SURVIVAL IN PATIENTS WITH HISTOLOGIC VARIANTS OF UROTHELIAL TYPE BLADDER CANCER

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ABSTRACT

Objective: *This study aims to determine the life expectancy of patients with histologic variants in urothelial type bladder cancer and the highest or lowest mortality rate in Hasan Sadikin Academic Medical Centre.* ***Material & Methods:*** *A cross-sectional study with total sampling. The samples in this study were patients with histologic variants of urothelial cell carcinoma bladder who received treatment at Hasan Sadikin Academic Medical Centre during the period of 2011 to 2022.* ***Results:****A total of 470 patients with a diagnosis of urothelial bladder cancer, 62 patients (13.19%) with histologic variants of urothelial bladder cancer treated with radical cystectomy or TURBT + intravesical chemotherapy at Hasan Sadikin Academic Medical Centre. The highest survival rate was in patients diagnosed with giant cell (66.7%) followed by small cell (50%) and glandular differentiation (40.0%). The 5-yearr survival rate of patients treated with radical cystectomy alone had a higher survival rate of 75.3% followed by radical cystectomy and adjuvant therapy, which was 75.2%.****Conclusion:****Histologic variants of bladder carcinoma that have the highest mortality rate are tropoblastic differentiation, nested type, micropappilary, and sarcomatoid with the lowest survival rate of 0%. Also, histologic variant of bladder carcinoma that has the lowest mortality rate is giant cell with a survival rate of 66.7%.*

Keywords: *Bladder carcinoma, chemotherapy, trophoblastic differentiation.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk mengetahui harapan hidup pasien dengan varian histologis pada kanker kandung kemih tipe urothelial dan angka kematian tertinggi atau terendah di Hasan Sadikin Academic Medical Center.* ***Bahan& Cara****: Studi potong lintang dengan total sampling. Sampel dalam penelitian ini adalah pasien dengan varian histologi kandung kemih karsinoma sel urothelial yang mendapatkan perawatan di Pusat Medis Akademik Hasan Sadikin selama periode 2011 hingga 2022.* ***Hasil:*** *Sebanyak 470 pasien dengan diagnosis kanker kandung kemih urothelial, 62 pasien (13.19%) dengan varian histologis kanker kandung kemih urothelial diobati dengan kistektomi radikal atau TURBT + kemoterapi intravesikal di Hasan Sadikin Academic Medical Center. Tingkat kelangsungan hidup tertinggi adalah pada pasien yang didiagnosis dengan sel raksasa (66.7%) diikuti oleh sel kecil (50%) dan diferensiasi kelenjar (40.0%). Tingkat kelangsungan hidup 5 tahun pasien yang diobati dengan kistektomi radikal saja memiliki tingkat kelangsungan hidup yang lebih tinggi sebesar 75.3% diikuti dengan kistektomi radikal dan terapi tambahan, yaitu 75.2%.* ***Simpulan:*** *Varian histologi karsinoma buli-buli yang memiliki angka kematian tertinggi adalah diferensiasi tropoblastik, nested type, mikropapilar, dan sarcomatoid dengan angka kelangsungan hidup terendah yaitu 0%. Selain itu, varian histologi karsinoma kandung kemih yang memiliki tingkat kematian terendah adalah sel raksasa dengan tingkat kelangsungan hidup sebesar 66.7%.*

Kata kunci: *Karsinoma kandung kemih, kemoterapi, diferensiasi trofoblas.*

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INTRODUCTION

Urinary bladder cancer (BC) is the 7th most common cancer in men and 17th most common cancer in women worldwide. Approximately 75% of newly diagnosed BC is non-invasive, while the remainder is invasive with the need for more radical treatment. The incidence of bladder carcinoma in the European Union (EU) is approximately 100,000 new cases per year.[1] Histologic variants include bladder malignancies other than urothelial cancer, such as UC with aberrant differentiation as well as non-UC resulting from metaplasia.[2] The World Health Organization (WHO) classification of urothelial

cancer recently listed 13 different histologic variants of urothelial cancer.[3] Non-urothelial BC can be further classified as epithelial and non-epithelial non-urothelial BC.[4] Approximately 90% of non-urothelial BCs are epithelial, including squamous cell carcinoma (SCC), adenocarcinoma, and small cell carcinoma.[3] As most BC subtypes differ by their cellular origin and the exact BC variant must be identified in each individual as prognosis and preferred therapy may differ significantly.[5]

