Clinicopathological characteristics and treatment outcomes of 162 Chinese patients with metastatic bladder cancer: results from a tertiary teaching hospital

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Background: To explore the relationship between clinicopathological features and prognosis of metastatic bladder cancer (MBC) patients in the real world, and to provide peculiar data support for the management of such patients.

Methods: A retrospective analysis of 162 MBC patients who underwent radical cystectomy (RC) in West China Hospital, Sichuan University from September 2010 to December 2015 was conducted. The study included the clinical, pathological and metastatic features of these patients. Chi-square test, Kaplan-Meier method and Cox proportional hazard model were used to assess the relationship between clinicopathological factors and outcomes.

Results: Of the 162 patients enrolled, 137 (84.6%) were male and 25 (15.4%) were female. The ages at which the tumors metastasize for men and women were 64.8±9.4 and 66.2±12.7 years, respectively (P=0.52). The median follow-up time was 13.6 months (IQR: 5.8–33.1 months). Smoking history, pathological stages, and marginal status were independent predictors of the metastasis-free interval (MFI); Pathological stages, local recurrence, liver metastasis, and surgical approaches were significantly associated with cancer-specific survival (CSS) and overall survival (OS). Besides, OS was associated with lymphovascular invasion (LVI) and age at metastasis.

Conclusions: Our study suggests that tumors in MBC patients with a smoking history, positive margins, pT3 or more advanced tumors are more likely to metastasize. Besides, patients with a minimally invasive surgery, local recurrence, and liver metastases are at greater risk of death from bladder cancer; Taken together, our study provides data support for an optimal management of patients with MBC in current real-world practice.

Keywords: Bladder cancer; lymph node metastasis (LNM); visceral metastasis; prognosis

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Introduction

Bladder cancer is one of the most common malignant tumors of the genitourinary system, remaining the 10th most common cancer worldwide, with an estimated 549,000 new cases and 200,000 deaths each year (1). Although the incidence of bladder cancer in China is much lower than that in western developed countries, it has increased year by year in both urban and rural areas, regardless of gender (2). Therefore, enough attention should be paid to bladder cancer.

Half of the patients encounter muscle-invasive bladder cancer (MIBC) relapse after radical cystectomy (RC), in which distant metastasis accounts for 70% (3). Besides, only about 5% of metastatic cancer patients survive for at least 5 years post-diagnosis (4). Thus, metastasis is one of the most important causes of death from bladder cancer.

There is currently no cure for metastatic bladder cancer (MBC), whose prognosis is much worse than that of kidney cancer and prostate cancer (1), and the prognosis varies greatly. Currently, the relationship between clinicopathological features and MBC is unclear. Thus, it is essential to identify the clinicopathological factors associated with metastasis and their impact on prognosis, thereby helping clinicians communicate with patients and implement decision-making. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-737).

Methods

Study design

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study and disclaimer of informed consent were approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (No. 2020366). A retrospective analysis of 420 patients who underwent RC in West China Hospital, Sichuan University from September 2010 to December 2015 was conducted. There were 172 cases of lymph node metastasis (LNM) or visceral metastasis diagnosed by histopathological or radiological examinations, including 9 cases with prostate cancer and 1 with rectal cancer; so, 162 patients were finally included in the statistical analysis. The clinical features included age, gender, smoking history, preoperative abdominal computed tomography (CT) or magnetic resonance imaging (MRI), adjuvant

chemotherapy, surgical procedures, local treatment of metastases, metastasectomy, treatment types of metastases, and post-metastasis chemotherapy regimens. Adjuvant chemotherapy was defined as treatment given within 3 months after surgery. The pathological characteristics of primary tumor included pathological stage, grade, tumor size, growth pattern, pathological types, location, marginal status, and whether or not carcinoma *in situ* (CIS) and lymphovascular invasion (LVI) were combined. The metastatic characteristics included types of metastasis, local recurrence, LNM, numbers of removed lymph nodes, number of positive lymph nodes, bilaterality of positive lymph node, lymph node density (LND), and location or number of visceral metastases. LND was defined as the percentage of metastatic lymph nodes and the total number of lymph nodes removed, i.e., the detection rate of positive lymph nodes. Metastasis within 2 months was synchronous, otherwise it was metachronous. The TNM staging system of 2009 Union for International Cancer Control (UICC) was used for pathological stage and the World Health Organization (WHO) 2004 classification method was used for histological grade. The outcomes included metastasis-free interval (MFI), cancer-specific survival (CSS) and overall survival (OS). MFI was defined as the interval from the diagnosis of bladder cancer to the determination of the first metastatic lesion. OS was defined as the time from the onset of the metastasis to the death of any cause or last follow-up. CSS was defined as the time from the onset of metastasis to death from bladder cancer or last follow-up. All patients underwent abdominal and pelvic CT or MRI before surgery. Besides, they underwent chest X-ray or CT, abdominal and pelvic CT every 3 to 6 months within 2–3 years after surgery and every 6–12 months thereafter. A bone scan and a head CT or MRI were performed only when symptoms occurred.

