

REVIEW

## Current standards and practice changing studies in genitourinary (GU) cancers—a review of studies in localized/early GU cancers<sup>☆</sup>

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Optimizing treatment of genitourinary cancers in the early-stage setting continues to remain an area of need, given that the development of distant metastases is often the life-limiting factor in the natural history of these cancers. The use of perioperative therapies in the treatment of these cancers deemed to be at high risk of recurrence has shown considerable benefits in outcomes in recent studies. In this article, we review the recently published studies in early-stage genitourinary cancers (renal cell, urothelial and prostate carcinomas), and their impact on disease outcomes and treatment practices. The results of subgroup analysis from some of these trials, with Asian patients enrolled, give assurance of the clinical efficacy and safety of these therapies in early-stage urological malignancies in the Asian setting.

**Key words:** genitourinary cancer, renal cell carcinoma, urothelial carcinoma, prostate carcinoma

### INTRODUCTION

The treatment of urological malignancies has seen several significant advancements in recent years. For locoregional disease, treatment often consists of a multimodality approach, with the addition of systemic therapy to radical local therapy in the form of surgical resection or radiotherapy, in a bid to improve disease outcomes. Optimising treatment in the early-stage setting is especially crucial, since the development of distant metastases is often the life-limiting factor in the natural history of urological malignancies.

The past year has seen publication of results from several randomised phase III studies showing benefit in adjuvant or neoadjuvant systemic therapy in the setting of locoregional urological malignancies. These studies are reviewed in this publication below.

#### Renal cell carcinoma

Renal cell carcinomas (RCCs) are malignancies arising from the renal cortex, and comprise multiple distinct histological subtypes,<sup>1</sup> the most common and extensively studied being the clear-cell histological subtype. Even within the clear-cell

subtype of RCC, varying disease behavior and clinical course underlies the heterogeneity inherent in the disease, with various risk stratification models in the advanced setting which guide treatment and prognosis.

In the early-stage setting, trials investigating the benefit of adjuvant tyrosine kinase inhibitors have largely been negative. The ASSURE,<sup>2</sup> PROTECT<sup>3</sup> and ATLAS<sup>4</sup> trials for adjuvant sorafenib, pazopanib and axitinib, respectively, failed to demonstrate a disease-free survival (DFS) or overall survival (OS) benefit. The S-TRAC study compared adjuvant sunitinib given for 1 year against placebo in completely resected clear-cell RCC at high risk of relapse, as defined by stage III and/or the presence of regional nodal disease. A significant 5-year DFS benefit of 59.3% for sunitinib versus 51.3% in the placebo arm was demonstrated [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.59-0.95] in the study,<sup>5</sup> although OS data have not reached statistical significance at the last publication.<sup>6</sup>

Most recently, KEYNOTE-564 investigated the benefit of adjuvant pembrolizumab for 17 cycles versus placebo in surgically resected clear-cell RCC at high risk of recurrence, as defined by stage II disease with nuclear grade 4 or sarcomatoid differentiation, stage III disease, presence of regional nodal metastases, or stage IV with no evidence of disease (after metastasectomy). With a median follow-up of 14.1 months (range 14.9-41.5 months), a significantly decreased risk of recurrence or death was observed in the pembrolizumab arm (HR 0.68, 95% CI 0.53-0.87), with the median DFS not reached in either group.<sup>7</sup> The trial included 36.3% of patients recruited from outside North

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America and Europe, with DFS in this subgroup favoring the pembrolizumab arm (HR 0.81, 95% CI 0.55-1.21). Notably, DFS results also favored the pembrolizumab arm in the subgroups of programmed death-ligand 1 (PD-L1) combined positive score (<1 or ≥1) and metastatic staging (M0 or M1 no evidence of disease).

Treatment-related adverse events were as expected with pembrolizumab, with no new safety signals detected. OS results from KEYNOTE-564 were immature at the time of data cut-off, with only 26% of total expected deaths as prespecified for the final analysis observed (HR 0.54, 95% CI 0.30-0.96, 96.6% versus 93.5% alive at 24 months). KEYNOTE-564 is the first phase III study to show a sustained DFS benefit with the use of an adjuvant immunotherapy for clear-cell RCC, and its results suggests that administration of 17 cycles of adjuvant pembrolizumab is a new standard-of-care for surgically resected RCC at high risk of recurrence, although at this point the OS results are still not mature.

