

Prognostic and therapeutic role of HER2 expression in micropapillary carcinoma of the bladder (Review)

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Abstract. Micropapillary carcinoma of the bladder (MPBC) is a variant type of infiltrating urothelial carcinoma, which portends a poor biological behavior in terms of disease stage at first diagnosis and clinical outcome; its peculiar morphology raises issues concerning the ability of tumor detection by imaging techniques and proper biopsy procedure, and the appropriate treatment for non-muscle infiltrating and muscle-infiltrating MPBC remains a matter of debate. On the basis of its established prognostic and therapeutic role in breast and gastro-esophageal cancer in the first instance, the human epidermal growth factor receptor-2 (HER2) has been investigated in selected case series of MPBC over the last 10 years. The aim of the present review was to summarize the existing evidence on HER2 status in MPBC, and to discuss its present and future utility in risk assessment and treatment choice of this uncommon, yet aggressive, disease.

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1. Introduction

The micropapillary variant of carcinoma (MPC) has been reported in several organs, including bladder, lung, breast, salivary gland, gastrointestinal tract and ovary (1-6). This variant exhibits a peculiar morphology; depending on whether tumor cells are superficial or invasive, they may aggregate

as slender delicate papillary projections or small compact infiltrating nests of four or five cells lacking central vascular cores, floating within clear spaces similar to lymphatic channels due to the production of peritumoral stromal retraction artifacts (7-11). Tumor cells usually feature peripherally located high-grade nuclei and cytoplasmic vacuoles (12,13), as well as an inverted cellular polarity to the external surface of neoplastic clusters which, according to certain studies, may result in the basal surface acquiring apical secretory properties that promote tumor invasion, and a highly aggressive clinical outcome [(3), reviewed in (14)]. In fact, MPC typically leads to a poor prognosis with a greater risk of nodal metastases in comparison with corresponding conventional carcinoma (1-5,8,15,16). It has been postulated that, on the basis of its molecular profile, MPC represents a distinct entity (17,18).

The morphological similarities between MPC from different organs as well as the high frequency of metastases accounts for the requirement to differentiate between primary and secondary MPC of the bladder; therefore, a proper immunohistochemical panel as well as disclosing a simultaneous component of conventional urothelial carcinoma may support a correct diagnosis (19).

The aim of the present review was to summarize current knowledge on human epidermal growth factor receptor-2 (HER2) expression in micropapillary bladder carcinoma (MPBC) because this marker is considered to be a potential prognostic and therapeutic marker in this tumor.

2. MPBC

Epidemiology. MPBC was first described in 1994 as a rare variant of urothelial bladder cancer (UBC) resembling papillary serous carcinoma of the ovary (1); its incidence has been reported as 0.6-8.2% of all bladder tumors [(1), reviewed in (10); (11,15), reviewed in (20-22)], with the majority of recent studies reporting the highest values, possibly due to more accurate diagnosis, notwithstanding a suboptimal inter-observer reproducibility (9).

This tumor predominantly affects men, with a male-to-female ratio of 5-10:1, which is higher than conventional UBC [(1,9,22,12), reviewed in (10)]. The age range at presentation is wide (between 22 and 81 years; mean, 67.6 years), and the most common reported symptoms are

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hematuria, dysuria, urgency, frequency, urinary obstruction, urinary tract infection, weight loss and, as for upper tract tumors, flank pain [(1,21-26), reviewed in (10)].

Cytology. Urine cytological smears feature papillary/spheroid aggregates of tumor cells with high nuclear grade together with rare single cells in a clear background, due to the endophytic rather than exophytic nature of the tumor (27).

Macroscopy. Gross appearance of MPBC is varied, since it can range from papillary and polypoid to ulcerative and infiltrating, and can differ in size from microscopic to a huge mass (22).