Pathological assessment

All pathological specimens were evaluated by the pathology department of West China Hospital, Sichuan University, but the prognoses of the patients were not known.

Statistical methods

The Kaplan-Meier method was used to evaluate CSS, MFI, and OS. The duration of follow-up was calculated from the date of surgery to the date of death or last follow-up. Univariate and multivariate Cox proportional hazards

models were used to assess the clinicopathological features associated with metastasis and prognosis. A multivariate model was constructed using forward stepwise regression (Forward: LR) based on maximum likelihood estimation, where the P value of the variable entering the model set was 0.05, and the P value of the variable culling model set was 0.1. The Schoenfeld residual trend test was used to validate the Cox proportional hazard assumption. Chi-square test was used to estimate clinical and pathological factors associated with LNM and visceral metastasis. All reported P values were bilateral and statistically significant at P<0.05. Pairwise comparisons of chi-square tests used Bonferroni to correct significant levels. All statistical analyses were accomplished by the software .

Results

Clinicopathologic characteristics

The clinicopathological features of the 162 patients included in the study were summarized in *Table 1*. Of the 162 patients, 137 (84.6%) were male and 25 (15.4%) were female. The ages of diagnosis for men and women were 63.7±9.5 and 64.8±13.3, respectively (P=0.63). The ages at which metastasis occurred in men and women were 64.8±9.4 and 66.2±12.7, respectively (P=0.52). The mean follow-up time and median follow-up time was 21.4±19.9 months (range, 0.3–93.8 months) and 13.6 months (IQR: 5.8–33.1 months). Additionally, factors associated with LNM and visceral metastasis were shown in *Tables S1,S2*, separately.

MFI

The relationship between clinicopathological factors and MFI was summarized in *Table 2*. The average time from diagnosis to metastasis was 13.8 months (median time: 5.2 months; IQR: 0.9–18.4 months). Notably, adenocarcinoma may be an independent predictor of MFI (P=0.05).

CSS and OS

The average time to CSS and OS was 35.2 and 33.6 months, respectively. The CSS and OS rates of this cohort were shown in *Figure 1*. The estimated CSS rates [standard error (SE)] at 1, 3, and 5 years were 69% (4.3%), 38% (5.0%), and 20% (6%), singly. The characteristics

and corresponding HRs that were significantly associated with CSS and OS were summarized in *Table 3*. Besides, the univariate analyses of clinicopathological factors associated with MFI, CSS and OS were summarized (https://cdn.amegroups.cn/static/application/e9aa8f6cc613c010ef51e992ad8f7b42/tcr-20-737-1.pdf).

Discussion

Bladder cancer is a common malignant tumor of the urinary system, and its metastasis is one of the most important causes of death. Despite advances in its treatment, there has been little improvement in survival for patients with MBC over the last 2 decades (4). Currently, little research has been done on the risk factors associated with organ metastasis. Our purpose is to clarify the clinicopathological factors associated with metastasis and prognosis to optimize clinical management.

Similar to previous studies (5,6), our study shows that the most common metastatic site for MBC is lymph nodes, followed by lung, bone and liver. Xie *et al.* (5) believe that the MFI of bladder urothelial carcinoma (UC) is only significantly associated with the grade of primary tumor and local recurrence. Surprisingly, local recurrence is a favorable factor for MFI. They suppose that recurrence and metastasis are two biological behaviors of UC. During a certain period of time, the malignant tumor and the host are in an equilibrium. However, surgical resection may rebalance the residual cancer cells by recurrence or metastasis. Therefore, once local recurrence has occurred successfully, the transfer time may be delayed. Besides, MFI becomes shorter as tumor grade increases (5,7). However, our results suggest that tumor grade is not a predictor of MFI in MBC, probably due to a small sample size of low-Grade cases (only 10). Based on traditional transfer theory (8), tissue infiltration is an important step in the metastatic process. Our study suggests that bladder cancer with an advanced pathological stage is more likely to metastasize. In addition, we also find that smoking history and positive margins are risk factors for MFI.