### **Urothelial carcinoma**

Bladder cancer is the most common malignancy arising from the urinary tract, with the most common histology being urothelial carcinoma.<sup>8</sup> Whereas radical surgery with a radical cystectomy for malignancies arising from the bladder and nephroureterectomy for malignancies arising from the upper urinary tract remain standard-of-care, metastatic relapse occurs in >50% of patients with muscle invasive disease.<sup>9-12</sup> This underscores the need for effective peri-operative systemic therapy in the early-stage setting in order to reduce relapse risk. Neoadjuvant chemotherapy with a platinum-containing regimen, based on results from the INT-0080/SWOG-317 trial, showed DFS and OS for such an approach over surgery alone.<sup>13</sup> Adjuvant chemotherapy, based on results of a meta-analysis,<sup>14</sup> is another commonly used treatment approach in the treatment of muscle invasive bladder carcinoma. For upper tract urothelial cancers, the role for adjuvant therapy was established with the POUT study, which showed a benefit for DFS and metastases-free survival with adjuvant platinum-based chemotherapy in resected stage II and above disease.<sup>15</sup>

Most recently, the results of two phase III studies investigating the role of adjuvant immune checkpoint inhibitors in early-stage urothelial cancers were published. CHECKMATE-274 was a multicenter, double-blind, randomized trial comparing adjuvant nivolumab given for up to 1 year against placebo, in patients with completely resected urothelial carcinoma with a high risk of recurrence, as defined by pathological stage pT3, pT4a or pN+ who had not received neoadjuvant chemotherapy, or pathological stage ypT2 to ypT4a, or ypN+ for those who had received neoadjuvant chemotherapy.<sup>16</sup> Of note, patients who had not received neoadjuvant chemotherapy were only allowed on trial if they were deemed unfit or had refused adjuvant chemotherapy. In the study population, 43.4% of patients had received neoadjuvant chemotherapy before the trial, and 21.0% of patients had upper tract urothelial cancers.

CHECKMATE-274 showed a significant improvement in its co-primary endpoints of DFS in the intention-to-treat population (HR 0.70, 95% CI 0.55-0.90) and in the PD-L1 expression ≥1% population (HR 0.55, 95% CI 0.35-0.85). Subgroup analysis showed a trend towards DFS benefit in the nivolumab arm regardless of nodal status, PD-L1 expression or use of neoadjuvant chemotherapy. In addition, patients across subgroups by geographical region, including those in Asia (HR 0.85), showed a trend towards DFS benefit, as did subgroups in the USA (HR 0.45), Europe (HR 0.84) and the rest of the world (HR 0.39). Nivolumab, however, did not seem to benefit patients with ureteric (HR 1.56, 95% CI 0.70-3.48) or renal pelvis (HR 1.23, 95% CI 0.67-2.23) primaries, although numbers of these patients included in the trial were small.

On the other hand, IMvigor-010 compared adjuvant atezolizumab, given for a total of 16 cycles or up to 1 year whichever came first, against observation.<sup>17</sup> Inclusion criteria for the trial were similar to those of CHECKMATE-274, including patients with completely resected urothelial carcinoma with a high risk of recurrence, as defined by pathological stage pT3, pT4a or pN+ who had not received neoadjuvant chemotherapy, or pathological stage ypT2 to ypT4a, or ypN+ for those who had received neoadjuvant chemotherapy. Similar to CHECKMATE-274, patients who had not received neoadjuvant chemotherapy were only allowed on trial if they were deemed unfit or had refused adjuvant chemotherapy. For IMvigor-010, 47.6% of patients had received neoadjuvant chemotherapy before the trial, and only 6.7% of patients had upper tract urothelial cancers.

In contrast to CHECKMATE-274, IMvigor-010 failed to show a statistically significant benefit for adjuvant atezolizumab in its primary endpoint of investigator-assessed DFS (HR 0.89, 95% CI 0.74-1.08), as well as its secondary endpoint of OS (HR 0.85, 95% CI 0.66-1.09). None of the prespecified subgroups, such as PD-L1 status, primary tumor site or nodal status, showed a significant DFS benefit with atezolizumab. There was also no significant DFS benefit observed for the Asian subgroup of patients included in IMvigor-010 (HR 0.96, 95% CI 0.57-1.61).