Microscopy. MPBC is associated with conventional UBC and carcinoma *in situ* (CIS) in 85 and 65% of patients, respectively (15,28), and coexistence has been reported with other variants of UBC as well as other histotypes (15,24,26); sometimes it has been described as infiltrating the lamina propria under areas of normal overlying mucosa (28). Although a correct diagnosis of MPBC is of pivotal importance, it may be difficult to distinguish such a variant from typical invasive UBC with noticeable retraction artifacts, as identified by Sangoi *et al* (9) in an assessment of the inter-observer agreement among uropathologists for the diagnosis of MPBC (Fig. 1). Their observations suggest that the size and pattern of tumor cell aggregates (i.e., small multiple nests within the same lacunar space compared with large branching) may support the diagnosis of MPBC and conventional UBC, respectively.

Further categorization is required between invasive and non-invasive MPBC, since the latter may not portend a poor prognosis (29). In fact, it is now recognized that a micropapillary (MP)-like architecture may be seen in non-muscle-invasive bladder cancer (NMIBC) and CIS; therefore, if the MP component is limited to the non-invasive component, the tumor should not be defined as MPBC (9,29-36). On the other hand, mixed neoplasms (conventional BC combined with MPBC) often exhibit a poorer biological behavior as well as metastases with MP morphology only, supporting the aggressive nature of this variant (1,12,31,37). Evidence exists that the higher the proportion of MPBC present, the poorer the biological behavior in terms of stage of disease and clinical outcome; a relative mortality risk of 2.4 exists when the component of MPBC is >50% compared with those with pure conventional UBC or <50% MPC (24). Furthermore, cases with <10% and/or superficial MP component may be more frequently detected at an early stage (31). Therefore, despite the absence of accepted criteria for the cut-off proportion of MP component to qualify a UBC as MPBC alone, it is recommended to report the presence and the proportion of MP component in the pathology report (37,38), possibly quantifying it in percentage terms.

Immunohistochemistry and molecular biology. MPBC features an immunohistochemical profile similar as the one described in conventional UBC, exhibiting cytokeratin (CK)7 expression in all cases, as well as reactivity for uroplakin III, CK34 β E12, CK20, p63, thrombomodulin and high-molecular-weight CK, with decreasing frequency (19,31). Furthermore, MPBC is negative for estrogen receptor, mammaglobin, paired box

gene 8, thyroid transcription factor 1 and Wilms' tumor protein 1, which allows the differentiation of a primary bladder cancer from lung, breast and ovary cancer, but not from pancreatic and salivary gland cancer (1,19). Eventually, a correct diagnosis of secondary MPC requires proper clinical and radiological correlation.

With the aim of discriminating between MPBC and conventional UBC, molecules such as mucin 1, cancer antigen 125, HER2/neu and Krebs von den Lungen-6 have been studied as putative diagnostic markers for MPBC, yielding conflicting results (7,9,15,28,29,31-35,39-45).

In a recent gene expression profile study, downregulation of microRNA-296 and activation of chromatin-remodeling complex RuvB-like 1 that may be associated with epidermal growth factor receptor (EGFR) have been reported as prominent features of MPBC (46). Furthermore, according to recent molecular data, most MPBC, even as part of conventional UBC, refers to the luminal molecular subtype (26,46), consistent with the MP variant of breast cancer (17).

Diagnostic methods. Since MPBC may not form discrete lesions unlike most conventional UBC, computed tomography or other imaging studies may fail to detect such diffuse neoplasms (28,47).

When MPBC grows under normal mucosa, routine follow-up cystoscopy and urine cytology are unable to detect neoplastic cells (28), and cold cup biopsy may miss an MPBC invading the muscle layer under the benign surface epithelium; thus, deep biopsies are recommended (1,47,48).

Clinical outcome and treatment. In the bladder as well, MPC is considered to portend an aggressive clinical course, with most patients presenting at an advanced stage with muscle-invasive or metastatic disease (1,15).

