



Original Article

Impact of urothelial carcinoma with divergent differentiation on tumor stage

Chalise S¹, Jha A², Neupane PR³, Pradhan SB¹, Pathak R⁴

¹Department of Pathology, Kathmandu Medical College, Sinamangal, Nepal.

²Department of Pathology, Institute of Medicine, Maharajgunj, Nepal.

³Department of Surgery, Bhaktapur Cancer Hospital, Bhaktapur, Nepal

⁴Department of Pathology, Nepal Medical College, Jorpati, Nepal.

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ABSTRACT

Background: Urinary bladder cancer is classified as urothelial or non-urothelial. Ninety percent of bladder cancer are urothelial and has propensity for divergent differentiation. Squamous differentiation is associated with unfavourable prognostic features. The aim of this study is to determine the significance of urothelial carcinoma with divergent differentiation in relation to tumor stage and lymphovascular as well as perineural invasion in radical cystectomy and partial cystectomy specimen.

Materials and Methods: This prospective study was done among 51 patients who underwent radical cystectomy or partial cystectomy at Bhaktapur Cancer Hospital from 1st August 2013 to 31st December 2015. Received specimen was grossed following standard protocol and histopathological evaluation was done in relation to tumor type, depth of invasion, Lymphovascular and perineural invasion.

RESULTS: Pure urothelial carcinoma comprises 47.1% of cases. Among the divergent differentiation, urothelial carcinoma with squamous differentiation was the commonest one (39.2%) followed by glandular differentiation (5.9%), sarcomatoid differentiation (3.9%), clear cell variant (2.0%) and squamous along with sarcomatoid variant (2.0%). Statistical significant correlation was found between urothelial carcinoma with divergent differentiation and tumor stage ($p < 0.012$). Statistically significant correlation was also found between urothelial carcinoma with divergent differentiation and lymphovascular invasion ($p = 0.012$) as well as perineural invasion ($p = 0.037$).

CONCLUSION: Most common divergent differentiation was squamous differentiation. Urothelial carcinoma with divergent differentiation was associated with higher stage and lymphovascular as well as perineural invasion. So it is mandatory to search for the divergent differentiation in urothelial carcinoma as this may be associated with unfavourable prognosis.

INTRODUCTION

Urinary bladder cancer is the 7th most common cancer

Correspondence:

Dr. Sanat Chalise, MD

Department of Pathology, Kathmandu Medical College, Kathmandu, Nepal
and Bhaktapur Cancer hospital, Bhaktapur, Nepal

E-mail: sanatchalise@hotmail.com, sanat_chalise@yahoo.com

worldwide, with an estimated 260000 new cases occurring each year in men and 76000 in women.¹ The prevalence of these tumor is higher in developed countries as compared to developing countries. In the United States alone, an estimated 70980 new cases were diagnosed with an estimated 14330 deaths in 2009.²

The most common type is urothelial carcinoma derived

Table 1: Frequency of urothelial carcinoma

Variants of urothelial carcinoma	No (%)
Infiltrating urothelial carcinoma	24 (47.1)
Infiltrating urothelial carcinoma with squamous differentiation	20 (39.2)
Infiltrating urothelial carcinoma with glandular differentiation	3 (5.9)
Infiltrating urothelial carcinoma with sarcomatoid variant	2 (3.9)
Infiltrating urothelial carcinoma with clear cell variant	1 (2.0)
Infiltrating urothelial carcinoma with squamous and sarcomatoid variant	1 (2.0)
Total	51 (100)

from urothelium which constitute more than 90% of bladder cancer in America, France and Italy.¹ Urothelial carcinoma is known to show variant histological features, otherwise known as divergent differentiation, with an estimate ranging from 7% to 81% in a series specifically reporting the differentiation patterns of urothelial cancer.³

The recognition of histological variants in urothelial neoplasm is important because some type may be associated with different clinical outcomes, some may have different therapeutic approach and awareness of unusual pattern may be critical in avoiding diagnostic misinterpretation.⁴

