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Clinicopathological and Prognostic Value of Plasmacytoid subtype in Bladder Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: The World Health Organization, in 2004, published a new classification that recognizes different histological variants (HV) of urothelial carcinomas. Plasmacytoid urothelial carcinoma (PUC) is one of these subtypes. Information on outcomes is limited.

Material and Methods: A comprehensive literature search for relevant studies published up to April 30, 2018, was performed using PubMed and Scielo. The clinicopathological characteristic and outcomes in patients with PUC compared to pure urothelial carcinoma.

Results: Seven studies with 3240 PUC patients were selected for evaluation. The profiles of UC and PUC patients can be considered as distinct ($R = 0.59$, $p = 0.025$) for the incidence between men and women, the tumor stages, NACT treatment, and compromised surgical margin. However, there is no statistical difference in survival between UC and PUC ($t = -0.81$, $p = 0.449$) and mortality ($t = 0.51$, $p = 0.63$), which makes UC and PUC variations independent of prognosis.

Conclusion: PUC is associated with locally advanced disease and positive lymph nodes compared with UC. PUC was not an independent predictor of long-term survival, so it is not an independent prognostic factor.neoadjuvant chemotherapy, followed by radical cystectomy, showed less rate of positive surgical margins.

Keywords: Bladder Cancer; Plasmacytoid Urothelial Carcinoma; Prognosis

Introduction

Bladder cancer causes approximately 150,000 deaths per year, and it is the second most prevalent genitourinary malignancy after prostate adenocarcinoma. The most common histological type is the urothelial carcinoma (UC), which accounts for approximately 90% of all bladder cancer [1]. UC is formed of fused papillary stalks, a disordered growth pattern, numerous mitotic figures, and pleomorphic cells with exaggerated nuclei. One of the attributes of UC is the invasiveness of the lesion in over 80% of the cases [2].

UC of the bladder had previously been described as transitional cell carcinoma due to its known susceptibility for cellular differentiation into other tumor types [2]. In 2004, the World Health Organization published a new classification that recognizes different histological variants (HV) of urothelial carcinomas, suspecting that these variants may not similarly respond to systemic chemotherapy as traditional UC [3]. Even these distinct variations having been described many years ago, their actual prevalence, clinical significance, and prognosis are still not well understood.

Plasmacytoid is one of these subtypes, which was first reported in 2002 [4]. Over the next years, others cases reports were published and, with their information, was possible to define the histological characteristics of the plasmacytoid tumor, which, differently of UC, is composed of an eccentrically placed nuclei with abundant eosinophilic cytoplasm; highly proliferative and multiples mitoses; express the presence of CD138 marker and absence of MUM-1 [5]. Studies demonstrate that the plasmacytoid urothelial carcinoma (PUC) at diagnosis is common in advanced pathological stage, with approximately 90% of cases extending outside the bladder. It is also related to poor prognosis [6,7].

Information on outcomes for patients with PUC histology is limited due to the rarity of the disease and the scarce relative publications. In this study, we performed a literature review and meta-analysis to explore the relationship between PUC and its prognostic value in bladder cancer. The results could help clinicians to determine treatment, counseling, and follow-up strategies of patients with PUC.

Materials and Methods

Study strategy

The PubMed and Scielo databases were searched systematically for relevant articles published up to April 30, 2018. Because the data in this study were extracted from previous studies, ethical approval from ethics committees was not required. The search terms used were "CARCINOMA and UROTHELIAL and PLASMACYTOID".

Inclusion and exclusion criteria

The criteria for eligibility were as follows:

1. Description of the clinical-pathological characteristics of the subgroup with plasmacytoid tumors
2. Articles wrote in English, Spanish, Portuguese and French
3. Enough information to realize the meta-analysis

Papers containing any of the following were excluded:

1. Duplicate literature or duplicate data presented at conferences;
2. Reviews articles
3. No available data, or abstract only;
4. Upper urinary tract plasmacytoid carcinoma.
5. Overlap Studies

Data extraction and methodological assessment

The following info was recorded for each study: publication year, the first author's name, number of cases, median of patient age, gender, age group, with six levels (minimum, maximum, average); complexity of carcinoma (pure or subtypes); stage of tumor development (pT1, pT2, pT3, pT4); location of cancer related to lymph nodes (n1/2); overall survival rate; and tumor stage mortality.

We collected multivariate analysis data. If data were not accessible, information from univariate analyses of survival outcomes were obtained;

Statistical analysis

The meta-analysis database was constructed from information published in previous studies, extracted directly from the text and tables or the charts, using digital tools WEBPLOTDIGITIZER 3.9 and Data Thief III. It was corrected to reduce the influence of the contrasts between methodologies and, if necessary, for the insertion of additional data. Firstly, the homogeneity and representativeness of the sample group contained in the database within the sample universe were evaluated. Hypothesis testing was performed through a description of trends and evaluation of incidence/pre-test frequencies between control and positive prognostic groups. The correlation between condition factor and occurrence of bladder tumors was tested using likelihood tests, contingency tables (e.g., chi-square test), Mann-Whitney test, and the possible application of multivariate analyses restricted to the sample number (e.g., Cluster eANOSIM).

