC, the intravesical recurrence rate was 48% and 5-yr disease-specific mortality was 10%. Thus, avoiding immediate RC did not cure all patients.

How can active surveillance after radical TURB followed by NAC be safely integrated into current treatment algorithms for MIBC? One might argue that the efficacy and safety of this approach should be tested in randomized clinical trials (RCTs). Unfortunately, RCT design is challenging given the limits of our current definition of cCR and the lack of definitive predictors of cancer aggressiveness routinely available in clinical practice. Moreover, even though RCTs might potentially answer very important questions from a clinician's perspective, patients are reluctant to enroll in such RCTs with huge discrepancies between treatment arms [5].

In this light, our vision is that tailoring MIBC treatment in the era of precision oncology requires a comprehensive understanding of bladder cancer as a "whole". The paradigm shift might be represented by considering bladder cancer as a "single" heterogeneous disease rather than two different entities (muscle-invasive vs non-muscle-invasive). In other words, as clinicians we need reliable classification systems that can show the "full picture" of bladder cancer, with direct implications for its management.

Interpretation of the literature according to the current classification of bladder cancer is rather misleading. In particular, cancer-specific mortality among patients with high-risk non-muscle-invasive bladder cancer is as high as 10–20% and RC is considered the first-line therapy for selected

patients [6]. Moreover, only a proportion of patients with MIBC benefit from NAC, and patients who progress to MIBC after treatment for prior noninvasive disease (secondary MIBC) treated with NAC have worse clinical outcomes than similarly treated patients with primary MIBC [7].

To pool the available evidence and move forward, we need to change from prognostication to prediction and elaborate modern classification systems taking into account the nature of bladder cancer from a biological rather than histopathological perspective. Biomarkers are urgently needed to select the patients who are most likely to benefit from upfront active surveillance after TURB and NAC or immunotherapy [8]. We believe that while waiting for such biomarker-driven management of bladder cancer, the current standard treatment for most patients with MIBC should still be NAC followed by RC. Patients who elect for bladder preservation strategies should be treated at high-volume institutions by multidisciplinary bladder cancer teams and should be enrolled in prospective studies with appropriate patient-centered endpoints.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Milowsky MI, Rumble RB, Booth CM, et al. Guideline on muscle-invasive and metastatic bladder cancer (European Association of Urology guideline): American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2016;34:1945–52.

[2] Audenet F, Waingankar N, Ferket BS, et al. Effectiveness of transurethral resection plus systemic chemotherapy as definitive treatment for muscle invasive bladder cancer in population level data. J Urol 2018;200:996–1004.

[3] Moran GW, Li G, Robins DJ, et al. Systematic review and meta-analysis on the efficacy of chemotherapy with transurethral resection of bladder tumors as definitive therapy for muscle invasive bladder cancer. Bladder Cancer 2017;3:245–58.

[4] Cha EK, Sfakianos JP, Sukhu R, et al. Poor prognosis of bladder cancer patients with occult lymph node metastases treated with neoadjuvant chemotherapy. BJU Int 2018;122:627–32.

[5] Huddart RA, Birtle A, Maynard L, et al. Clinical and patient-reported outcomes of SPARE—a randomised feasibility study of selective bladder preservation versus radical cystectomy. BJU Int 2017;120:639–50.

[6] Klaassen Z, Kamat AM, Kassouf W, et al. Treatment strategy for newly diagnosed T1 high-grade bladder urothelial carcinoma: new insights and updated recommendations. Eur Urol 2018;74:597–608.

[7] Pietzak EJ, Zabor EC, Bagrodia A, et al. Genomic differences between "primary" and "secondary" muscle-invasive bladder cancer as a basis for disparate outcomes to cisplatin-based neoadjuvant chemotherapy. Eur Urol 2019;75:231–9.

[8] Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. J Clin Oncol 2018;36:3353–60.

Riccardo Campi[a,b], Morgan Roupret[c,*]

[a]*Department of Urology, Careggi Hospital, University of Florence, Florence, Italy*

[b]*Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*

[c]*Department of Urology, Hôpital Pitié-Salpêtrière, Sorbonne Université, Paris, France*

*Corresponding author. Department of Urology, Hôpital Pitié-Salpêtrière, Sorbonne Université, 83 Boulevard de l'Hôpital, 75013 Paris, France.
E-mail address: morgan.roupret@aphp.fr (M. Roupret).

https://doi.org/10.1016/j.eururo.2019.03.001

Re: Evaluation of Cancer Specific Mortality with Surgery versus Radiation as Primary Therapy for Localized High Grade Prostate Cancer in Men Younger than 60 Years

Huang H, Muscatelli S, Naslund M, Badiyan SN, Kaiser A, Siddiqui MM

J Urol 2019;201:120–8

Experts' summary:

This study is a classic retrospective cohort study using the Surveillance, Epidemiology and End-Results (SEER) database to compare survival rates between primary surgery and radiation as treatment options for patients with high-grade (Gleason score $\geq$8) prostate cancer (PC). The study restricted the cohort to men younger than 60 yr to minimize competing risks of mortality. Among a total of 2228 men, 1459 (65.5%) had primary surgery and 769 (34.5%) had primary radiation. PC-specific and overall mortality rates were lower among patients who underwent surgery than among patients who had radiation (hazard ratios ranging from 0.28 to 0.57 in favor of surgery). Baseline covariates included age, Gleason score, stage, and prostate-specific antigen (PSA) level at diagnosis. Inverse-probability, treatment-weighted, multivariate Cox modeling was performed to account for selection bias.

Experts' comments:

The debate continues on whether surgery or radiation provides better cancer control for patients with nonmetastatic PC. Indeed, the largest meta-analysis and systematic review of studies comparing surgery versus radiation in *European Urology* [1] was one of the most downloaded articles in its publication year. The widely anticipated results from the ProtecT trial comparing survival rates among patients with screen-detected PC treated with surveillance, surgery, or radiation [2] were disappointing owing to the lack of study power and over-representation of patients with low-risk PC [3]. No further clinical trials are expected and the research community will continue to have to rely on nonexperimental methods in evaluating this issue.

Selection bias and the inability to account for unmeasured confounding variables are key limitations in conducting these studies (which randomized studies obviate). Opponents to such studies argue that it is impossible to properly address these problems and that therefore these