Squamous differentiation is the most important histological variant of urothelial carcinoma followed by glandular differentiation.⁵ Upto 60% of tumor exhibit squamous differentiation and approximately 10% of urothelial carcinoma contains foci of glandular differentiation.⁴ Radical cystectomy with bilateral pelvic lymphnode dissection is currently the gold standard treatment for muscle invasive urinary bladder carcinoma. Unfortunately, 40% of patient with organ confined disease at the time of cystectomy urinary bladder subsequently suffer recurrence.⁶

In a large study done by Wasco and colleague, it was found that urothelial carcinoma with divergent differentiation were most likely to be invasive ($p < 0.001$).³ The aim of the present study is to evaluate the urothelial carcinoma and its differentiation in radical cystectomy and partial cystectomy specimens and correlate the divergent differentiation with tumor stage as well as lymphovascular and perineural invasions.

MATERIALS AND METHODS

This is a prospective study done in the Department of Pathology, Bhaktapur Cancer Hospital. A total of 51 patients who underwent radical cystectomy and partial cystectomy with bilateral pelvic lymphnode dissection during the period of 1st August 2013 to 31st December 2015 were included in the study. Prior to study permission from ethical review committee has been obtained.

The received specimens were grossed and processed using standard technique. Tumor type, differentiation, depth of invasion, lymphovascular invasion and perineural invasion were assessed. Tumor staging and grading were done according to American joint committee of cancer (AJCC). Statistical analysis was done using Pearson chi-square test and statistically significant value was set at $p < 0.05$.

RESULTS

The study comprises of 51 patient of which 41 (80.4%) were male and 10 (9.6%) were female, treated with radical cystectomy ($n=43$) and partial cystectomy ($n=8$) with pelvic lymphnode dissection. The age of the patient ranged from 45-85 years with mean age of 66.1 years.

Pure urothelial carcinoma was diagnosed in 24 patients (47.1%). Among the divergent differentiation, squamous differentiation was diagnosed in 20 patient (39.2%) followed by glandular differentiation in 3 patient (5.9%), sarcomatoid variant in 2 patient (3.9%), clear cell variant in 1 patient (2%) and squamous along with sarcomatoid variant in 1 patient (2%) as shown in Table 1 and Figure 1-3.

Urothelial carcinoma with divergent differentiation were staged as pT3a in 25.4% of cases or even higher stage (Table 2 and 3). Using pearson chi-square test, statistical significant correlation was obtained between UC with divergent differentiation and tumor stage ($p=0.012$) which signifies that divergent differentiation is associated with higher stage (Table 4).

Lymphovascular and perineural invasion were present in 64.7% of cases. Most of the cases with divergent differentiation were positive for lymphovascular and perineural invasion (Table 5 and 6). Statistical significant correlation was also obtained between UC with divergent differentiation and lymphovascular as well as perineural invasion (Table 7 and 8)

DISCUSSION

Urothelial carcinoma are the commonest urothelial neoplasm and have a great capacity for divergent differentiation. Squamous differentiation is the commonest divergent differentiation.⁷ Pathological stage and lymphnode status are the common primary prognostic factors after radical cystectomy as they are the strong predictors for the survival.⁸ The clinical significance of squamous differentiation remains uncertain, but seems to be an unfavourable prognostic features predicting local recurrence after cystectomy.⁷

In this study, the mean age was found to be 66.1 of which 41 (80.4%) were male and 10 (19.6%) were female. Among 51 cases, 27 (52.9%) had a infiltrating carcinoma with divergent differentiation, the commonest being squamous differentiation (39.2%) followed by glandular differentiation

Table 2: Distribution of histopathological types of urothelial carcinoma and tumor stage

Tumor type	Tumor Stage							Total
	T1	T2a	T2b	T3a	T3b	T4a	T4b	
Infiltrating urothelial carcinoma	5	8	5	5	1	0	0	24(47.1%)
Infiltrating urothelial carcinoma with squamous differentiation	0	0	1	12	3	3	1	20(39.2%)
Infiltrating urothelial carcinoma with glandular differentiation	1	0	1	1	0	0	0	3(5.9%)
Infiltrating urothelial carcinoma with sarcomatoid variant	0	0	0	0	1	1	0	2(3.9%)
Infiltrating urothelial carcinoma with clear cell variant	0	0	1	0	0	0	0	1(2.0%)
Infiltrating urothelial carcinoma with squamous and sarcomatoid variant	0	0	0	0	0	1	0	1(2.0%)
Total	6(11.8%)	8(15.7%)	8(15.7%)	18(35.3%)	5(9.8%)	5(9.8%)	1(2%)	51(100%)

