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Micropapillary Bladder Cancer: Current Treatment Patterns and Review of the Literature

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Abstract

Objectives—No guidelines exist for management of micropapillary bladder cancer (MPBC) and the majority of reports of this variant of urothelial carcinoma (UC) are case series comprised of 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—The majority of 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. 78% treat MPBC differently than conventional UC with 81% reporting that they would treat cT1 MPBC with upfront radical cystectomy. However, the respondents were split 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. While the majority favors early cystectomy for cT1 MPBC, there is no consensus on the use of neoadjuvant chemotherapy for muscle-invasive MPBC.

Keywords

micropapillary; bladder cancer; review; survey

Introduction

Micropapillary bladder cancer (MPBC) was first reported in 1994 [1] and is listed under the most recent WHO 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. While 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 that clinical significance has been associated with even a small amount of micropapillary histology relative to conventional UC (>10%) [7].

Early reports of micropapillary bladder cancer 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 (n=100) 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 BCG and the authors advocated for early cystectomy for organ confined disease [8,9]. Concern was also raised related to a potential poor response to neoadjuvant chemotherapy (NAC). While 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 neoadjuvant chemotherapy [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 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.

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 Society of Urologic Oncology (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.

Results

Table 1 summarizes the composition of the 118 responders who completed the survey. 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 25-50% of their practice. 65% reported managing 1-5 cases of MPBC in the last year, while 16% did not treat MPBC in the last year.

Table 2 summarizes the respondents opinions related to MPBC. While 78% of the survey population reported an affiliation with a dedicated genitourinary pathologist, only 49% responded that the diagnosis of MPBC utilizes strict, reproducible pathologic criteria. 51%

reported that the diagnosis of MPBC is based on variable pathologic diagnostic criteria. 95% reported that MPBC represents a subtype/variant of urothelial carcinoma. 20% responded that micropapillary histology was clinically irrelevant if it is reported as “focal,” while 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 <5-25% of the specimen. 78% treat MPBC differently than conventional UC, while 13% reported that it depends on the percentage of MPBC in the 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 cTa MPBC, 28% advocated early radical cystectomy, 36% advocated intravesical BCG, while 22% favored TUR alone followed by observation. In contrast, 81% preferred upfront radical cystectomy for cT1 MPBC; (8% would recommend neoadjuvant chemotherapy in addition to cystectomy). 11% report that they would treat cT1 MPBC with intravesical BCG.

For muscle-invasive MPBC, 50% would recommend neoadjuvant cisplatin-based chemotherapy for cT2 MPBC. 48% would recommend early radical cystectomy with adjuvant chemotherapy based on pathology. Additionally, 12% reserved neoadjuvant chemotherapy only for those with high risk features such as lymphovascular invasion or hydronephrosis. For locally advanced MPBC (cT3-cT4a), the majority responded that they would treat with preoperative chemotherapy followed by consolidative surgery (63%). 28% would still advocate early cystectomy followed by adjuvant chemotherapy based on pathology while 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, while 10% report lymph nodes that are composed primarily of non-micropapillary tumor. 64% reported that they did not know the makeup of lymph node metastasis in MPBC.

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.

Diagnosis

While 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 respondents reporting that pathologists use strict, reproducible criteria with the other half reporting variability in diagnostic criteria; although this is largely based on the impression of respondents on the criteria that pathologist employ for diagnosis. This highlights one 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 the result 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 variable mitotic activity may also be present [2]. True angiolymphatic invasion is identified in the majority of cases and is typically found peripheral to the primary tumor mass [1].

An enlightening study by Sangoi and colleagues in 2010 further demonstrates why comparison between MPBC studies may be difficult. In this report, 14 genitourinary subspecialist pathologists reviewed representative H&E images of 30 cases initially identified as invasive micropapillary bladder cancer in an attempt to evaluate diagnostic variation among pathologists for MPBC. While 93% agreement was obtained among 10 cases of “classic” MPBC, the overall inter-observer agreement was only moderate for the remaining 20 cases whose morphologic features were not classic for MPBC as a result of inconsistent interpretations of extensive retraction and varying sized tumor nests (kappa of 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 under-reported 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. In contrast, 20% felt that focal MPBC was clinically irrelevant. While 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 conventional UC patients while 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 [7] that 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.

Treatment

The vast majority of 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 pathological stage.