The primary treatment for patients with histological variants of BC and presenting with local symptom is surgery. 75% of all cases represent non-muscle-invasive bladder cancer (NMIBC) and are treated locally with transurethral resection of the bladder (TUR-B) followed by instillation of adjuvant intravesical therapy.[6] For invasive tumors, radical cystectomy (RC) should be performed including pelvic lymph node dissection.[7] However, there is little data and evidence on the treatment of non-urothelial BC currently available.

The presence of histologic variant BC represents high-risk BC even if not muscle-invasive and therefore recommendations generally include early aggressive intervention with RC, especially in patients with histologic variants such as SCC, adenocarcinoma and sarcoma cancer. In patients with non-urothelial BC or patients who cannot undergo surgery, including those with metastatic disease, the treatment options used are palliative care, RTX or CTX. However, aggressive non-UC bladder cancer shows poor outcomes with standard chemotherapy regimens. As there are no data showing a survival or quality of life benefit from CTX for non-urothelial BC, palliative care as an alternative to CTX should be offered and the limitations of available treatments should be discussed with patients.[7]

Radical cystectomy (RC) with pelvic lymph node dissection is the mainstay therapy for muscle-invasive disease.[8] However, despite definitive therapy, the overall 5-year survival of patients undergoing radical cystectomy remains below 60%.[9] Histological variants have been identified as the main pathological feature indicating the clinical behavior of individual urothelial carcinoma of the bladder. UC shows morphological and clinical diversity. From this background, researchers are interested in knowing the histological variants in bladder carcinoma treated with radical cystectomy on the 5-year life expectancy of sufferers.

OBJECTIVE

This study aims to determine the life expectancy of patients with histologic variants in urothelial type bladder cancer and the highest or lowest mortality rate in Hasan Sadikin Academic Medical Centre.

MATERIALS & METHODS

This descriptive study used a cross-sectional design with total sampling. The samples in this study were patients with histologic variants of urothelial cell carcinoma bladder who received therapy at Hasan Sadikin Academic Medical Centre during the period 2011 to 2022, and met the inclusion and exclusion criteria. Data was taken from medical records at Hasan Sadikin Academic Medical Centre.

The inclusion criteria in this study were patients diagnosed with one of the histological variants of bladder urothelial cell carcinoma and there were patient data regarding age, gender, anatomical pathology examination results, therapy, and TNM staging. While the exclusion criteria in this study were data on the patient's anatomical pathology that did not explain one of the histological variants of bladder urothelial cell carcinoma and did not receive therapy at Hasan Sadikin Academic Medical Centre. Data were processed and analyzed using SPSS version 20.0. The p-value that is considered significant is ≤ 0.05.

RESULTS

A total of 470 patients with a diagnosis of urothelial bladder cancer, 62 patients with histologic variants of urothelial bladder cancer treated with radical cystectomy or TURBT + intravesical chemotherapy at Hasan Sadikin Academic Medical Centre during the period 2011 to 2022 can be seen in Table 1.

In Table 1, 56 patients (90.32%) were male. A total of 39 patients (62.90%) were less than 65 years old. Histological results showed that most patients had muscle invasive bladder cancer (MIBC) histology, as many as 56 people (90.32%) while 6 patients (9.68%) showed non-muscle invasive bladder cancer (NMIBC) histology. In this study, the number of patients treated with radical cystectomy was 41 patients (66.13%) and 10 patients (16.13%) received radical cystectomy + adjuvant chemotherapy.

