The Changing Face of Urothelial Bladder Cancer

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EDITORIAL

Survival for patients undergoing radical cystectomy for urothelial bladder cancer has remained relatively unchanged throughout the past three decades [1]. This is despite improvements in surgical technique, supportive care during surgery, administration of systemic therapy, and lastly, despite evidence of an associated survival benefit, neoadjuvant chemotherapy [2]. While the reason for this lack of advance in survival outcomes remains unclear, advances have been made in our understanding of bladder cancer that may allow better stratification within the disease itself. Molecular markers are beginning to be identified that may be implicated in worse outcomes, response to chemotherapy, or outlining which patients have progression of disease. These developments are in infant stages, but recent advances may shape future management. Notable among these advances is the classification of morphologic subtypes within urothelial bladder cancer by the World Health Organization. The recognition of variant histology within urothelial carcinoma is changing the way institutions opt to manage such patients. However, there is poor consensus among experts regarding the most appropriate management strategy and the extent to which this should vary by individual variants.

Radical cystectomy remains the gold-standard for patients with muscle invasive disease. Less than 20% of urothelial bladder cancer patients currently receive neoadjuvant chemotherapy [3]. This is despite Level 1 evidence demonstrating a survival benefit associated with the administration of Methotrexate, Vinblastine, Adriamycin and Cisplatin [MVAC] neoadjuvant chemotherapy [2]. It remains unclear if this small but significant benefit applies to patients with specific histologic variants as clinical trials either did not assess or excluded patients with variants other than squamous and glandular differentiation. In a secondary analysis of the SWOG 8710 trial data, Scorsyrev et al. demonstrated equivalent responses to MVAC for patients with Squamous [SQD] or Glandular Differentiation [GLD] [4], a finding echoed in retrospective studies. As such, patients with these variants should perhaps be managed similarly to non-variant urothelial carcinoma with MVAC neoadjuvant chemotherapy and radical cystectomy for muscle invasive disease, along with corresponding guidelines for non-muscle invasive disease. However, the management of patients with less common variants is poorly defined, with concerns raised as to the utility of similar guidelines with conventional chemotherapy regimens in the case of more aggressive variants vs. pursuing novel neoadjuvant trials or undergoing upfront cystectomy.

Although less common than SQD, Micropapillary Variant [MPV] is one of the best described variants of urothelial carcinoma with several studies suggesting poor survival and response to chemotherapy, whereas few favor chemotherapy [5-8]. Plasmacytoid Variant [PCV], one of the less well-described variants, is generally considered more aggressive than traditional non-variant urothelial carcinoma [9,10]. In a contemporary cohort of patients undergoing radical cystectomy since 2008, Kaimakliotis et al. reported that the presence of PCV on cystectomy was associated with twice the risk of mortality as non-variant after adjusting for pathologic features and systemic chemotherapy [10]. Interestingly, it has been reported that PCV demonstrates aggressive spread along fascial planes [11]. This may be associated with loss of E-cadherin proteins, although further molecular characterization will likely be required to fully elucidate the mechanism of invasion and spread [11]. Sarcomatoid variant and other infrequently described variants such as nested and lymphoepithelioma-like variants are also considered to be more aggressive than non-variant urothelial carcinoma. However, small sample sizes limit the statistical power of these case series [12]. A recent study suggested that sarcomatoid variant is the ultimate de-differentiation product of variant histology, highlighting its aggressive clinical course [13].

Multiple institutions, including our own, advocate early radical cystectomy for patients with MPV,PCV and sarcomatoid, regardless of presence of muscle invasive disease [6,9,10]. Alternatively, some have advocated for conservative management protocols rather than immediate radical cystectomy for non-muscle invasive disease [7,8]. Part of the debate over the management of more aggressive variants such as MPV and PCV is due to conflicting chemo sensitivity studies. Although the majority of studies suggest that neither MPV nor PCV are chemo sensitive [5,6,9] small case studies have suggested that there may be some benefit to administration of neoadjuvant chemotherapy [7,14].

The long term impact of chemo sensitivity should be carefully considered in MPV and PCV patients as there have been reports that even among MPV and PCV patients who experience an initial response to neoadjuvant chemotherapy, the response is short-lived and prognosis continues to be poor [14]. In addition, many
of these patients will experience pathologic upstaging at time of cystectomy and progression of disease through chemotherapy. More than half of MPV and PCV patients who underwent neoadjuvant chemotherapy at our institutional cohort had lymph node positive disease on final pathology [15]. Even if these patients respond locally to neoadjuvant chemotherapy, the risk of metastatic spread and mortality remains high. Lack of response to neoadjuvant chemotherapy may compromise the window of surgical cure; as such, immediate cystectomy in the absence of clinical node involvement may confer the best oncologic results. The development of personalized medicine pathways using novel biomarkers will allow response profiling and will be critical moving forward in identifying chemotherapeutic regimens that are most effective for managing individual variant histologies of urothelial carcinoma in the neoadjuvant and adjuvant setting. It seems likely that urothelial carcinoma like renal carcinoma is not one disease, but many diseases each with unique genetic alterations which confer different growth characteristics and hence require different therapeutic options.

Although survival for patients with urothelial carcinoma has remained relatively unchanged throughout the past three decades, our understanding of the diversity of histology has increased considerably only recently with identification of less common and more aggressive variant in contemporary cohorts of urothelial bladder cancer. Patients with aggressive variants such as MPV, PCV and sarcomatoid should perhaps be considered as candidates for early cystectomy for oncologic control in an era of conflicting or absence of knowledge regarding chemotherapeutic responses. Tailoring therapeutic approaches to the individual variants along with increasing utilization of neoadjuvant chemotherapy for non-variant urothelial carcinoma offers the opportunity to dramatically improve survival for all patients with urothelial bladder cancer. Further characterization and understanding of the fundamental alterations in each of these variants will advance our management of this disease and allow for personalized care pathways in a disease with little progress over the recent past.

REFERENCES