Non-muscle invasive MPBC

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 non-muscle invasive MPBC (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% CIS, 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. In contrast, 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 reported 10 patients diagnosed with cTis-cT1 disease, of whom 7 received intravesical BCG and 3 underwent upfront radical cystectomy [10]. 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. Comperat et al reported on a 72 patient cohort of MPBC including 12 cTa MPBC cases, of which 8 were treated with radical cystectomy [11]. All 8 were found to have invasive carcinoma at the time of surgery including 5 (63%) with pT2-pT4 disease. A recent 120 patient SEER 17-based study also showed that NMI-MPBC was associated with worse overall and disease specific survival outcomes in a population based study when compared to 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 muscle-invasive MPBC (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 was available on 13: 7 (54%) underwent primary intravesical therapy, 5 (38%) underwent initial surveillance only, and 1 (8%) underwent primary surgery. Three patients progressed to muscle invasion (pT2, pT3, pT3N2). One patient died of bladder cancer, one died of other causes, and 64% are alive with an intact bladder after a median follow up of 14 months. In a report by Gaya et al 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% [15]. 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 neoadjuvant chemotherapy) 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.

Muscle invasive MPBC

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 respondents recommending early radical cystectomy with adjuvant chemotherapy and 50% recommending neoadjuvant chemotherapy followed by radical cystectomy. Interestingly, a slightly higher proportion (63%) recommended neoadjuvant chemotherapy followed by consolidative surgery for cT3-4a N0 disease. A review of the MPBC literature for muscle invasive 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-year CSS of 31%). However, when stage matched with patients with pure UC, micropapillary tumors had similar rates of local/distant recurrence and cancer specific survival [12]. Similarly, Fairey et al compared a cohort of MPBC (n=33, 82% diagnosed incidentally at cystectomy) to conventional UC and also reported similar survival outcomes after controlling for clinical and pathological factors. Vourganti et al compared MPBC to conventional UC in a SEER based outcome study and found that stage for stage, MPBC had a similar survival profile to conventional UC except for in non-muscle invasive disease where NMI-MPBC was associated with worse survival [25]. 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 due to its association with locally advanced and distant disease. In the survey, 50% believed MPBC responded to cisplatin-based chemotherapy regimens while 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 raised a concern that existing conventional UC chemotherapy regimens might not provide a survival advantage to patients with MPBC [9]. 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-yr OS of 63% and 10-yr OS 32% compared to 5-yr OS 71% and 10-yr OS 52% with upfront radical cystectomy (n=32). While the

neoadjuvant chemotherapy and upfront cystectomy groups were similar in terms of clinical staging, they differed in terms of LVI at TUR (47.8% vs. 12.5%, p=0.004 respectively) and use of adjuvant chemotherapy (8.7% vs. 53.1%, p=0.002 respectively).

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 made this recommendation based on the poor disease specific survival associated with 15 patients who received adjuvant chemotherapy in their series [10]. In a recent retrospective report from Memorial Sloan-Kettering Cancer Center (MSKCC), Meeks et al focused on the use of neoadjuvant chemotherapy in MI-MPBC [14]. The NAC arm contained 29 patients, the majority of whom received neoadjuvant gemcitabine-cisplatin prior to surgery and this was compared to a cohort of 19 patients who underwent upfront radical cystectomy. They reported a pT0 rate of 45% (defined as pT0+CIS) in the NAC group compared to 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 MSKCC report showed a significant survival benefit favoring patients who were downstaged versus those with residual tumor (2-yr CSS of 78% and 25% respectively, p=0.05), though the follow-up was relatively short. To date, all series on neoadjuvant chemotherapy are limited by small sample sizes, retrospective studies, selection bias, failure to quantify the extent of MPPBC, and poor understanding into the optimal chemotherapy strategy for MPBC. However, an encouraging pathologic response has been noted with pre-operative chemotherapy, but there remains concern regarding OS, particularly in the MD Anderson cohort. While the report from Ghoneim et al reports that most patients received gemcitabine-cisplatin chemotherapy, the vast majority from the larger MD Anderson cohort received Methotrexate-Vinblastine-Adriamycin-Cisplatin (MVAC) chemotherapy; it is possible that differences in the chemotherapy regimens may contribute to differences in outcome.

In summary, a review of the literature supports the results of our survey, with the conclusion that the management of MPBC remains controversial and clearly merits further research. One limitation of our report is the specialized subset of physicians made up of predominantly academic, urologic oncologists with access to a specialized urologic pathologist. A greater sampling of medical oncologists, radiation oncologists, and community practitioners may have yielded different results. However, variations in management strategies were noted even among this specialized group representing those who might have the greatest insight into MPBC. A second limitation of this report is the relatively low, 20% survey response rate obtained from the SUO membership. While this response rate is not ideal, 20% is an acceptable response rate based on a search of the literature which demonstrates similar rates of response from other survey-based studies with rates ranging from 6.5-32% among health care providers including nurses, physicians, residents, and medical students [28-32]. The present survey may represent a self-selection bias as most respondents claimed to have a special interest in bladder cancer and thus reflects the proportion of SUO members with expertise in the field. The response rate of 20% is likely reflective of a core group of bladder cancer experts who have some view on the management of micropapillary bladder cancer, which is an uncommon variant and hence we would caution the reader that this reflects a selected group of SUO members.

