



Consensus statements from the EAU-ESMO collaboration for advanced and variant bladder cancer: can we move the needle to improve survival?

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Bladder cancer caused an estimated 17,980 deaths in the United States in 2020 (1). Unfortunately, death from bladder cancer has not decreased over the last few decades, with an estimated 12,200 deaths in 2000, a trend corroborated by independent analysis (2,3). Over the past years we have witnessed an explosion of advances in bladder cancer treatment, spanning from novel bladder-sparing treatments for non-muscle invasive disease to the development and rapid adoption of immune checkpoint inhibition for advanced stages (4,5). How do we harness these advances to move the needle and improve oncologic outcomes for bladder cancer? One facet will be to contextualize all advances across specialties rather than viewing them in isolation from a single standpoint. Advances in the management of non-muscle invasive disease, trimodal therapy, and immune checkpoint inhibition should not be relegated exclusively to the domains of urologists, radiation oncologists, and medical oncologists, respectively. To improve outcomes for patients with bladder cancer, inclusive multi-specialty collaboration is required to synthesize a succinct and centralized best practice resource.

The recent EAU-ESMO Consensus statements by Witjes *et al.* on the management of advanced and variant bladder cancer is a colossal and timely international multi-specialty effort (6). The authors utilized Delphi methodology to draw from 134 experts from 23 countries, comprised of urologists, oncologists (including medical and radiation oncologists), and “other” stakeholders (including

radiologists, pathologists, specialist nurses, clinical oncologists, and nuclear medicine specialists). While the entirety of the 143 consensus statements warrant careful review, several statements are of particular interest and importance across the landscape of bladder cancer.

Variant histology

First, considering non-muscle invasive bladder cancer, there are several salient points made regarding urothelial histologic variants. There was 86% agreement for the consensus statement advocating immediate radical cystectomy and lymphadenectomy for patients with T1 urothelial carcinoma (UC) with variant micropapillary histology. The strength of this recommendation contrasts the equipoise demonstrated in a recent systematic review and meta-analysis, which highlights more controversy in considering bladder-sparing management strategies for some cases of bladder UC with limited proportion, extent, and depth of micropapillary component (7). Recommendations regarding the rarer plasmacytoid, sarcomatoid, and nested variants showed more variability, with 64% of urologists, 52% of oncologists, and 18% of other stakeholders advocating for immediate radical cystectomy. Particularly for the plasmacytoid variant, due to its predilection for aggressive and diffuse local invasion with characteristically indiscernible radiologic characteristics, immediate extirpative surgery for clinical T1 disease is warranted (8).

Regarding pure divergent muscle-invasive histologies, there was near universal agreement to administer neoadjuvant chemotherapy potentially followed by local consolidative surgery for small cell neuroendocrine variants, and to proceed with primary radical cystectomy and lymphadenectomy for squamous cell carcinoma and adenocarcinoma. For UC with variant histologies, there was less agreement. Only 63% recommended neoadjuvant chemotherapy for micropapillary, plasmacytoid, squamous or glandular differentiation histologies. The lack of consensus in the paper results from numerous competing issues of variant histologies. First, the clear association with variant histology and clinical understaging with respect to local extension and micrometastatic disease supports consideration for neoadjuvant systemic therapy in addition to timely cystectomy. Second, aberrant tumor biology and the presence of tumor heterogeneity may also reduce the efficacy of systemic treatments (9). Additionally, each of these variant histologies possesses variable response rates to systemic treatments. Molecular sequencing, subtyping, and profiling are currently under investigation and may supplement the predominant use of clinical factors and immunohistochemistry for management decisions. As a final note, it is important to stress that optimal decision making for histologic variants hinges on a meticulous and high-quality transurethral resection of bladder tumor with expert pathologic review (10,11).

Neoadjuvant therapy

While the overall survival benefit of neoadjuvant cisplatin-based chemotherapy for patients with muscle-invasive bladder cancer is well established, there does exist a distinct subset of patients who do not respond (12,13). Thus, effective patient selection is critical to determine who benefits from immediate radical cystectomy versus surgery preceded by neoadjuvant therapy. For example, the consensus paper highlights a landmark study by Seiler *et al.* that recommends molecular subtyping with prioritization of neoadjuvant chemotherapy for patients with basal tumors (14). While some data supports using biomarkers to guide neoadjuvant systemic therapy, prospective validation is needed (15). Prognostic molecular markers certainly hold promise, but the authors conclude that biomarkers are not yet ready for prime time. Regarding neoadjuvant immunotherapy, there is promising data from the PURE-01 and ABACUS trials for neoadjuvant pembrolizumab and Atezolizumab, respectively, but these agents have not

been validated in phase III studies (16,17). Therefore, there was strong consensus to not use neoadjuvant immune checkpoint inhibitors outside of a clinical trial.