This research was based on 3420 patients, women and men, in a total of +7902 participants declared in the studies evaluating differences between patients diagnosed with pure urothelial carcinoma (UC) and plasmacytoid urothelial carcinoma (PUC). These data represent the growing sample universe (U) with an average incidence rate in the world population of 2.2 (women) and 9.0 (men) new cases per 100,000 people [7]. These values were used as a reference when necessary for hypothesis testing. The tests assumed a 95% confidence interval.

The meta-analysis assumed the following assumptions guaranteeing the homogeneity between the studies:

1. Temporality and simultaneity, and the articles considered broad temporal windows representative of approximately three decades (1980s to early 2000s) with data between 1980-2014, assuming recent and simultaneous conditions as the periods of investigation overlap;
2. Representativeness of the sample size, including that the patient information was grouped, and the results did not have different weights in the comparisons;
3. The similarity of age group, around 66 years;
4. Gender proportions and contrasts, with little distinction in gender ratios (F/M) in the studies but results with a bias for males where the highest incidence of this carcinoma occurred.

The profile of patients diagnosed with pure urothelial carcinoma (UC) and carcinoma plasmacytoid urothelial (PUC) was plotted considering as evaluation factors and classification levels: age group, with six levels (minimum, maximum, average); complexity of carcinoma (pure or subtypes); stage of tumor development (pT1, pT2, pT3, pT4); location of cancer related to lymph nodes (n1 / 2); overall survival rate; and tumor stage mortality [8].

The difference between the incidence frequencies between UC and PUC was evaluated through t-test and analysis of variance (Sokal and Rohlf, 2003), with n = 5 (each referring to a study). For the calculations, two of the studies were excluded (Fox *et al.* [9] and Dayyani *et al.* [10]) due to the lack of information on the total number of cases. The differences between the profiles of the patients diagnosed with UC and PUC were evaluated through similarity analysis (ANOSIM) [11]. In the profile analysis, it was possible to only consider as frequency descriptors the incidence frequencies between men and women, the tumor stages, the treatment with neoadjuvant chemotherapy (NACT), and the compromise of the surgical margin. The UC/PUC and the prognostic relationship were assessed by t-test, considering survival and lethality variables separately [12]. The analyses were performed using the R project software (R Core Team 2013, vegan package [13], and the graphs and tables Numbers software 5.1. (MacOs).

Results

Eligible studies

Our search strategy initially yielded 110 articles. Seven studies were excluded because of: the language (n=2 German, n=4 Japanese, and n=1 Chinese. Reviewers screened the identified titles and abstracts. After manually testing them, twenty-four studies were excluded because they were: geared towards pathology or immunohistochemistry (n=27), case reports (n = 29), review articles (n = 18), or unavailable content (n=3). Four items were ultimately excluded due to overlap with previously reported studies (n = 4) and other fives because the material was on the upper urinary tract (n=5). Thus, based on the criteria described above, seven publications were eligible for inclusion in this meta-analysis. The search strategy and filters applied are shown in Figure 1.

Of the seven studies included in our research, six were conducted in America and one in Germany. The follow-up period of the studies varied from 17,7 months to 60 months. The median age of the patients ranged from 62 to 68 years, and the overall proportion of males ranged from 73% to 89%.

Meta-analysis

The results of the meta-analysis revealed that there are essential differences in the profiles of patients identified with pure urothelial carcinoma (UC) and plasmacytoid urothelial carcinoma (PUC) (Table 1). Only a small percentage of patients with bladder cancer are identified with the PUC variant (2%), and almost half are affected by the purest form of UC carcinoma (41%) (test t, t = -5.3, p = 0.005). There is no difference in the average age of those diagnosed, being approximately 65 years for both types. The proportion of female and male patients did not differ between UC and PUC and is higher among men (F= 904.2, p <0.001).