Putative mechanisms accounting for the dismal prognosis of such disease are: i) A high level of inherent chromosomal or genomic instability, with excess DNA contents [DNA index (the ratio between the DNA content of a tumor cell and that of a normal diploid cell), 1.75] compared with conventional UBC, which is further increased in metastatic MPBC (1,37); and ii) an increased expression of the markers of poor prognosis p53, Mindbomb E3 ubiquitin protein ligase 1, Aurora-A and survivin (49-52). In a large case series of MPBC, >50% were at least clinical tumor stage 2 at first diagnosis [reviewed in (10)], and subsequent pathological upstaging may occur in <75% of patients with NMIBC. Other studies identified a lower proportion of patients at advanced stage at cystectomy (53), and even no differences in outcome following radical cystectomy between MPBC and conventional UBC when matched for stage and other clinicopathological variables (29).

Lymphovascular invasion, which is a strong marker of adverse prognosis, is present in <75% cases at diagnosis, and occult nodal disease may be present in <38% patients [reviewed in (10)]. In case series of MPBC, 5- and 10-year survival rates of 25-74 and 24-54% have been reported, due either to its high growth rate or to its inherent biologically aggressive behavior [(47,54), reviewed in (10)]. As a consequence: i) Even in the absence of evidence of muscularis propria invasion in a biopsy, muscle invasion is often assumed (55) and/or additional tissue sampling and restaging should be considered; and

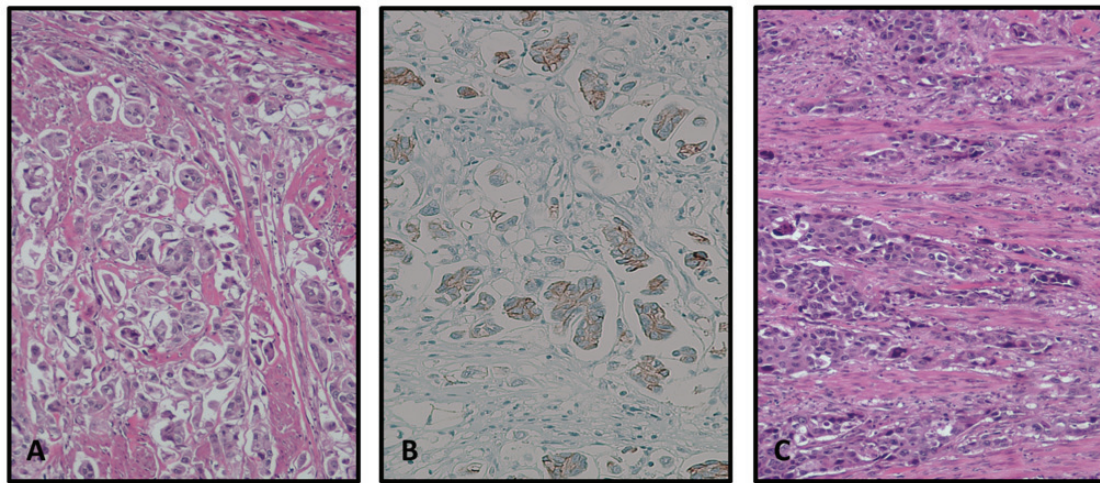


Figure 1. (A) Hematoxylin and eosin staining of MPBC revealing small multiple nests within the same lacunar space. (B) Conventional urothelial bladder cancer featuring wide anastomosing cords of pleomorphic cells. (C) Membrane staining of MPBC tumor cells for HER2. MPBC, micropapillary carcinoma; HER2, human epidermal growth factor receptor-2.