Table 1. Demographic and Clinical Characteristics of Bladder Cancer Patients.

	N=62	%
Gender		
Male	56	90.32
Female	6	9.68
Age		
< 65 years old	39	62.90
≥ 65 years old	23	37.10
Variant Histology		
Squamous differentiation	24	38.71
Glandular differentiation	5	8.06
Trophoblastic differentiation	1	1.61
Nested Type	9	14.52
Micropapillary variant	2	3.23
Plasmacytoid variant	8	12.90
Sarcomatoid variant	2	3.23
Giant cell variant	3	4.84
Clear cell variant	6	9.68
Small cell variant	2	3.23
Stage		
NMIBC	6	9.68
MIBC	56	90.32
Treatment		
TURBT + Intravesical chemotherapy	6	9.68
Radical Cystectomy	41	66.13
Radikal Cystectomy + NAC	5	8.06
Radikal Cystectomy + AC	10	16.13

*NAC = Neoadjuvant chemotherapy, AC = Adjuvant chemotherapy.

Table 3. Histopathology Variant Distribution of Study Subjects.

Histology Variant	Data (%)	Review (%)
Squamous differentiation	38.71	16.8 – 22.1 (39%)
Glandular differentiation	8.06	10 (11%)[11]
Trophoblastic differentiation	1.61	5.5
Nested Type	14.52	0.3 – 2.7 (13%)
Micropapillary variant	3.23	0.7 – 2.2 (28%)[12]
Plasmacytoid variant	12.90	< 1 (20%)[13]
Sarcomatoid variant	3.23	0.3 – 0.6 (4%)[14]
Giant cell variant	4.84	2.7 (7%)
Clear cell variant	9.68	0.5 – 2[15]
Small cell variant	3.23	0.35 – 1.8 (9%)[16]
NMIBC		
Squamous differentiation	50	14 – 21.74
Glandular differentiation	0	3.1
Trophoblastic differentiation	0	-
Nested Type	33.33	22.73
Micropapillary variant	0	34.09
Plasmacytoid variant	0	27
Sarcomatoid variant	0	-
Giant cell variant	0	-
Clear cell variant	16.67	-
Small cell variant	0	4.17
MIBC stage		
Squamous differentiation	37.5	78.26
Glandular differentiation	8.93	-
Trophoblastic differentiation	1.79	-
Nested Type	12.5	77.27
Micropapillary variant	3.57	65.91
Plasmacytoid variant	14.29	73
Sarcomatoid variant	3.57	34
Giant cell variant	5.36	-
Clear cell variant	8.93	-
Small cell variant	3.57	84 - 95.83

Table 2shows that of the 6 patients with non-muscle-invasive bladder cancer (NMIBC) histology, 4 patients were less than 65 years old and 2 patients were 65 years old or older. All patients with NMBIC were male. Meanwhile, of the 56 patients with muscle invasive bladder cancer (MIBC), 38 patients were less than 65 years old and 18 patients were 65 years old or older. MIBC patients were predominantly male, with 49 patients (87.5%) while 7 patients (12.5%) were female.

Table 3 shows the histopathology variants in the study subjects. Squamous differentiation histology variant was the most common variant found in this study, as many as 24 patients (38.71%). The nested type variant was the second most common variant with 9 patients (14.52%) and the third most common plasmacytoid variant with 8 patients (12.90%).

Table 2. Cancer Histology Distribution by Age and Gender.

Staging of bladder cancer	N	Age (years)		Gender	
		< 65	≥ 65	Male (n, %)	Female (n, %)
NMIBC	6	4	2	6, 100	0
MIBC	56	38	18	49, 87.5	7, 12.5

Figure 1 shows the survival rate based on variant histology. The highest survival rate was in patients diagnosed with giant cell (66.7%) followed by small cell (50%) and glandular differentiation (40.0%). Meanwhile, tropoblastic, nested type, micropappilary, and sarcomatoid differentiation had the lowest survival rate of 0% at year five.

