Micropapillary bladder cancer: Current treatment patterns and review of the literature

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Abstract

Objectives: No guidelines exist for the management of micropapillary bladder cancer (MPBC) and most reports of this variant of urothelial carcinoma are case series comprising small numbers of patients. We sought to determine current practice patterns for MPBC using a survey sent to the Society of Urologic Oncology (SUO) and to present those results in the setting of a comprehensive review of the existing literature.

Materials and methods: A survey developed by the Translational Science Working Group of the Bladder Cancer Advocacy Network–sponsored Think Tank meeting was distributed to members of the SUO. The results from 118 respondents were analyzed and presented with a literature review.

Results: Most survey respondents were urologists, with 80% considering bladder cancer their primary area of interest. Although 78% of the respondents reported a dedicated genitourinary pathologist at their institution, there were discrepant opinions on how a pathologic diagnosis of MPBC is determined as well as variability on the proportion of MPBC that is clinically significant. Among them, 78% treat MPBC differently than conventional urothelial carcinoma, with 81% reporting that they would treat cT1 MPBC with upfront radical cystectomy. However, the respondents had split opinions regarding the sensitivity of MPBC to cisplatin-based chemotherapy, which affected utilization of neoadjuvant chemotherapy in muscle-invasive disease.

Conclusions: The management of MPBC is diverse among members of the SUO. Although most favors early cystectomy for cT1 MPBC, there is no consensus on the use of neoadjuvant chemotherapy for muscle-invasive MPBC. © 2014 Elsevier Inc. All rights reserved.

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1. Introduction

Micropapillary bladder cancer (MPBC) was first reported in 1994 [1] and is listed under the most recent World Health
Organization classification as a variant form of infiltrating urothelial carcinoma (UC). Micropapillary morphology exists in several other organ sites, namely lung, breast, and gastrointestinal tract, and seems to display aggressive behavior regardless of tissue of origin [2]. The biology of MPBC is poorly understood. Although it is most commonly detected in a background of conventional UC, it can also be associated with squamous cell carcinoma [3], adenocarcinoma [4], small cell carcinoma [5], and sarcomatoid carcinoma [6]. MPBC is also unique in the fact that clinical significance has been associated with even a small amount of micropapillary histology relative to conventional UC (> 10%) [7].

Early reports of MPBC demonstrated an association with locally advanced and metastatic disease [1,3–5,7]. In the largest retrospective report of MPBC to date by Kamat et al. [8,9] (n = 100 patients) from MD Anderson Cancer Center, the overall prognosis of patients with MPBC was poor despite the inclusion of a large proportion of patients with non–muscle-invasive (NMI) micropapillary disease. NMI-MPBC demonstrated a poor response to bacillus Calmette-Guérin (BCG), and the authors advocated for early cystectomy for organ-confined disease. Concern was also raised related to a potential poor response to neoadjuvant chemotherapy (NAC). Although several series have demonstrated similar findings [10,11], other smaller single-institution studies have suggested that outcomes may be comparable for MPBC and conventional UC after controlling for stage [12,13]. Others have also suggested that the use of NAC [10,14] and BCG may be appropriate in MPBC [15].

Given the limitations of the current literature for MPBC, physicians often base management on personal experience and expert opinion. To better understand MPBC, the Translational Science Working Group of the Bladder Cancer Advocacy Network (BCAN) Bladder Cancer Think Tank meeting [16] established a multi-institutional collaborative effort to study MPBC to provide improved insights into the biology and management of this disease. As an initial step, a survey was sent to the members of the Society of Urologic Oncology (SUO) to determine current opinions and practice patterns for MPBC. The results of the survey are presented herein in the context of a comprehensive review of existing literature.

2. Materials and methods

The MPBC survey was designed based on input and review from the Translational Science Working Group of the BCAN–sponsored Bladder Cancer Think Tank and distributed among registered members (n = 632) of the SUO using SurveyMonkey Inc (Palo Alto, CA, USA) [17]. SurveyMonkey was used to collect and analyze the results of the survey. A total of 130 responses were recorded, providing a response rate of 20%; of these, 91% (n = 118) completed the entire survey.