	UC	PUC
Patients	41%	2%
Gender		
Male	81%	77%
Female	19%	23%
Age		
Min.	29 years	45 years
Max.	75 years	86 years
Average	65 years	66 years
Complexity		
Pure	-	87%
With sub-types	-	13%
Stage		
pT1	28%	14%
pT2	26%	18%
pT3/T4	41%	70%
Location of lymph node		
n1/2	19%	34%
Reoccurrence	-	40%
Survival	3 years	2 years
Mortality	36%	43%

*confidence intervals in the sum of % (95-105) due to variations of results from the source studies

Table 1: Characteristics of the patients with urothelial carcinoma by histological type (UC, pure urothelial carcinoma) and (PUC, urothelial carcinoma with plasmacytoid identification), according to the meta-analysis (global n = 7902, total n = 3420)

The relation between urothelial carcinoma type and tumor stage also varied, with differences in the pT3 / 4 stage, where the incidence frequency was 41% for UC and 70% for PUC. The same contrast was observed for the localization of cancer in the lymph nodes (n1 / 2), with 19% for UC and 34% for PUC. As for the years of survival and mortality, there were few differences between the groups. Regarding the treatment of carcinoma, a more significant proportion of patients diagnosed with PUC were treated with adjuvant and non-adjuvant chemotherapy (Figure 2). However, fewer patients with PUC had a compromised surgical margin (Figure 3), and 96.7% underwent cystectomy.

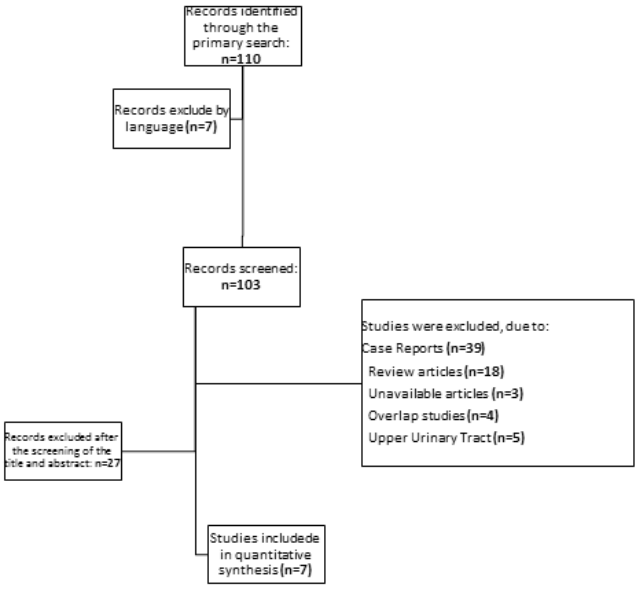

Figure 1: Flow chart shows study selection procedure

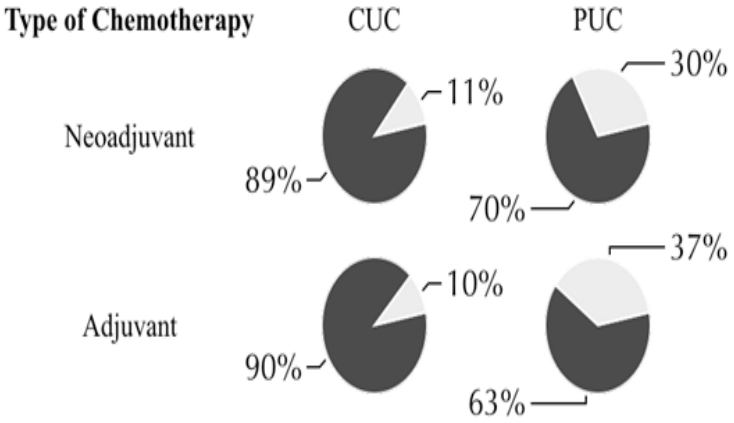

Figure 2: Variations in the frequency [%] of use of chemotherapy treatment in urothelial carcinoma patients between the two histological types, conventional urothelial carcinoma (CUC) and plasmacytoid urothelial carcinoma (PUC) according to the meta-analysis (global n=7902; total n = 3420)

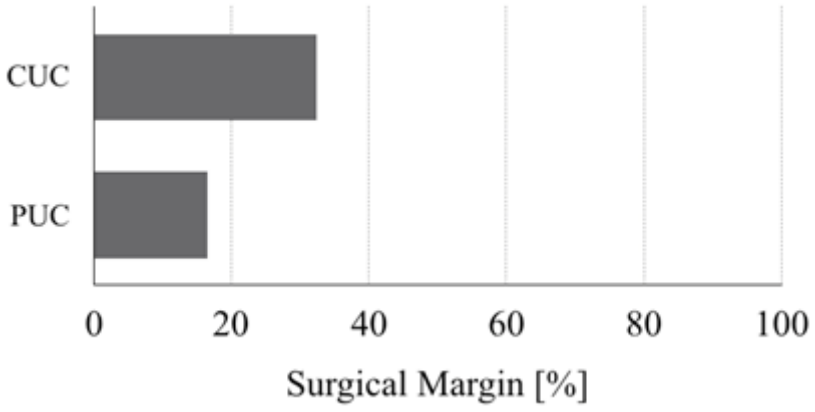

Figure 3: Surgical margin (%) affected by conventional urothelial carcinoma (UC) and plasmacytoid urothelial carcinoma (PUC) according to the meta-analysis (global: 7902; total = 3420)

According to the similarity analysis, the profiles of UC and PUC patients can be considered as distinct (R = 0.59, p = 0.025) for the incidence between men and women, the tumor stages, NACT treatment, and compromised surgical margin. However, there is no statistical difference in survival between UC and PUC (t = -0.81, p = 0.449) and mortality (t = 0.51, p = 0.63), which makes UC and PUC variations independent of prognosis (Figure 4).