Differing outcomes of CHECKMATE-274 and IMvigor-010 may merit further study as to whether certain subgroups of patients with urothelial carcinoma may benefit from adjuvant immunotherapy. Nevertheless, based on the results of CHECKMATE-274, adjuvant nivolumab is now included in the National Comprehensive Cancer Network (NCCN) guidelines (category 2A recommendation) for high-risk patients who had not received neoadjuvant chemotherapy, or pathological stage ypT2 to ypT4a, or ypN+ for those who had received neoadjuvant chemotherapy.<sup>10</sup>

### **Prostate carcinoma**

Treatment of early-stage prostate cancer has traditionally been guided by a risk stratification model based on the local extent of disease, serum prostate-specific antigen (PSA) levels and the Gleason's score.<sup>18</sup> Patients with low- to very

low-risk prostate cancer are often put on active surveillance, whereas patients with intermediate-risk disease with a life expectancy of >10 years are usually treated with radical local therapy with either surgery or radiotherapy. Patients with high- to very high-risk disease are usually treated with radical local therapy, either radiotherapy with concomitant androgen deprivation therapy (ADT), or radical prostatectomy in selected cases. Concomitant ADT administered with radical radiotherapy has shown benefits in recurrence-free survival<sup>19,20</sup> and OS,<sup>19-21</sup> whereas immediate administration of ADT following radical prostatectomy has only shown a DFS benefit but no OS benefit in a meta-analysis.<sup>22</sup> Whereas the optimal duration of ADT has not been established, the European Society of Medical Oncology (ESMO) consensus guidelines recommend a duration of at least 6 months, and up to 24 months in patients with high-risk disease,<sup>23</sup> whereas guidelines from the American Society for Clinical Oncology recommend a duration of 18-36 months.<sup>24</sup>

The importance of optimizing treatment of early-stage prostate cancer is underscored by the fact that the majority of the mortality from prostate cancer occurs in patients who had non-metastatic disease at initial diagnosis,<sup>25,26</sup> with metastases-free survival being shown as a valid surrogate marker for OS in M0 patients.<sup>27</sup> As such, optimizing therapy in the high- and very high-risk subgroups of early-stage prostate cancer, where rates of disease relapse are high, has been the basis of many recent phase III trials in this area.

**Radical radiotherapy.** Radical radiotherapy is a commonly used approach for the treatment of localized prostate cancer. Recently, the POP-RT phase III study investigated the benefit of prophylactic whole-pelvic nodal radiotherapy over prostate-only radiotherapy in the treatment of early-stage prostate cancer.<sup>28</sup> This trial included Asian (Indian) patients with clinically node-negative prostate cancer who were deemed to be at significant risk of occult nodal disease involvement ( $\geq 20\%$ ). Of note, all patients enrolled received image-guided, intensity modulated radiotherapy, as well as at least 2 years systemic treatment with ADT, in accordance with contemporary standard-of-care treatment of high-risk early-stage disease.

The POP-RT trial showed a benefit for prophylactic whole-pelvic radiotherapy over prostate-only radiotherapy in its primary endpoint of 5-year biochemical failure-free survival (HR 0.23, 95% CI 0.10-0.52), its secondary endpoint of DFS (HR 0.40, 95% CI 0.22-0.73), as well as its exploratory endpoint of distant metastases-free survival (HR 0.35, 95% CI 0.15-0.82). It did not, however, show any benefit in OS (HR 0.92, 95% CI 0.41-2.05) which was a secondary endpoint in the study. The lack of demonstrable OS benefit stands in contrast to the other outcomes with significant benefit described in the trial, in particular that of the exploratory endpoint of distant metastases-free survival.<sup>27</sup> This raises questions as to the reasons for the lack of OS benefit seen in the POP-RT trial at the current time. Deaths due to non-cancer-related causes could be a

reason, given the higher rates of cumulative grade 2 late genitourinary toxicities with whole-pelvic radiotherapy compared with prostate-only radiotherapy (20.0% versus 8.9%). Moreover, recent improvements in the treatment setting of advanced disease may have also impacted the endpoint of OS.