In this study, we noted that tumors in some (4/162) patients with superficial low-grade bladder cancer did not develop to MIBC and metastasized directly, similar to previous studies (5,9). These phenomena suggested that more attention and consideration should be given to the treatment of early staged bladder cancer, and more researches are needed to clarify the metastasis mechanism of such patients.

Table 1 The clinicopathological features of the metastatic bladder cancer patients.

Features	Data
Clinical features	
Median age, year (IQR)	
Age at diagnosis	64.8 (58.4–69.8)
Age at metastasis	66.6 (60.0–71.4)
Gender	
Male	137 (84.6%)
Female	25 (15.4%)
Smoking history	
Yes	74 (45.7%)
No	88 (54.3%)
Abdominal CT or MRI	
Negative	78 (55.3%)
Enlarged lymph node	31 (22%)
visceral metastasis	48 (34%)
Adjuvant therapy	
Yes	33 (20.4%)
No	129 (79.6%)
Metastases treatment	
Yes	113 (69.8%)
No	49 (30.2%)
Surgical approach	
Open	130 (80.2%)
Laparoscopic	29 (17.9%)
Robot-assisted	3 (1.9%)
Treatment regimens for metastases	
GP	19 (46.3%)
Gemox	9 (22.0%)
M-VAC	1 (2.4%)
TS	4 (9.8%)
TP	3 (7.3%)
TC	2 (4.9%)
Apatinib	1 (2.4%)
GA	2 (4.9%)
GTC	2 (4.9%)

Table 1 (*Continued*)

Table 1 (*Continued*)

Features	Data
Other chemotherapy regimens	13 (31.7%)
Radiotherapy	9 (22.0%)
Pathological features	
Size (cm)	
Mean ± SD (range)	3.73±1.72 (1–10)
median (IQR)	3.70 (2.5–5.0)
Type of size	
<3 cm	50 (30.9%)
≥3 cm	112 (69.1%)
Growth pattern	
Single	44 (27.2%)
Multifocal	118 (72.8%)
Grade	
G1/2	10 (6.2%)
G3	152 (93.8%)
Pathological stage	
PTa/1	11 (6.8%)
PT2	28 (17.3%)
PT3	60 (37%)
PT4	63 (38.9%)
CIS	
Yes	4 (2.5%)
No	158 (97.5%)
LVI	
Positive	46 (28.4%)
Negative	116 (71.6%)
Types of cancer	
Urothelial carcinoma	158 (97.5%)
Adenocarcinoma	34 (21%)
Squamous cell carcinoma	23 (14.2%)
Sarcomatoid carcinoma	4 (2.5%)
Others	2 (1.2%)
Margin status	
Negative	135 (83.3%)

Table 1 (*Continued*)

Table 1 (*Continued*)

Features	Data
Positive	27 (16.7%)
Location	
Lateral wall	96 (59.3%)
Posterior wall	35 (21.6%)
Anterior wall	27 (16.7%)
Trigone	72 (44.4%)
Dome	17 (10.5%)
bladder neck	16 (9.9%)
Metastatic features	
Synchronous	62 (38.3%)
Metachronous	100 (61.7%)
Local recurrence	
Yes	56 (34.6%)
No	106 (65.4%)
Lymph node metastasis	94 (58%)
Only lymph node metastasis	18 (11.1%)
Visceral metastasis	
Lung	53 (32.7%)
Bone	33 (20.4%)
Liver	39 (24.1%)
Prostate	37 (22.8%)
Brain	3 (1.9%)
Others	81 (50%)
Number of visceral metastasis	
0	15 (9.3%)
1	69 (42.6%)
2	44 (27.2%)
≥3	34 (21%)
Lymph node dissection	
Yes	123 (75.9%)
No	39 (24.1%)
Removed lymph node	
Mean ± SD (range)	8.42±5.45 (1–32)

Table 1 (*Continued*)

Table 1 (*Continued*)