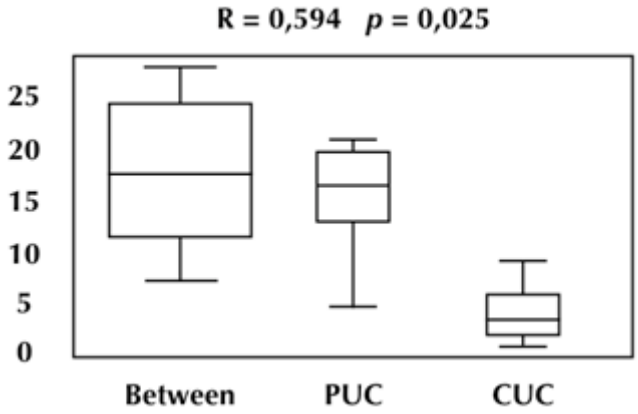

Figure 4: Results of the similarity analysis ANOSIM to access differences between patients with conventional urothelial carcinoma (CUC) and plasmacytoid urothelial carcinoma (PUC) according to the incidence in men and women, tumor stages, treatment by neoadjuvant chemotherapy, and surgical margins

Discussion

First described by Zuckemberg [14], plasmacytoid carcinoma of the urinary bladder is rare cancer, which the incidence in this review was 2%. This value is small than the finding of literature (3-5%) [6]. This data may be underestimated due to the pathologist's disregard for the HV of bladder neoplasia. The histological differences between UC and PUC can be find in Table 2, adapted from Straccia [15]. Monn suggests that the implementation of the centralized pathologic review can increase the identification of these variants and amply the numbers of HV cases [16].

Feature	PUC	UC
Nuclear Shape	Oval	Irregular
Nucleoli	Absent	Present (prominent)
Cytoplasm	Abundant (eccentric nuclei)	Dense (vacuoles)
Flat Sheet	Absent	Present
Papillae	Absent	Present
Atypical mitosis	Absent	Present
Chromatin	Coarse (fine distributed)	Coarse/clumped

Table 2: Morphological features of plasmacytoid variants related to the UC category; adapted by Straccia *et al.* [15]

About the clinical feature of the PUC, no statistical difference was observed between gender and age about the UC, as already demonstrated by other authors [9,17,18]. About histopathological staging, it keeping with the data of the literature, our study confirmed that patient with PUC frequently present advanced-stage cancer (>pT2), with over 70% of patients presenting with stage pT3/pT4 disease and it was noted in this review that the PUC is more diagnosed in advanced stages and with positive lymph nodes when compared to urothelial carcinoma [15]. However, despite these characteristics, this study did not show a significant difference in patient survival, contradicting the previous researchs [6,10].

We justify this behavior of PUC due to its sessile and nonpapillary tumor growth patterns. It can be usually infiltrative and may penetrate the urinary bladder in a *linitis plastica–like* manner and spread along the fascial planes and into the peritoneum [19]. Therefore, plasmacytoid lesions occur with less macroscopic hematuria, which takes these patients to later diagnosis. Our meta-analysis indicates that this variant histology is associated with cancer-specific mortality in univariable analysis, but they are not independent predictors of outcomes.

According to our review, surgical margins were less compromised in PUC, which could be explained by the greater use of NACT this subtype about UC. Dayanni *et al.* [10] noticed pathologic downstaging in 80%of patients (n = 4 of 5) treated with NACT and a complete response in 3 of them, ranking it as a chemosensitive tumor.

With the information collected, it was not possible to relate the higher percentage of PUC in cystectomies with a worse prognosis. More studies are needed to conclude that.

Among the limitations of our research, we highlight two: the rarity of the diseases leads to few studies published in the literature and, when available, have a low number of patients, and the lack of homogeneity in the literature impairs statistical analysis of some data.

Conclusion

The presence of PUC is associated with locally advanced disease and positive lymph nodes compared with UC. Yet, PUC was not an independent predictor of long-term survival, so it is not an independent prognostic factor. The optimal treatment modality continues to be defined; neoadjuvant chemotherapy followed by radical cystectomy showed less rate of positive surgical margins.

Due to the low number of patients in the encompassed studies, we suggest a multicenter study to understand this histological variant better.

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