A review of the literature was performed for all original articles published before July 1, 2013, by incorporating the following terms in a Medline database search: micropapillary and bladder cancer. All articles were reviewed for relevance and sample size for inclusion in the review.

3. Results

Table 1 summarizes the composition of the 118 respondents who completed the survey. Among them, 94% were urologists, 5% were medical oncologists, and 1% were pathologists. A majority (80%) of the survey population considered bladder cancer their primary practice focus, with 49% reporting that bladder cancer occupies 25% to 50% of their practice. Moreover, 65% reported managing 1 to 5 cases of MPBC in the last year, whereas 16% did not treat MPBC in the last year.

Table 2 summarizes the respondents opinions related to MPBC. Although 78% of the survey population reported an affiliation with a dedicated genitourinary pathologist, only 49% responded that the diagnosis of MPBC uses strict, reproducible pathologic criteria; 51% reported that the diagnosis of MPBC is based on variable pathologic diagnostic criteria. Moreover, 95% reported that MPBC represents a subtype/variant of UC. In addition, 20% responded that micropapillary histology was clinically irrelevant if it is reported as “focal,” whereas the majority felt that the mere presence of micropapillary architecture is clinically relevant (75%). A few members of the survey (4%) further clarified that they considered MPBC as clinically irrelevant if it represented <5% to 25% of the specimen. Furthermore, 78% treat MPBC differently than conventional UC, whereas 13% reported that it depends on the percentage of MPBC in the transurethral resection (TUR) specimen; 9.5% reported that they treat MPBC the same as conventional UC.

Stage-specific practice patterns for MPBC are summarized in Table 3. For cT1 MPBC, 28% advocated early radical cystectomy, 36% advocated intravesical BCG, and 22% favored TUR alone followed by observation. On the contrary, 81% preferred upfront radical cystectomy for cT1 MPBC (8% would recommend NAC in addition to cystectomy); 11% report that they would treat cT1 MPBC with intravesical BCG.

For muscle-invasive (MI) MPBC, 50% would recommend neoadjuvant cisplatin-based chemotherapy for cT2 MPBC and 48% would recommend early radical cystectomy with adjuvant chemotherapy based on pathology. Additionally, 12% reserved NAC only for those with high-risk features such as lymphovascular invasion or hydronephrosis. For locally advanced MPBC (cT3-cT4a), the majority (63%) responded that they would treat with preoperative chemotherapy followed by consolidative surgery; 28% would still advocate early cystectomy followed by adjuvant chemotherapy based on pathology, whereas
only 5% would use primary chemotherapy. In patients with MPBC who have lymph node metastasis at radical cystectomy, 26% report that the micropapillary component represented the dominant histology of the metastatic tumor, whereas 10% report lymph nodes that are composed primarily of nonmicropapillary tumor; 64% reported that they did not know the makeup of lymph node metastasis in MPBC.

4. Discussion and review of literature

The results of this web-based survey reflect the current state of opinions and management of MPBC by practitioners focused on bladder cancer. In the discussion, we attempt to place these results in the context of existing data on this variant histology.

4.1. Diagnosis

Although there was consensus on the definition of MPBC as a subtype/variant of UC, there were different opinions on the pathologic diagnosis of MIBC, with approximately half of the respondents reporting that pathologists use strict, reproducible criteria and the other half reporting variability in diagnostic criteria, although this is largely based on the impression of the respondents on the criteria that pathologist employ for diagnosis. This highlights a potential problem in interpreting the existing literature on MPBC, which involves the reliability and accuracy of the pathologic diagnosis of MPBC variant histology. This difficulty in diagnosis may be partially because of sampling error and tumor heterogeneity as TUR specimens have been reported to detect only 39% of variant histology [18,19].