Features	Data
Positive lymph node	
Mean ± SD (range)	2.47±2.09 (1–11)
LND	
Median (IQR)	25 (11.1–58.8)
Bilateral positive lymph node	
Yes	21 (17.1%)
No	102 (82.9%)
MFI (months)	
<12	110 (67.9%)
12–24	19 (11.7%)
24–36	10 (6.2%)
36–48	9 (5.6%)
48–60	8 (4.9%)
≥60	6 (3.7%)

IQR, interquartile range; CT, computer tomography; MRI, magnetic resonance imaging; GP, gemcitabine and cisplatin; Gemox, gemcitabine and oxaliplatin; TS, paclitaxel and tiggio; M-VAC, methotrexate; vinblastine; doxorubicin; and cisplatin; TP, paclitaxel and cisplatin; TC, paclitaxel and carboplatin; GA, gemcitabine and epirubicin; GTC, gemcitabine; paclitaxel and cisplatin. LVI, lymphovascular invasion. LND, Lymph node density; SD, standard deviation; MFI, metastasis-free interval.

Since the 1990s, minimally invasive surgery, represented by laparoscopy, has begun to spread. However, two studies published in the *New England Journal of Medicine* in 2018 indicate that survival rate and no recurrence rate were significantly better in the open group than in the minimally invasive group (10,11). Similarly, our study corroborated that open surgery is an independent favorable factor for CSS and OS. Some scholars believe that laparoscopic surgery needs to fill the abdominal cavity with carbon dioxide when establishing an artificial pneumoperitoneum, which will promote the proliferation and metastasis of cancer cells (12).

Infiltration of tumor cells into blood vessels or lymphatic vessels is an important step in tumor transmission because these pathways provide access to distant organs (13). Similar to previous studies (13,14), ours proved that positive LVI is

Table 2 The multivariate analysis of metastasis-free interval

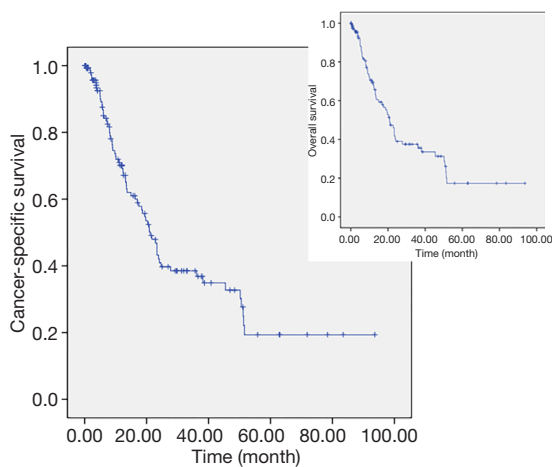| Variable	Category	HR	95% CI	P value
Smoking history	1 = Yes, 2 = No	1.54	1.13–2.12	0.007
Pathological stage	PTa-2 *vs.* PT3-4	2.08	1.43–3.02	<0.001
Adenocarcinoma	Yes = 1, No = 0	1.49	1.00–2.20	0.048
Margin status	Positive = 1, Negative = 2	1.99	1.30–3.05	0.002

HR, hazard ratios.

Figure 1 The CSS and OS rates of the metastatic bladder cancer patients assessed through Kaplan-Meier curves. CSS, cancer-specific survival; OS, overall survival.

an independent factor of poor prognosis for OS. However, the prognosis and clinical application of LVI are still controversial and further research is needed to prove the practical value of LVI in clinical decision-making.

Resembling previous studies (7,15), our study indicated that liver metastasis is a disadvantage for prognosis. This may be explained by the loss of general immune infiltration accompanied by the loss of PD-1 and PD-L1 on immune cells commonly in liver metastases (57%) (16). In addition, our study demonstrated that patients with local recurrence were more prone to lymph node and visceral metastasis, which affected the patients' prognoses.

Surprisingly, we found that the risk of visceral metastasis in pT4 was higher than that in pT3, but the risk of death in pT4 was lower than that in pT3. We believed that this may be due to the limited effect of metastasectomy or chemoradiation, and that some patients did not even undergo relevant treatment after metastasis. On the other hand, parts of metastases in

pT4 were limited in locality and were treated with RC. Therefore, the prognosis of patients with pT4 is highly variable. Although 56% of patients die of metastatic disease within 2 years after surgery, 32% of patients have no disease recurrence within 10 years after surgery (13). Consequently, subgroup analysis of pT4 patients ensued. The estimated CSS rates (SE) at 1 year, 3 years, and 5 years were 88% (6%), 50.6% (8.2%), and 24% (8.5%), severally; and this result was similar to that in a previous study (17). In a multivariate analysis, multifocality of primary tumors, margin-positiveness, local recurrence, and liver metastasis were detrimental to CSS, while lateral wall and local treatments of metastases were beneficial to CSS. The prognosis of female patients was worse than that of male patients, but the difference was not statistically significant (P=0.337), which is probably due to the small sample size (only 8 female cases).