Bladder-sparing approaches and pelvic lymphadenectomy

Trimodal therapy for muscle invasive disease appears to be gaining traction in some areas but interest is noted to be geographically specific, particularly with respect to country. Specialist bias may play a large role in patient selection, and for this reason, the bladder-sparing consensus statement recommending multidisciplinary consultation with a urologist, oncologist and a neutral party such as a specialist nurse, had 83% agreement. Advocacy groups such as the Bladder Cancer Advocacy Network (BCAN) can help serve a key role by connecting patients to others who have previously undergone these treatments. While most of the technical aspects of radiosensitizing chemotherapy and radiotherapy techniques had strong consensus, the role of pelvic lymphadenectomy within bladder-sparing algorithms provides some controversy. Only 64% agreed to not perform pelvic lymphadenectomy for clinically node negative muscle invasive disease. Interestingly, “other” stakeholders (83%) supported the use of pelvic lymphadenectomy compared to urologists (47%) and oncologists (25%). This is likely secondary to different perceptions of patient selection between types of specialists, as urologists note that well selected trimodal therapy patients often have less aggressive disease, with lower risk of nodal metastases. Further highlighting the potential for selection bias, it was noted that less than 10% of patients had lymph node relapse in the BC2001 trial, which is lower than the 25% node positive rate typically seen in large cystectomy series (18).

Oligometastatic disease

The EAU-ESMO Consensus statement was the first to discuss the nuances of surgical selection for oligometastatic disease, distinguishing it from prior guidelines in this space. There was strong 91% consensus that cure is possible in some patients with a single metastatic lesion. There was less consensus for patients with two metastatic lesions as supported by retrospective data and a recent systematic review (19). When stratified by specific metastatic site, lymph node only disease was deemed most favorable, followed by lung, liver, and bone.

There were also comments regarding the role of PET-CT for patients in consideration of radical treatment for oligometastatic disease. While 88% agreed that PET-CT should be performed for these patients, the data for this is relatively limited and requires further study (20). Most agreed with the intuitive concept that radical treatment of oligometastatic disease should be accompanied by systemic therapy. However, there was less clarity regarding optimal type and duration of systemic regimens. A particular conundrum is for isolated clinically node positive disease, where some retrospective data suggests benefit from longer induction regimens over shorter neoadjuvant courses, although this lacks prospective validation (21).

Immune checkpoint inhibition

Regarding immune checkpoint inhibition, the most definitive consensus was achieved regarding the lack of pseudoprogression observed for UC, therefore necessitating that radiographic progression on checkpoint inhibition should be promptly followed by a switch to chemotherapy. The role of sequencing and combining chemotherapy and immunotherapy is currently being assessed by a myriad of trials. While this paper demonstrates relatively strong consensus against combination chemotherapy and immunotherapy for metastatic disease, this has the potential to rapidly change, as a study was just recently published demonstrating the efficacy of combination Atezolizumab with platinum-based chemotherapy for first line metastatic disease (22). Ultimately, the authors wisely recommend supporting clinical trials to allow for the safe adoption of rapidly changing available treatment regimens.

Consensus process

The importance of an inclusive multi-disciplinary process was shown by several examples of consensus changes between the initial Delphi survey and post-conference consensus statements. This reflects the presence of uncertainty and lack of definitive authority from a single specialty. For example, 80% of urologists initially disagreed with stopping regular surveillance after 5 years following cystectomy, while 88% of participants agreed to stop regular surveillance after this time on the final consensus statement. The viewpoint that was lacking in the paper was the patient perspective, which is of particular importance when considering the psychosocial implications for follow-up and survivorship. This can be better voiced with the

inclusion of patient advocacy groups.

Future directions

In summary, the consensus statements provided under the direction of the EAU-ESMO Committees is an invaluable resource for physicians managing bladder cancer. There will inevitably be a need to amend some of these recommendations as advances rapidly continue to arrive. For example, the role of checkpoint inhibition for non-muscle invasive bladder cancer, while not supported in these consensus statements, has rapidly shifted with the recent FDA approval for Pembrolizumab following the KEYNOTE-057 trial (23). There are many other questions that remain to be answered and can further improve oncologic outcomes. The role of MRI imaging and the VIRADS system for bladder cancer is intriguing, with implications for both non-muscle invasive and muscle-invasive disease (24). Patient selection for neoadjuvant chemotherapy needs further optimization based on staging, variant histology, and molecular profiling. Optimizing management of clinically node positive disease is currently understudied. The role of both imaging, such as PET-CT, and biomarkers, such as circulating tumor cells, for restaging during neoadjuvant treatment and for detection of metastatic and recurrent disease, needs to be further investigated. Finally, the role of bladder sparing approaches, both for initial management of muscle invasive disease and in the setting of clinical response following systemic therapy, requires careful evaluation. Ultimately, further studies and the effective dissemination of their results will allow the needle to move, improving oncologic outcomes and quality of life for patients with bladder cancer.

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