MPBC classically shows small, tight clusters of neoplastic cells generally devoid of fibrovascular cores and arranged in clear lacunar spaces. This key feature of prominent retraction artifact surrounding these epithelial nests can mimic angiolymphatic invasion by the tumor and can make interpretation difficult. The neoplastic cells often demonstrate eosinophilic cytoplasm and nuclear polarization to the external surface of the micropapillary clusters. Vesicular nuclei, marked atypia, prominent nucleoli, and
Typically found peripheral to the primary tumor mass [1]. Angiolymphatic invasion is identified, and variable mitotic activity may also be present [2]. True angiolymphatic invasion is identified in most cases and is typically found peripheral to the primary tumor mass [1].

An enlightening study by Sangoi et al. [20] further demonstrates why comparison between MPBC studies may be difficult. In this report, 14 genitourinary subspecialist pathologists reviewed representative hematoxylin and eosin images of 30 cases initially identified as invasive MPBC in an attempt to evaluate diagnostic variation among pathologists for MPBC. Although 93% agreement was obtained among 10 cases of “classic” MPBC, the overall interobserver agreement was only moderate for the remaining 20 cases whose morphologic features were not classic for MPBC because of inconsistent interpretations of extensive retraction and varying sized tumor nests (κ = 0.54) [20]. Furthermore, there may be a general lack of awareness of MPBC based on additional reports suggesting that variant histology may be missed or underreported in up to 44% of cases, particularly outside of academic institutions [21]. Unfortunately, further attempts to identify reliable immunohistochemical markers for MPBC to improve diagnosis have also proven unsuccessful because of low specificity and sensitivity [22,23].

A separate pathology-based question that has been raised in the management of MPBC involves the clinical significance of MPBC in mixed tumors. Based on the survey, approximately 75% of physicians reported that any amount of MPBC is clinically significant. On the contrary, 20% felt that focal MPBC was clinically irrelevant. Although limited by small sample sizes, a correlation between increasing proportion of MPBC and worse prognosis has been reported [7,24]. Alvarado-Cabrero reported that patients with >50% MPBC have a relative mortality risk of 2.4 compared with patients with conventional UC, whereas patients with <50% were at similar risk. In a separate study, a 10% cutoff was reported as a clinically significant effect on disease-specific survival (DSS) [7], which has led to the reporting of even focal amounts of MPBC. However, many conflicting reports exist ranging from those stating that the mere presence of MPBC is clinically relevant [11] to others stating that focal MPBC portends better outcomes than extensive disease [15,24]. A large scale, detailed analysis of the effect of extent of micropapillary histology and clinical outcomes is lacking. Determining the clinical significance of the extent of MPBC may be an important guide to direct clinical management of MPBC and represents an important future area of collaboration between clinicians and pathologist.

### 4.2. Treatment

Most experts (77%) agree that MPBC should be treated differently than conventional UC. However, there is significant variability about how the disease should be treated within each pathologic stage.

### 4.3. Non–muscle-invasive micropapillary bladder cancer

The greatest consistency appears to be in the management of cT1 tumors as most respondents recommend early radical cystectomy. This approach to the management of NMI-MPBC was first suggested by MD Anderson in 2006 based on one of the largest cohorts of MPBC reported to date [8]. In that analysis, the NMI-MPBC cohort included 44 patients (11% Ta, 9% carcinoma in situ, and 80% CT1, n = 44) treated with intravesical BCG or upfront radical cystectomy. Among patients treated initially with BCG...
therapy, 67% progressed (defined as ≥ cT2), including 22% in whom metastases developed. Only 19% of the primary BCG cohort remained disease free with an intact bladder after a median follow-up of 30 months. Among patients who underwent cystectomy after progression, median cancer-specific survival (CSS) was 61.7 months, with no patients surviving at 10 years. On the contrary, those patients receiving upfront cystectomy had a 10-year CSS rate of 72%, and median survival was not reached. These poor response rates to BCG led to the author's recommendation for early cystectomy. This study also reported a 42% rate of pathologic upstaging in the upfront cystectomy patients (n = 12), including a 25% rate of occult nodal disease, which raises concern for clinical understaging for NMI-MPBC.