Figure 2 shows the survival rate based on the treatment. The survival rate of patients treated with radical cystectomy alone had a higher survival rate of 75.3% followed by radical cystectomy and adjuvant therapy, which was 75.2%. Treatment with TURBT and intravesical chemotherapy had a survival rate of 65.6%. Treatment with radical cystectomy and neoadjuvant therapy has the lowest survival rate, which is 0% at year five.

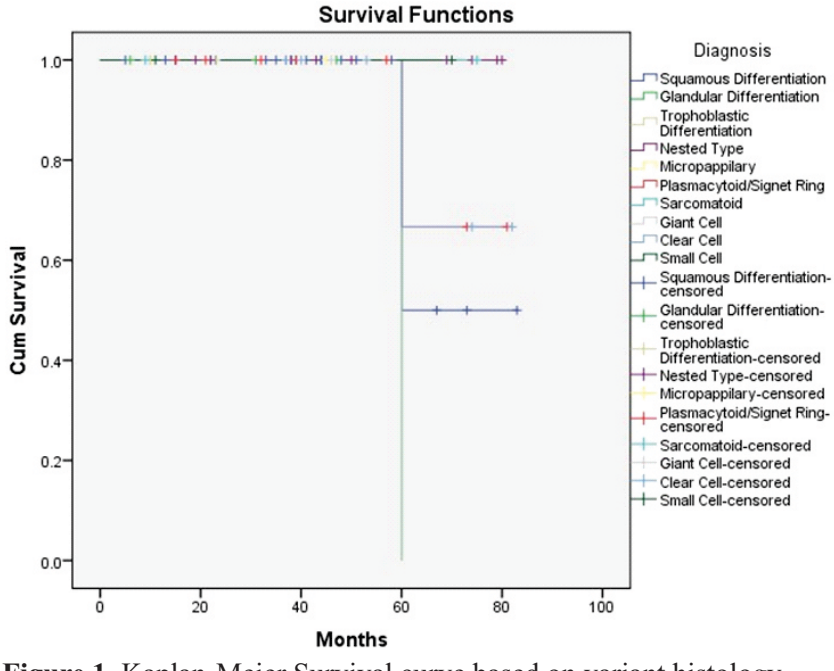

Figure 1. Kaplan-Meier Survival curve based on variant histology.

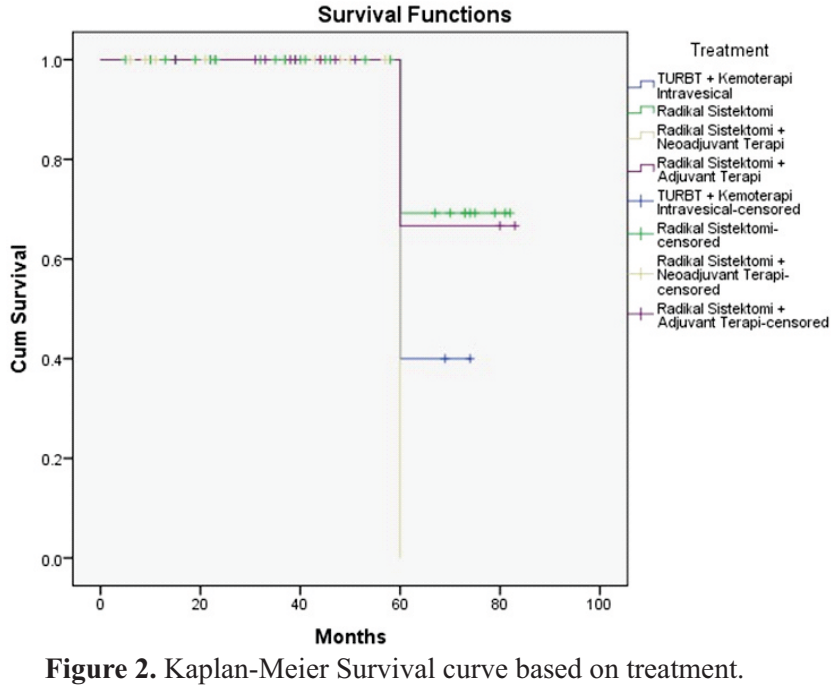

Figure 2. Kaplan-Meier Survival curve based on treatment.