ii) radical cystectomy has been suggested as a first-line therapy in place of neoadjuvant chemotherapy in muscle-invasive disease and conservative therapy with intravesical Bacillus Calmette-Guérin in NMIBC [(28,54,55), reviewed in (10)]; the latter has been identified to be critically ineffective in patients with MPBC [(15,54,56), reviewed in (10)]. For patients submitted to early cystectomy for NMIBC, 10-year survival rates of 72% have been reported, compared with 0% following conventional therapies [reviewed in (10)], although subsequent studies yielded conflicting results. Meeks *et al* (53) identified no residual disease at cystectomy in 45% of the patients who received neoadjuvant chemotherapy (four cycles of gemcitabine and cisplatin in the majority of cases), in keeping with a Phase III trial which documented an improved response to neoadjuvant chemotherapy in tumors with mixed histology compared with in pure UBC (57). Other studies failed to demonstrate any significant difference in outcomes with the addition of neoadjuvant chemotherapy in patients with muscle-invasive MPBC undergoing radical cystectomy (32,58).

Recently, Fernández *et al* (59) reported that neoadjuvant chemotherapy appears to confer benefit to patients with MPBC without tumor-associated hydronephrosis, whereas patients with clinical tumor stage 1 disease may undergo standard surgical treatment.

3. HER2

Background. HER2 (ERBB2; HER2/neu) is a type I transmembrane 185 kDa tyrosine kinase receptor whose encoding gene is on chromosome 17q21 (60,61). HER2 is usually present as an inactive monomer on the cell membrane of various cell types undergoing homo- or heterodimerization with other EGFR family members (62) via activation by corresponding ligands in response to extracellular signals. HER2 is normally responsible for regulating cell proliferation and survival, inhibiting apoptosis, increasing angiogenesis and decreasing cell-cell adhesion by the activation of various cell signaling pathways (63-65), which are important factors in oncogenesis and tumor progression (65-67). Thus, HER2

overexpression has been identified in several tumor types, including bladder, breast, ovarian, salivary gland, endometrial, pancreatic and non-small cell lung cancer (65,66,68). HER2 protein overexpression was initially and has been most extensively researched in breast cancer, in which it occurs in almost 20% of primary invasive carcinomas (69), and is associated with poor prognosis with decreased disease-free and overall survival (65,69); similar evidence has been reported for bladder cancer (70).

Therapeutic target. At present, HER2-targeted therapies are established clinical routines for HER2-overexpressing/amplified carcinomas of the breast (71,72) and stomach (73) via the application of the anti-HER2 humanized monoclonal antibody trastuzumab (72). HER2-targeted therapy in combination with standard chemotherapy has resulted in a significantly increased survival rate in patients with HER2 amplification in breast and gastro-esophageal cancer (73,74).

HER2 in bladder cancer. There are conflicting data in the literature regarding HER2 status in BC samples. Previous investigation has identified a highly variable frequency of gene amplification ranging between 0 and 59% of cases (66,75-80), with HER2 protein expression reported in between 31 and 65.5% of samples (75,81,82). Nevertheless, according to the majority of studies, HER2 protein expression seems to be correlated with tumor stage, tumor grade and outcome (82-89); in fact, the reason for this variability of results has been attributed to high heterogeneity of case series, which include different grades and histological variants of BC (34,35,90-94). A previous study identified that the 5-year disease-free survival rate decreased from 48.5% in HER2-negative patients to 9.7% in those who were HER2-positive (86). Skagias *et al* (85), also identified that HER2 expression was correlated with decreased disease-specific survival ($P=0.002$) and overall survival rates ($P=0.025$).

Previous studies have highlighted the apparent lack of a marked association between HER2 protein expression and gene amplification in BC (81), with the latter being characterized by extreme heterogeneity within the same tumor (95). In addition,

Table I. HER2 expression in MPBC determined from previous studies.