Other smaller retrospective series that contain patients with NMI-MPBC have been reported. Ghoneim et al. [10] reported 10 patients diagnosed with cTis-cT1 disease, of whom 7 received intravesical BCG and 3 underwent upfront radical cystectomy. All 7 patients treated with BCG recurred (4 progressed) and underwent delayed radical cystectomy with resultant pT3 disease. Furthermore, positive lymph nodes were detected in 6 patients. Comparat et al. [11] reported on a 72-patient cohort of MPBC including 12 cTa MPBC cases, of which 8 were treated with radical cystectomy. All 8 were found to have invasive carcinoma at the time of surgery including 5 (63%) with pT2-pT4 disease. A recent 120-patient Surveillance, Epidemiology and End Results (SEER) 17–based study also showed that NMI-MPBC was associated with worse overall and DSS outcomes when compared with conventional UC [25]. These studies all suggest that NMI-MPBC is associated with more aggressive disease and worse survival than would be expected for conventional NMIBC and may warrant more aggressive intervention.

Another study argues that NMI-MBPC may have a different histologic presentation than MI-MPBC as the authors suggest that true NMI-MPBC is more “urothelial” in appearance than the often “glandular” MI-MPBC [26]. Of the 18 patients in this report, treatment data were available on 13 patients—7 (54%) underwent primary intravesical therapy, 5 (38%) underwent initial surveillance only, and 1 (8%) underwent primary surgery. Among them, 3 patients progressed to muscle invasion (pT2, pT3, and pT3N2). One patient died of bladder cancer and 1 died of other causes; 64% are alive with an intact bladder after a median follow-up of 14 months. In a report by Gaya et al. [15] on 8 patients with NMI-MPBC, 6 (75%) patients (small proportion of MPBC relative to conventional UC) were reported to be disease free after BCG therapy with a 5-year DSS of 87.5%. Despite the limited sample size, this report has been cited to suggest that BCG may be appropriate for NMI-MPBC.

Overall, the data suggest that the biology of NMI-MPBC is different than conventional UC and is associated with an aggressive phenotype with high failure rates of intravesical therapy. This viewpoint is consistent with the opinion of the respondents to this survey, with 80.5% advocating for early cystectomy (7.6% with NAC) for cT1 MPBC, representing one of the few therapeutic approaches with relative consensus. Further validation would still be beneficial to establish the proper management approach for NMI-MPBC.

4.4. Muscle-invasive micropapillary bladder cancer

In contrast to some areas of agreement on the treatment of NMI-MPBC, the survey response reflects differences of opinion related to management of MI-MPBC. The differences relate predominantly to the sensitivity of MPBC to chemotherapy and whether it should be incorporated in the neoadjuvant setting. Thus, for cT2 MPBC, no consensus on the use of perioperative chemotherapy was seen, with 47.5% of the respondents recommending early radical cystectomy with adjuvant chemotherapy and 50% recommending NAC followed by radical cystectomy. Interestingly, a slightly higher proportion (63%) recommended NAC followed by consolidative surgery for cT3-a N0 disease. A review of the MPBC literature for MI disease demonstrates a relatively consistent conclusion that MI-MPBC is associated with high rates of locally advanced and distant disease and is associated with poor survival [4,5,7,10,25]. In one of the largest series of MPBC (n = 100), patients were reported to have poor 5- and 10-year survival rates of 54% and 27%, respectively, despite a high proportion of NMI-MPBC disease at presentation [9]. In this cohort, high rates of upstaging (52.7%) and occult lymph node metastases (27.3%) were also reported after cystectomy (n = 65 with curative intent). This is similar to the French series, which reported a 79% rate of upstaging at cystectomy (n = 57) with metastasis present in 35% [11]. Wang et al. reported (n = 73) that 66% were found to have pT3/4 disease and 50% had pN+ disease (10-y CSS of 31%). However, when stage matched with patients with pure UC, micropapillary tumors had similar rates of local/distant recurrence and CSS [12]. Similarly, Fairey et al. compared a cohort of MPBC (n = 33, 82% diagnosed incidentally at cystectomy) with conventional UC and also reported similar survival outcomes after controlling for clinical and pathologic factors. Vourganti et al. [25] compared MPBC with conventional UC in a Surveillance, Epidemiology and End Results–based outcome study and found that stage for stage, MPBC had a similar survival profile to conventional UC except for in NMI disease where NMI-MPBC was associated with worse survival. This provides further support for upfront aggressive management of NMI-MPBC and the fact that accurate staging may be the major prognostic factor for both micropapillary and conventional MI-MPBC.