Nevertheless, based on the results of this study, prophylactic whole-pelvic nodal radiotherapy may be offered as a treatment option for prostate cancer patients at high risk of nodal metastases. Despite the lack of OS benefit demonstrated in the POP-RT trial, improvements in biochemical failure-free survival and DFS may still serve to benefit patients with prostate cancer, from the perspective of an improvement in quality of life.

**Adjuvant radiotherapy after prostatectomy.** The NCCN guidelines lists adjuvant external beam radiotherapy as an option after radical prostatectomy in the presence of adverse pathological features such as positive resection margins, seminal vesicle invasion, extracapsular extension or detectable PSA levels after resection, as well as the presence of pelvic nodal metastases.<sup>18</sup> Recently published randomized trials have brought into question the benefit of adjuvant radiotherapy for resected early-stage prostate cancer, however, even in the presence of high-risk pathological features.

The RADICALS-RT trial compared an approach of adjuvant radiotherapy versus observation followed by salvage radiotherapy on progression in patients with resected early-stage prostate cancer with high-risk factors, as defined by pathological T3/4 stage, Gleason's score 7-10, positive resection margins, or a preoperative PSA  $\geq 10$  ng/ml.<sup>29</sup> The use of concomitant ADT for up to 2 years was allowed for in the trial design. No significant improvements in biochemical PFS were shown for the adjuvant radiotherapy arm of the trial (HR 1.10, 95% CI 0.81-1.49), with a 5-year biochemical PFS of 85% in the adjuvant radiotherapy arm against 88% in the control arm. In addition, the occurrence of both early and late toxicities was higher in the intervention arm with adjuvant radiotherapy.

Two other randomized trials were also conducted to compare adjuvant radiotherapy against observation followed by salvage radiotherapy in resected early-stage prostate cancer. The multicentre French randomized study GETUG-AFU17 included patients with pathological T3/4 disease with positive surgical resection margins, who had no or unknown pathologically-proven nodal disease (N0 or Nx if no pelvic lymph node dissection carried out).<sup>30</sup> All patients received 6 months of ADT with triptorelin. The trial closed recruitment prematurely, after a total of 424 of a planned 718 patients were recruited, due to an unexpectedly low event rate. Nevertheless, based on the intention-to-treat population of 424 patients, 5-year event-free survival (EFS) was 92% in the adjuvant radiotherapy group versus 90% in the salvage radiotherapy group (HR 0.81, 95% CI 0.48-1.36), with the authors concluding that EFS was not significantly different between the two groups, despite the trial not being sufficiently powered to show this.

Similarly, the RAVES trial included patients with high-risk pathological features of positive surgical resection margins, extraprostatic extension or seminal vesicle invasion, and did not allow for use of ADT.<sup>31</sup> As with GETUG-AFU17, recruitment in the RAVES trial was closed early due to low event rates. Although salvage radiotherapy did not meet the trial-specified criteria for non-inferiority, with 5-year freedom from biochemical progression rates of 86% with adjuvant radiotherapy versus 87% for salvage radiotherapy (HR 1.12, 95% CI 0.65-1.90), the authors concluded that salvage radiotherapy results in similar biochemical control to adjuvant radiotherapy. Both the RAVES and GETUG-AFU17 trials, as with the RADICALS-RT trial, showed an increase in treatment-related toxicities, particularly with genitourinary toxicities, with an approach of adjuvant radiotherapy compared with salvage radiotherapy.

The results of the RADICALS-RT, RAVES and GETUG-AFU17 trials thus do not support an approach of adjuvant radiotherapy administration after surgical resection for prostate cancer, even in the presence of high-risk features, with a lack of efficacy and increased toxicities demonstrated in the trials. It should be noted, however, that the trials described did not include patients with proven regional lymph node metastases, and thus in cases where patients were found to have incidental nodal disease on resection, the use of adjuvant radiotherapy may still be considered as a treatment option.