Similar to some previous studies (15,18), patients with positive margins had a worse prognosis. Positive margins may be attributed to immature surgical techniques, inappropriate specimen handling or processing process, inaccurate pathological assessment and inadequate dissection extent; while extensive exfoliation of soft tissue around the bladder may result in negative margins (13).

Furthermore, our study also found that OS was correlated with the age at which patients were transferred. The risk of death for older-than-63 patients was 1.87 times higher than that of their younger-than-63 counterparts (P=0.039). We believe this is a result of the late onset of bladder cancer and the natural lifespan of human beings.

Previous studies showed that perioperative chemotherapy and RC can significantly improve the survival outcomes of patients (19,20). However, our study did not certify that the number of lymph nodes removed, the number of positive lymph nodes, or LND were associated with the prognosis of patients. We presumed that it was caused by insufficient lymph node dissection and visceral metastasis. Besides, the risk of LNM, a disadvantage of CSS and OS in a univariate

Table 3 The multivariate analysis of cancer-specific survival and overall survival

Variable	Category	HR	95% CI	P value
Cancer-specific survival				
Local recurrence	Yes = 1, No = 0	2	1.15–3.48	0.014
Pathological stage	PT3 *vs.* PT4	2.23	1.28–3.88	0.005
Liver metastasis	Yes = 1, No = 0	2.72	1.47–5.04	0.001
Surgical approach	Open = 1, mini-invasive = 2	2.3	1.12–4.74	0.023
Overall survival				
LVI	positive = 1, negative = 2	2.17	1.26–3.76	0.006
Pathological stage	PT3 *vs.* PT4	2.15	1.24–3.71	0.006
Local recurrence	Yes = 1, No = 0	2.23	1.28–3.89	0.005
Liver metastasis	Yes = 1, No = 0	2.17	1.19–3.95	0.012
Age at metastasis	<63 = 0, ≥63 = 1	1.87	1.03–3.37	0.039
Surgical approach	Open = 1, mini-invasive = 2	2.2	1.08–4.47	0.029

LVI, lymphovascular invasion.

analysis, was higher in MIBC than that in NMIBC. Therefore, we believed that pelvic lymphadenectomy was an important part of RC.

Some studies have shown that there is a disconnect between clinical trials and real-world treatment, which lacks in the standard 2-line treatment (21,22). Similarly, our study found that only 21.0% of patients received adjuvant chemotherapy, and 24.1% of patients chose post-metastatic chemotherapy. Gemcitabine and cisplatin are the most commonly used and second-line chemotherapy is uncommon. Additionally, the beneficial effect of neoadjuvant chemotherapy (NAC) on survival was established by level 1 evidence (23). However, mere 1.4–11% patients undergoing RC received NAC (24). Similarly, only 2 patients received NAC in our study. Interestingly, the survival advantage of NAC before RC remains controversial in current real-world practice (25).

There are some limitations in this study. First of all, the inherent limitations of retrospective studies are inevitable; Second, although we have found features that contribute to the stratification of prognosis in patients with MBC, we do not recommend discontinuation of adjuvant therapy and post-metastatic adjuvant therapy in patients with MBC. Because only a few patients receive postoperative chemotherapy in our study, the role of postoperative chemotherapy remains controversial. Third, surgery can be considered if necessary, but we cannot make relevant conclusions. In a subgroup analysis of pT4, we found that local treatment of metastases, including surgery, can improve patients' CSS. At last, the LNM rate of pT3 is higher than that of pT4, while the risk of visceral metastasis of pT4 is higher than that of pT3.Further studies are needed to investigate the relationship and mechanism between them.