An understanding of the role for chemotherapy is particularly important in MPBC owing to its association with locally advanced and distant disease. In the survey, 50% believed MPBC responded to cisplatin-based chemotherapy regimens, whereas 50% did not. The variability in
the recommendation for perioperative chemotherapy (i.e., neoadjuvant vs. adjuvant) was also an underlying theme for MI-MPBC disease. Kamat et al. [9] raised a concern that existing conventional UC chemotherapy regimens might not provide a survival advantage to patients with MPBC. Despite a downstaging rate of 61% with NAC and a 38% incidence of node-positive disease with upfront cystectomy (vs. 13% with NAC, \( P = 0.065 \)), patients receiving NAC plus radical cystectomy \(( n = 23 )\) had a 5-year overall survival (OS) of 63% and 10-year OS of 32% compared with 5-year OS of 71% and 10-year OS of 52% with upfront radical cystectomy \(( n = 32 )\). Although the NAC and upfront cystectomy groups were similar in terms of clinical staging, they differed in terms of lymphovascular invasion (LVI) at TUR (47.8% vs. 12.5%, respectively; \( P = 0.004 \)) and use of adjuvant chemotherapy (8.7% vs. 53.1%, respectively; \( P = 0.002 \)).

Others have argued that based on the high rates of upstaging and lymph node involvement at radical cystectomy, chemotherapy should be incorporated in the neoadjuvant setting. Ghoneim et al. [10] made this recommendation based on the poor DSS associated with 15 patients who received adjuvant chemotherapy in their series. In a recent retrospective report from Memorial Sloan-Kettering Cancer Center, Meeks et al. [14] focused on the use of NAC in MI-MPBC. The NAC arm contained 29 patients, most whom received neoadjuvant gemcitabine-cisplatin before surgery, and this was compared with a cohort of 19 patients who underwent upfront radical cystectomy. They reported a pT0 rate of 45% (defined as pT0 + carcinoma in situ) in the NAC group compared with 13% in the radical cystectomy alone group \( ( P = 0.049 ) \), which is similar (38% and 15%, respectively) to the pT0 rate seen in the neoadjuvant SWOG trial 8710 [27]. The Memorial Sloan-Kettering Cancer Center report showed a significant survival benefit favoring patients who were downstaged vs. those with residual tumor (2-y CSS of 78% and 25%, respectively; \( P = 0.05 \)), though the follow-up was relatively short. To date, all series on NAC are retrospective and inadequately powered. Furthermore, no clinical studies to date have been performed with centralized pathologic review that incorporates validation of MPBC by independent pathologist. As previously discussed, the interobserver variability among even the most experienced pathologists is relatively great and potentially confounds all current studies and limits the ability to interpret and compare current series. As early pathologic recognition of MPBC is likely to increase, there are potential opportunities in the future to improve the study of this disease. Future areas of research should center on the development of reproducible diagnostic pathologic criteria as well as the creation of appropriately controlled studies to allow more definitive guideline creation for MPBC. This will likely require collaborative and multi-institutional studies to increase sample size. The Translational Science Working Group of the BCAN-sponsored Bladder Cancer Think Tank is currently focusing their efforts on these and other questions in MPBC using a collaborative model for the study of uncommon bladder cancer variants through the creation of a centralized site for pathologic review, data collection, and molecular and gene expression profiling with collaborative data analysis.
5. Conclusion

The management of MPBC is diverse among members of the SUO. Although most favor early cystectomy for cT1 MPBC, there is no consensus on the incorporation of NAC with radical cystectomy for MI-MPBC. The Translational Science Working Group of the BCAN-sponsored Bladder Cancer Think Tank is currently focusing their efforts on developing a better understanding of MPBC by pooling resources across institutions with the goal to enhance our understanding of this disease and to develop evidence-based treatment guidelines.

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References