**Systemic therapy in early-stage prostate cancer.** Previous studies have demonstrated the benefit of adding docetaxel,<sup>32-34</sup> as well as second-generation anti-androgenic agents abiraterone,<sup>35-37</sup> enzalutamide<sup>38-40</sup> or apalutamide<sup>41</sup> to first-line therapy in metastatic (M1) disease. The addition of such agents in the setting of M0 disease, however, remains of questionable benefit. In particular, in a previously published analysis in the STAMPEDE trial, the addition of abiraterone to ADT did not show any significant benefit in OS in the subgroup of patients with M0 prostate cancer.<sup>37</sup>

The results of an updated analysis of the STAMPEDE trial was presented recently in ESMO 2021, which investigated the benefit of 2 years of abiraterone acetate with or without enzalutamide in non-metastatic (M0) high-risk prostate cancer.<sup>42</sup> High-risk disease was defined in newly-diagnosed disease as either nodal involvement or at least two of three high-risk clinic-pathological factors (T3 or T4 disease, PSA  $\geq 40$  ng/ml or Gleason's score  $\geq 8$ ), or in relapsed disease after previous radical prostatectomy or radiotherapy as nodal involvement, PSA  $\geq 4$  ng/ml with doubling time  $< 6$  months or an absolute PSA value of  $\geq 20$  ng/ml. The analysis showed a significant benefit in metastases-free survival (HR 0.53, 95% CI 0.44-0.64) and OS (HR 0.60, 95% CI 0.48-0.73) for the addition of abiraterone with or without enzalutamide. Subgroup analysis for metastases-free survival favoured the abiraterone with/without enzalutamide arm in all subgroups.

Further analysis of subgroups of patients who received only abiraterone or abiraterone with enzalutamide did not show any significant benefit in metastases-free survival or

OS for the addition of enzalutamide to abiraterone. Furthermore, rates of grade 3 and above toxicities were also higher with enzalutamide, with the most significant being those of erectile dysfunction, hypertension, fatigue and transaminitis. Thus, the presenters concluded that while addition of abiraterone resulted in a significant benefit in patients with high-risk prostate cancer, the addition of enzalutamide on top of abiraterone did not demonstrate any significant additional benefit, with increased rates of toxicities.

With the results of the updated STAMPEDE analysis as described, 2 years of abiraterone in addition to ADT should thus be considered as a treatment option for patients with high-risk, non-metastatic prostate cancer following radical local therapy.

## CONCLUSIONS

In conclusion, data published from the studies described in this review raises a few points. Firstly, the incorporation of systemic therapy to radical local therapy has shown much promise in the improvement of clinical outcomes in recent trials for early urological cancers. The interventions investigated in KEYNOTE-564 for renal cell cancers, CHECKMATE-274 for urothelial cancers and the STAMPEDE analysis for prostate cancers described in this review established a new standard-of-care for the adjuvant treatment of their respective diseases. In contrast, the approach of post-operative radiotherapy in the RADICALS-RT, GETUG-AFU17 and RAVES trials for prostate cancer showed a lack of efficacy in improving clinical outcomes. Whereas results from the POP-RT trial suggest that intensification of radiotherapy through the extension of radiotherapy fields may serve to reduce disease recurrence or progression, no demonstrable effects on OS were shown. This thus further underscores the importance of systemic disease control with the use of perioperative systemic therapy agents being key to the improvement of clinical outcomes in early-stage urological cancers, as metastatic disease relapse is often the life-limiting event in these instances.

Secondly, in recommending the use of adjuvant systemic therapy for patients with early urological malignancies, it is important to consider that the practice changing trials described in this review selected for patients with disease at higher risk of treatment failure, with benefit for the intervention investigated being demonstrated in this disease subset. Selection of patients with disease who fall into these subsets of being at high risk of recurrence is thus key in maximizing the benefit of systemic therapy in the early-stage setting, especially given the potential for toxicities for many systemic therapeutic agents as well.

Lastly, subgroup analysis from the KEYNOTE-564 and CHECKMATE-274 trials show that clinical benefit for immune checkpoint inhibitor therapy was consistent across ethnic subgroups, with their respective HRs for DFS favoring the intervention arms for patients recruited from outside North America and Europe for KEYNOTE-564, and for patients recruited from Asia in CHECKMATE-274. As patients



of Asian ethnicity are often under-represented in trials for urological cancers, the results of subgroup analysis from these trials give assurance of the clinical efficacy of immune checkpoint inhibitor therapy in early-stage urological malignancies in the Asian setting.

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## DISCLOSURE

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