DISCUSSION

Urothelial carcinoma of bladder with variant histology is more aggressive in appearance and has a worse prognosis than Primary urothelial bladder cancer. Urothelial cancer presents with different types of variant histology are dissimilar in their biological, clinical and prognostic impact. This study showed that the patient with variant histology of bladder cancer survival rate based on therapy was higher in patients who received radical cystectomy compared with TURBT and intravesical chemotherapy (75.3% vs 65.6%).

Survival rates in histologic variants of bladder urothelial carcinoma vary widely. The squamous differentiation histology variant has an overall survival rate ranging from 34% to 64.7%. The study of Minato et, al. showed an overall survival rate of about 50% - 60% in MIBC with this variant which was performed radical cystectomy.[10] The study of Li et, al. showed an overall survival rate of about 69% in the squamous differentiation variant. In addition, this study found a better median overall survival rate in the group treated with radical cystectomy (67 months) than those treated with Re-TURBT (33 months).[11]

In the nested type variant, the study of Linder et, al. showed an overall survival rate of about 29% in 10 years versus 23% with conventional bladder urothelial carcinoma. Tumors with pT2 and below had a survival rate of 74%, pT3 tumors had a survival rate of 44% and pT4 tumors had a survival rate of 0% in 5 years.[12]

In the micropapillary variant, the overall 5- and 10-year survival rates are 51% and 24%, respectively, which are lower compared to other histologic types. Although the plasmasitoid variant is chemosensitive and can be treated with neoadjuvant chemotherapy at any time when feasible, recurrence is frequent with a median survival among nonmetastatic patients of only 17.7 months.[13]

The sarcomatoid variant has a prevalence of 0.3% to 0.6% of all bladder cancers. Patients with the sarcomatoid variant are seen to have a large infiltrative mass, often at an advanced stage with survival within 5 years as low as 28.4% across all stages. The survival rate in the small cell variant is 1.7 years, with a stage II breakdown of 63.6%, stage III of 15.4% and stage IV of 10.5%. In the giant cell variant according to Lopez et al., patients with ≥pT3 disease have a survival rate of 12.5% in 2 years. The study from Samaratunga et al. showed 50% of patients died within 12 months. In clear cell variant, the median overall survival in patients was 11.5 months, with 1 to 3 year survival rates of 54% and 21.4%.[14]

Patients with high-risk NMIBC should be managed with intravesical chemotherapy after complete and careful TURBT. In patients with T1 tumors, a second resection of the same area may be required to accurately stage the disease and determine treatment. For patients with T2-T4a, N0, M0 clinical disease, radical cystectomy and bilateral pelvic lymph node dissection remains the gold standard of therapy to which all other treatment modalities should be compared.11 Patients with more invasive, but still localized tumors (T2, T3) are candidates for more aggressive local treatment, including partial or radical cystectomy, or a combination of radiation and systemic chemotherapy. Radical TUR alone may be a viable option in selected patients with T2 disease, especially if no tumor is found on repeat resection as the 10-year survival rate is 83%.[10] Meanwhile, the 5-year no-recurrence survival rate can reach 90%.[15]

In localized MIBC, TURBT is used for pathologic confirmation of muscle invasion. Therefore, radical cystectomy is usually performed. In cases of distant metastases such as lung or liver, the 5-year survival rate of patients with localized MIBC after radical cystectomy is reported to be only 50%.[16]

CONCLUSION

Histologic variants of bladder carcinoma that have the highest mortality rate are tropoblastic differentiation, nested type, micropappilary, and sarcomatoid with the lowest survival rate of 0%. Also, histologic variant of bladder carcinoma that has the lowest mortality rate is giant cell with a survival rate of 66.7%.

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