Author, year	Patients (n)	Method	IHC positivity, % of stained cells	ISH positivity (HER2/chr17 ratio)	IHC-ISH concordance	Percentage of positive cases	Limitations	Significant association	Independent predictor	Ref.
Sangoi <i>et al</i> , 2009	24	IHC	>30 ^a	NA	NA	25%	NA	NA	NA	(45)
Ching <i>et al</i> , 2011	19	IHC+dual-color ISH	>10 ^b	≥2.2	100%	68% (IHC), 42% (ISH)	NA	NA	NA	(34)
Li, 2015	16	IHC+FISH	>10 ^b	≥2.2	100% (3+)	87.5% (IHC), 25% (FISH)	Limited number of cases	NA	NA	(83)
Schneider <i>et al</i> , 2014	61	IHC+FISH	>10	≥2.0	83%	49% (IHC), 15% (FISH)	Relatively limited number of cystectomy cases, retrospective and non-randomized study	Cancer-specific survival	Cancer-specific survival	(35)
Behzatoğlu <i>et al</i> , 2016	60	IHC	>10 ^c	NA	NA	56%	NA	NA	NA	(97)
Goodman and Osunkoya, 2016	27	IHC	>10	NA	NA	74%	Lack of routine performance of FISH	NA	NA	(99)

^aUniform intense membrane staining of >30% of cells; ^b2+, complete but weak membrane staining in >10% of cells; 3+, intense membrane staining in >30% of cells; ^ccomplete intense circumferential membrane staining. IHC, immunohistochemistry; ISH, *in situ* hybridization; FISH, fluorescence ISH; chr17, chromosome 17; NA, not applicable/not available.

it has been considered that gene amplification may not be the mechanism underlying protein overexpression (96).

4. HER2 in MPBC

As MPC exhibits a morphology and behavior distinct from that of conventional UBC, it has been hypothesized that such differences could be an effect of differences in growth-promoting factors such as HER2 (34).

Tschui *et al* (61), described an aggressive HER2-amplified subtype of UBC with specific features, comprising frequent (77%) MP tumor growth and high morphological heterogeneity, as well as brisk tumor-associated chronic inflammation.

The most representative studies investigating HER2 status in MPBC are summarized in Table I.

Immunohistochemistry. Attempts have been made to investigate HER2 as a marker in the differential diagnosis between MPBC and UBC. In 2004, Zhang *et al* (43) identified overexpression of HER2 in 10 MPBC vs. 59 conventional UBC cases, reporting a sensitivity and specificity of 100 and 57%, respectively. Conversely, Sangoi *et al* (45) reported specificity as high as 92% for HER2 positivity by immunohistochemistry (IHC) (comprising 2+ and 3+ staining) in MPBC compared with conventional UBC with retraction artifacts; furthermore, in the same study, a very low sensitivity (25%) was achieved and statistical significance was lacking (45). In keeping with such data, HER2 protein overexpression has been identified in a significantly higher proportion of cases of MPBC compared with UBC (56-87.5 vs. 31.25-50%, respectively) (34,92,97), with higher homogeneity (97), as well as in invasive conventional or variant histology UBC in combination with MPBC (97,98). In a recent series of MPBC only, the frequency of HER2 positivity was as high as 74% (99). The most recent studies have failed to identify a statistically significant association between HER2 expression and MP differentiation (100,101).

Such conflicting results may arise for several reasons, including fixation issues, heterogeneity in stage and grade, use of different antibodies and use of tissue sections rather than tissue microarray (35,92,97). A further limitation is the heterogeneity of cut-off used to determine HER2 positivity. Unlike for breast and gastro-esophageal cancer, established guidelines for HER2 assessment in UBC do not exist, and the literature regarding HER2 expression in UBC often defines overexpression as 2+ and 3+ staining (66,70,72,81,102,103), whereas current breast and gastro-esophageal guidelines consider positive 3+ cases only.

HER2 overexpression has been advocated as an early event in urothelial tumorigenesis and only rarely in subsequent tumor development, also because of the occurrence of HER2-positive CIS in cases of infiltrating HER2-overexpressing UBC (61), as well as its higher frequency in less advanced disease (99).