Table 3: Frequency of urothelial carcinoma with divergent differentiation and tumor stage

Tumor type	Tumor Stage							Total
	T1	T2a	T2b	T3a	T3b	T4a	T4b	
Infiltrating urothelial carcinoma with squamous differentiation	0	0	1	12	3	3	1	20(39.2%)
Infiltrating urothelial carcinoma with glandular differentiation	1	0	1	1	0	0	0	3(5.9%)
Infiltrating urothelial carcinoma with sarcomatoid variant	0	0	0	0	1	1	0	2(3.9%)
Infiltrating urothelial carcinoma with clear cell variant	0	0	1	0	0	0	0	1(2.0%)
Infiltrating urothelial carcinoma with squamous and sarcomatoid variant	0	0	0	0	0	1	0	1(2.0%)
Total	1(1.9%)	0(0%)	3(5.8%)	13(25.4%)	4(7.8%)	5(9.8%)	1(1.9%)	27(100%)

Table 4: Correlation between urothelial carcinoma with divergent differentiation and tumor stage

Urothelial carcinoma with divergent differentiation and tumor stage	Pearson Chi-Square	
	value	Asymp. Sig. (2-sided) P Value
	49.998	0.012

Table 5: Frequency of urothelial carcinoma associated with lymphovascular invasion

Tumor type	Lymphovascular invasion		Total
	Positive	Negative	
Infiltrating urothelial carcinoma	9	15	24(47.1%)
Infiltrating urothelial carcinoma with squamous differentiation	16	4	20(39.2%)
Infiltrating urothelial carcinoma with glandular differentiation	1	2	3(5.9%)
Infiltrating urothelial carcinoma with sarcomatoid variant	2	0	2(3.9%)
Infiltrating urothelial carcinoma with clear cell variant	1	0	1(2.0%)
Infiltrating urothelial carcinoma with squamous and sarcomatoid variant	1	0	1(2.0%)
Total	33(64.7%)	18(35.3%)	51(100%)

Table 6: Correlation between urothelial carcinoma with divergent differentiation and lymphovascular invasion

Urothelial carcinoma with divergent differentiation and lymphovascular invasion	Pearson Chi-Square	
	value	Asymp. Sig. (2-sided) P Value
	11.813	0.037

Table 7: Frequency of urothelial carcinoma associated with perineural invasion

Tumor type	Perineural invasion		Total
	Positive	Negative	
Infiltrating urothelial carcinoma	9	15	24(47.1%)
Infiltrating urothelial carcinoma with squamous differentiation	19	1	20(39.2%)
Infiltrating urothelial carcinoma with glandular differentiation	1	2	3(5.9%)
Infiltrating urothelial carcinoma with sarcomatoid variant	2	0	2(3.9%)
Infiltrating urothelial carcinoma with clear cell variant	1	0	1(2.0%)
Infiltrating urothelial carcinoma with squamous and sarcomatoid variant	1	0	1(2.0%)
Total	33(64.7%)	18(35.3%)	51(100%)

Table 8: Correlation between urothelial carcinoma with divergent differentiation and perineural invasion

Urothelial carcinoma with divergent differentiation and perineural invasion	Pearson Chi-Square	
	value	Asymp. Sig. (2-sided) P Value
	19.290	0.002

(5.9%). Kucuk U et al⁶ in their study found 45.2% of cases having divergent differentiation of which the commonest differentiation found was squamous differentiation (18.4%). In the study done by Kim SP et al⁹ and Mitra AP et al¹⁰, squamous differentiation was found to be the commonest divergent differentiation. Antunes AA et al¹¹ in their study found, 22.1% of cases with squamous differentiation.