The most fundamental question pertaining to MPBC is whether this histologic variant should be treated differently than conventional UC, and if so, how should the treatment algorithm differ? One could argue based on experience with conventional UC that high risk features warrant early cystectomy for NMIBC and a multi-modality treatment approach for MIBC. However, sensitivity to modalities such as chemotherapy, radiation therapy, and intravesical therapy must be adequately established as delaying surgery for ineffective therapy may result in worse outcomes for MPBC.

Unfortunately, all available studies on MPBC at this time 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 inter-observer 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.

Conclusion

The management of MPBC is diverse among members of the Society of Urologic Oncology. While most favor early cystectomy for cT1 MPBC, there is no consensus on the incorporation of neoadjuvant chemotherapy 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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Table 1

Characteristics of SUO survey respondents

Question	Response Percent
Specialty	
Urologist	94.7%
Medical oncologist	4.5%
Pathologist	0.8%
Radiation Oncologist	0%
Practice Experience	
In training	2.5%
0-5 years in practice	37.3%
5-20 years in practice	35.6%
>20 years in practice	24.6%
Retired	0%
Practice Affiliation	
Academic institution WITH a comprehensive, NCI designated cancer center	61.9%
Academic institution WITHOUT a comprehensive, NCI designated cancer center	27.1%
Large group private practice	5.1%
Small group private practice	5.9%
Percent of clinical practice focusing on bladder cancer	
>75%	7.6%
50-75%	22.9%
25-49%	49.2%
<25%	20.3%
The number of cases of MPBC seen in the last year	
0	15.3%
1-5	65.3%
6-10	16.1%
11-20	0.8%
>20	2.5%
Proportion reporting a dedicated GU pathologist	
Yes	78%
No	22%

Table 2

Survey results regarding opinions toward MPBC

Question	Response Percent
Reported opinions on the definition of MPBC	
Subtype/variant of urothelial carcinoma	94.9%
Form of bladder cancer that is unrelated to urothelial cancer	3.4%
Systemic entity that can also involve the bladder	0%
Descriptive term used by pathologists for an entity that does not have clinical relevance	1.7%
Reported opinions on the pathologic diagnosis of MPBC	
Utilizes strict criteria that are reproducible in most cases	49.2%
Depends on the pathologist as there is a lot of variability in the diagnostic criteria	50.8%
Is based on the clinical behavior of the lesion as no true pathologic criteria exists	0%
The proportion of MPBC felt to be clinically IRRELEVANT	
It is reported as only focal vs. extensive	20.3%
I do not think it matters as any quantity of micropapillary histology is clinically relevant	75.4%
It is reported as less than x%: (5%-25% reported)	4.2%
Proportion treating MPBC the same as conventional UC	
Yes	10.2%
No	77.1%
Depends on the percentage of MPBC in the TUR specimen	12.7%
Proportion considering MPBC to respond to BCG	
Yes	5.9%
No	73.7%
Not applicable to my practice	20.3%
Proportion considering MPBC to respond to cisplatin-based chemotherapy regimens	
Yes	50.0%
No	50.0%

Table 3

Survey results for stage specific management of MPBC

Question	Response Percent
Treatment recommendation for cTa stage MPBC	
TUR alone followed by observation	22.0%
Intravesical BCG	37.3%
Early radical cystectomy	28.0%
Neoadjuvant chemotherapy followed by radical cystectomy	0%
Not applicable to my practice	12.7%
Treatment recommendation for cT1 stage MPBC	
TUR alone followed by observation	1.7%
Intravesical BCG	11.9%
Early radical cystectomy	72.9%
Neoadjuvant chemotherapy followed by radical cystectomy	7.6%
Radiation therapy (+/− chemotherapy)	0%
Not applicable to my practice	5.9%
Proportion recommending neoadjuvant chemotherapy for cT2 stage (cN0) MPBC	
Yes	50.0%
No	34.7%
Only for high risk feature such as lymphovascular invasion or hydronephrosis	11.9%
Not applicable to my practice	3.4%
Treatment recommendation for cT2 (cN0) MPBC	
Early radical cystectomy with adjuvant chemotherapy based on pathology report	47.5%
Neoadjuvant chemotherapy followed by radical cystectomy	50.0%
TUR alone	0%
Radiation therapy (+/− chemotherapy)	0%
Not applicable to my practice	2.5%
Treatment recommendation for cT3-4a stage (cN0) MPBC	
Chemotherapy	5.1%
Neoadjuvant chemotherapy followed by consolidative surgery	62.7%
Early radical cystectomy with adjuvant chemotherapy based on pathology report	28.0%
Palliative care	0%
Radiation therapy (+/− chemotherapy)	0%
Not applicable to my practice	4.2%
Reported opinion on makeup of lymph node metastasis in MPBC	
Mainly the micropapillary component	26.3%
Mainly the non-micropapillary component	10.2%
Do not know	63.6%