In situ hybridization (ISH). In certain types of cancer, such as breast, ovarian, and gastric cancer, HER2 gene amplification assessed by ISH and protein expression are well-correlated (69,104), with HER2 gene amplification identified in >90% of patients with breast cancer demonstrating HER2 protein overexpression (65). Studies have revealed that MPBC exhibits HER2 amplification in <42%

cases (34,35,61,92), in comparison with a much lower frequency of <14% in UBC (35,75,105). As a prognostic factor, HER2 amplification (but not overexpression) exhibits a significant association with a significant increase in cancer-specific mortality (35), whereas another study failed to identify such an association in a smaller case series (34), possibly due to differences in patient selection criteria and methods, as well as the proportion of the MP component in the tumor and on the sample selected (99). On the basis of such results, it has been suggested that HER2 status may be a tool for pre-surgical risk stratification of these patients.

Previous studies identified a significant association between protein expression and gene amplification in MPBC, supporting the hypothesis that IHC may also provide reliable results in this setting (34,35,92). Schneider *et al* (35), highlighted that, despite a positive predictive value as high as 83%, IHC exhibited a very low negative predictive value (27%); it is well-known that other mechanisms may account for HER2 overexpression, including transcriptional or post-transcriptional dysregulation (95). On the other hand, those cases showing HER2 negativity by IHC and simultaneous HER2 amplification have been attributed to putative fixation artifacts (61).

Molecular biology. Genomic analyses identified that MPBC carries a significant high frequency of unique activating mutations in the extracellular domain of HER2 in comparison with conventional BC (34 vs 5%, respectively) (13,106). The point-mutated MPBC are not amplified nor overexpress HER2, thus being de facto undetectable using standard techniques (ISH and IHC).

In their series, Tschui *et al* (61) detected a novel D769N mutation in one case in association with HER2 amplification. As a marker of potential chromosomal and genomic instability, aneusomy 17 has been detected in >50% cases of MPBC in a series (34).

Therapeutic target. Although, to the best of our knowledge, there have not been any studies evaluating HER2-targeted therapy in MPBC, several trials have investigated its role in conventional BC (as aforementioned). Unfortunately, these studies have had limited success, possibly because of the low rates of gene amplification in this population. In a Phase II study of lapatinib, a dual tyrosine kinase inhibitor of EGFR and HER2, only 1.7% of patients with locally advanced or metastatic BC exhibited an objective response (75,107). A separate Phase II trial that combined trastuzumab (a monoclonal antibody against HER2) with carboplatin, paclitaxel and gemcitabine identified a complete response in 5/44 (11.4%) HER2-positive patients and a partial response in 26/44 (59.1%) patients (defined as a $\geq 50\%$ decrease in the size of the lesion) (80).

In the breast, MP histology was described as a predictor of lower response to standard adjuvant anti-HER2 targeted therapy (trastuzumab) and chemotherapy (108). Although a number of these studies used HER2 protein expression as a marker for potential therapeutic response, the lack of correlation between protein levels and gene amplification, and the low number of conventional urothelial carcinomas that exhibit HER2 gene amplification may explain these results. In contrast, the high frequency of gene amplification in MPBC (34) makes

this variant a candidate for targeted treatment with anti-HER2 antibody.

5. Conclusion

Over the last decade, studies focusing on HER2 assessment in MPBC have identified frequent overexpression of this marker, suggesting that it might aid in patient risk stratification and treatment selection in this aggressive type of BC. With this in mind, standardization of techniques and development of proper assessment guidelines are required, as well as larger multi-institutional studies in order to confirm such results. Furthermore, prospective clinical trials are required to examine the application of targeted therapy in this aggressive disease.

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FS, GC and LC were responsible for the conception of the review, acquisition, analysis and interpretation of data for the review, drafting the review and revising it critically for important intellectual content. DR, BC and VM were responsible for the analysis and interpretation of data for the review and drafting the review. OS was responsible for the analysis and interpretation of data for the review, drafting the review, creating the table and revising it critically for important intellectual content. All authors gave final approval of the version to be published.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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