The present study found that patient with divergent differentiation presented stage pT1, pT2a, pT2b, pT3a, pT3b, pT4a, pT4b in 1.9%, 0%, 5.8%, 25.4%, 7.8%, 9.8% and 1.9% respectively. Most of the cases with divergent differentiation were staged as pT3a. Using Pearson chi-square test, significant result was obtained between divergent tumor differentiation and tumor stage ($p=0.012$),

which signifies that the tumor stage was high when there is divergent differentiation. Similarly Lee YJ et al⁵ in their study found significant correlation ($p<0.001$) between Urothelial carcinoma with squamous and or glandular differentiation and tumor stage. Kim SP et al⁹ also concluded that Urothelial carcinoma with squamous and or glandular differentiation had higher stage as compared to the pure Urothelial carcinoma and in their study, 70% of the cases were pT3-T4 tumors. Similar result was obtained from the study done by Xylinas E et al¹², they also found significant correlation ($p<0.01$) between histological UC variants and tumor stage. In concordance to the present study, Lopez-Beltran A et al⁷ in their study concluded higher tumor stage and grade in the urinary bladder tumor with squamous differentiation. Similar to our study, Autunes AA et al¹¹

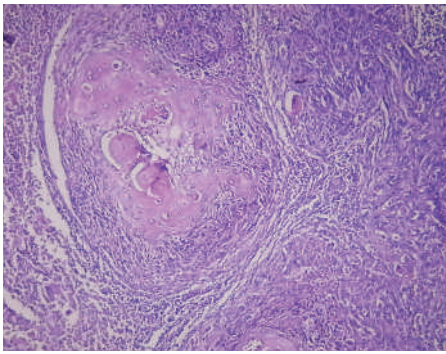


Figure 1: Urothelial carcinoma with squamous differentiation showing keratin pearls and intercellular bridges (H & E stain, X100).

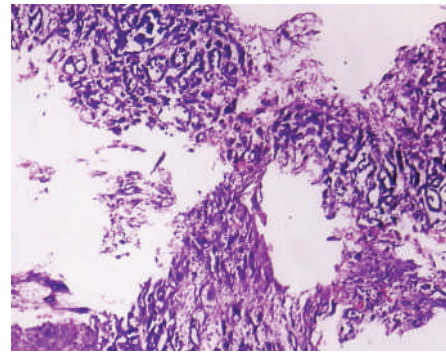


Figure 2: Urothelial carcinoma with glandular differentiation, showing well-formed glands (H & E stain, X100).

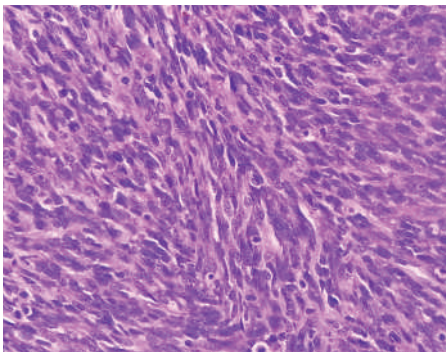


Figure 3: Urothelial carcinoma with sarcomatoid differentiation showing fascicles of spindle shaped cells. (H & E stain, X400).

also found squamous differentiation as a commonest tumor and significant correlation was obtained between UC with squamous differentiation and tumor stage ($p=0.031$).

Lymphovascular and perineural invasion were present in 64.7% of cases. Most of the cases with divergent differentiation were positive for lymphovascular and perineural invasion. Statistical significant correlation was obtained ($p<0.05$) between Urothelial carcinoma with divergent differentiation and lymphovascular as well as perineural invasion in the current study which was similar to the study done by Brunocilla E 13, Lee YJ et al 5, Kim SP et al 9 and Antunes AA et al 11 in their study also found significant statistical correlation between Urothelial carcinoma with divergent differentiation and lymphovascular as well as perineural invasion. In contrast to our study, Kucuk U et al 6 does not found significant correlation between divergent differentiation and lymphovascular invasion.

CONCLUSION

Squamous differentiation is the commonest divergent differentiation. Patient with divergent differentiation is associated with higher stage as well as lymphovascular and perineural invasion. Thus extensive search for the divergent differentiation should be done by the pathologist as these

factors which may be associated with adverse clinical outcomes of the patient should be taken into consideration in treatment planning.

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