Conclusions

Our study suggests that smoking history, positive margins, and pT3 or more advanced tumors in patients with MBC are more likely to be connected with metastasis. Besides, patients with minimally invasive surgery, local recurrence, and liver metastases are at greater risk of death from bladder cancer; Additionally, we should try to avoid the disconnections between clinical trials and realistic treatment. Taken together, our study provides data support for optimal management of patients with MBC in current real-world practice in western China.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study and disclaimer of informed consent were approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (No. 2020366).

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Table S1 Factors associated with LNM

Variables	Number	LNM (%)	χ^2 value	P value	OR	95% CI	Cramer's V (P value)
NMIBC	11	9.10	9.547	0.002	16.03	2.00–128.556	Phi=0.268 (0.001)
MIBC	151	61.60					
PT2	28	46.40	12.089	0.002			0.283 (0.002)
PT3	60	78.30					
PT4	63	52.40					
PT2 *vs.* PT3			8.958	0.003	4.17	1.59–10.94	Phi=0.32 (0.003)
PT2 *vs.* PT4			0.275	0.6			Phi=0.055 (0.6)
PT3 *vs.* PT4			9.103	0.003	0.3	0.14–0.67	Phi=0.272 (0.004)
Low grade	10	50.00	0.04	0.84	1.41	0.39–5.09	0.042 (0.596)
High grade	152	58.60					
Trigone	72	59.70	0.153	0.7			
Local recurrence	56	69.60	4.743	0.03	2.13	1.07–4.22	0.17 (0.03)
No Local recurrence	106	51.90					
Lymph node dissection	123	62.60	4.394	0.04	2.17	1.04–4.50	0.17(0.04)
No lymph node dissection	39	43.60					

LNM, lymph node metastasis; OR, odds ratio; NMIBC, non-muscle invasive bladder cancer; MIBC, muscle invasive bladder.

Table S2 Factors associated with visceral metastasis

Variable	Number	Visceral metastasis (%)	χ^2 value	P value	OR	95% CI	Cramer's V v (P value)
PT2	28	89.30	6.447	0.03			0.204 (0.037)
PT3	60	83.30					
PT4	63	96.80					
PT2 vs. PT3				0.68			
PT2 vs. PT4				0.17			
PT3 vs. PT4			6.354	0.012	6.1	1.28–29.13	0.23 (0.012)
Local recurrence	56	98.20	5.69	0.02	8.37	1.07–65.41	0.19 (0.02)
No local recurrence	106	86.80					
Lymph node metastasis	94	84	11.958	0.001			0.27 (0.001)
No lymph node metastasis	68	100					
Lymph node dissection	123	88	3.89	0.049			0.18 (0.022)
No lymph node dissection	39	100					
Bone metastasis							
PT2	28	35.70	6.422	0.04			0.21 (0.04)
PT3	60	23.30					
PT4	63	12.70					
PT2 vs. PT3				0.22			
PT2 vs. PT4			6.471	0.01	0.26	0.09–0.76	0.27 (0.01)
PT3 vs. PT4				0.12			
Liver metastasis							
PT2	28	42.90	8.789	0.01			0.241 (0.01)
PT3	60	25.00					
PT4	63	14.30					
PT2 vs. PT3				0.09			
PT2 vs. PT4			8.914	0.003	0.22	0.08–0.62	0.31(0.003)
PT3 vs. PT4				0.13			
Lymph node metastasis							
LVI							
1	69	18.80	6.066	0.048			0.203 (0.048)
2	44	36.40					
3	34	38.20					
1 vs. 2			4.324	0.04	0.41	0.172–0.961	0.20 (0.038)
1 vs. 3			4.54	0.03	0.375	0.15–0.94	0.21 (0.03)
2 vs. 3				0.865			
Local recurrence							
1		23.2	13.244	0.001			0.3 (0.001)
2		43.2					
3		58.8					
1 vs. 2			5.023	0.03	0.4	0.18–0.90	0.211 (0.03)
1 vs. 3			12.722	<0.001	4.73	1.96–11.44	0.35 (0.000)
2 vs. 3				0.17			
Lymph node metastasis							
1		36.20	20.212	P<0.001			0.371 (<0.001)
2		59.10					
3		82.40					
1 vs. 2			5.669	0.017	2.542	1.17–5.523	0.224 (0.017)
1 vs. 3			19.396	P<0.001	8.213	2.994–22.532	0.434 (<0.001)
2 vs. 3			4.872	0.027	3.231	1.111–9.391	0.25 (0.027)

LVI, lymphovascular invasion.