WITHDRAWN: Analysis of prognostic factors for recurrence and metastasis sites of high-grade upper tract urothelial carcinoma

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Abstract

Purpose: Metastatic recurrence takes place in more than 21.7% of patients with UTUC underwent RNU. Although metastatic recurrence suggested a poor prognosis, the effect of the specific recurrence site on prognosis is still to be discussed.

Methods: According to a retrospective analysis on 355 patients who underwent RNU for high-grade, node-negative upper urothelial carcinoma in our hospital from 2010 to 2020. The result showed that no one received neoadjuvant or adjuvant chemotherapy. So, Univariate and multivariate Cox regression analyses were then performed to assess predictors of metastatic recurrence as well as site-specific prognosis. In addition, Kaplan-Meier method and log-rank test were adopted for the estimation and comparison of the recurrence site-specific survival probabilities after metastatic recurrence.

Results: Of 355 patients, 77 recurred during a median follow-up of 17 months. In multivariate analysis, IVR, tumor size, and pT-stage were significant predictors of metastatic recurrence. Metastatic recurrence was most common in bone and multiple sites, with less median survival time for liver recurrence and multiple site recurrence.

Conclusion: A majority of patients with high-grade UTUC suffered from systematical recurrence after RNU. IVR, tumor size, and pT-stage are predictors of metastasis and recurrence. Besides, prevention of IVR after RNU may help improve the prognosis of patients with UTUC. Poor prognosis showed compared with other sites, liver, bone and multiple sites relapse relatively quickly. These findings are of great likelihood to contribute to the development of future site-specific treatment plans for recurrence. Plus, studying the genetic association of UTUC and elucidating the underlying mechanism of metastasis recurrence must be of paramount importance.

Introduction

Upper tract urothelial carcinoma (UTUC), as a rare malignant tumor, accounts for about 5-10% of all urothelial carcinomas, with poor prognosis[1], although urothelial carcinoma is the fourth most common tumor type[2]. Radical nephroureterectomy (RNU) with bladder cuff excision is the golden standard for the treatment of non-metastatic UTUC[3]. Postoperative adjuvant chemotherapy (AC) or neoadjuvant chemotherapy(NAC) were the primary solution for the treatment of postoperative recurrence and distant metastasis in patients with UTUC[4]. For the past few years, the diagnostic accuracy and surgical resection accuracy of UTUC have been evidently improved, but the survival prognosis of patients with UTUC has not been significantly modified[5]. Meanwhile, the high postoperative recurrence rate and distant metastasis rate have put much pressure on patients with UTUC. So far, the prognostic factors that affect patients' survival in metastatic UTUC has not been fully understood due to the lack of studies concerning the prognosis of metastatic UTUC patients and the limited number of cases of single institutional cohort. Nonetheless, we figured out the effects of different distant metastases in metastatic cancer in other types of cancer[6, 7]. One of the studies on metastatic bladder cancer showed that bone,

liver, lung, and brain metastases were associated with poor overall survival (OS) and cancer-specific survival (CSS) in patients with this cancer[8]. Based on this evidence, we inferred that organ-specific metastasis may also play a different role in the prognosis of patients with metastatic advanced UTUC. But this hypothesis remains to be tested.

The present study aims to comprehensively explore the organ-specific metastasis of advanced UTUC patients after RNU and the influence of the number of metastatic organs on the prognosis of patients with metastatic UTUC. It was assumed that the specific site of recurrence is related to poorer prognosis as measured according to recurrence to death duration. To this end, gaining a better understanding of the timing and site of systemic metastasis recurrence may do a great favor in customizing treatment plans for patients with high-grade UTUC after RNU.

Table 1 Clinicopathologic characteristics of high-grade, node-negative UTUC patients who did and did not recur systemically after underwent RNU without AC or NAC

Parameters	*Total*	*Recur*	*Did not recur*	*P value*
Number of patients, n (%)	355(100)	77(21.7)	278(78.3)	-
Median age (IQR) (years)	67[33-89]	66[37-84]	67[33-89]	0.467
Follow-up (IQR) (months)	45.2[3-140]	17[6-101]	52.4[3-140]	**<0.0001**
Sex, Male, n (%)	184(51.8)	52(67.5)	132(47.5)	**0.002**
BMI, ≥ 28, n (%)	36(10.1)	7(9.1)	29(10.4)	0.73
Smoking history, n (%)	109(30.7)	27(35.1)	82(29.5)	0.349
Family history of cancer, n (%)	26(7.3)	9(11.7)	17(6.1)	0.097
Prior or concomitant BC, n (%)	65(18.3)	25(32.5)	40(14.4)	**<0.0001**
IVR, n (%)	45(12.7)	14(18.2)	31(11.2)	0.101
Hydronephrosis, n (%)	256	66(25.8)	190(74.2)	**0.003**
Multifocality, n (%)	72(20.3)	29(37.7)	43(15.5)	**<0.0001**
LVI, n (%)	44(12.4)	37(48.1)	7(2.5)	**<0.0001**
RNU approach, Open, n (%)	140(39.4)	46(59.7)	94(33.8)	0.053
Tumor size,≥2 cm, n (%)	273(76.9)	67(87)	206(74.1)	**0.017**
Tumor side, Left, n (%)	173(48.7)	38(49.4)	135(48.6)	0.902
Tumor location, n (%)				0.003
Renal pelvis	178(50.1)	29(37.7)	149(56.6)	
Ureteral	150(42.3)	36(46.8)	114(41)	
Both	27(7.6)	12(15.6)	15(5.4)	
pT-stage, >T2,n (%)	168(47.3)	62(80.5)	106(38.1)	**<0.0001**
Renal function status				**0.009**
eGFR ≥ 60 (mL/min/1.73 m²)	225(63.4)	39(50.6)	186(66.9)	
eGFR < 60 (mL/min/1.73 m²)	130(36.6)	38(49.4)	92(36.6)	
Cr≥133μmol/l, n (%)	26(7.3)	11(14.3)	15(5.4)	**0.008**

eGFR=estimated glomerular filtration rate; BC=bladder cancer; LVI=lymph vascular invasion; IVR= intravesical recurrence；IQR = interquartile range

Table 2 Univariate and multivariate Cox regression analyses for evaluating the risk of recurrence and metastasis of high-grade, node-negative UTUC.

	Univariate		*Multivariate*	
Characteristic	HR (95% CI)	*P value*	HR (95% CI)	*P value*
Age	0.98(0.96-1.01)	0.148	-	-
Sex, male	0.98(0.61-1.60)	0.94	-	-
BMI ≥ 28	1.57(0.71-3.48)	0.265	-	-
Smoking history, yes	1.05(0.65-1.69)	0.848	-	-
Family history of cancer, yes	0.62(0.31-1.27)	0.192	-	-
LVI, yes	0.76(0.48-1.21)	0.248	-	-
Prior or concomitant BC, yes	1.27(0.78-2.07)	0.341		
Hydronephrosis, yes	1.72(0.89-3.29)	0.104	-	-
IVR	2.49(1.35-4.61)	**0.004**	2.17(1.14-4.13)	**0.018**
Multifocality, yes	0.94(0.59-1.51)	0.811	-	-
Tumor size ≥ 2 cm	0.51(0.26-1.00)	**0.049**	0.39(0.19-0.79)	**0.009**
Tumor side, Left	0.85(0.54-1.33)	0.471	-	-
Tumor location	-	0.378	-	-
Ureteral vs. Renal pelvis	0.76(0.47-1.26)	0.296	-	-
Both vs. Renal pelvis	1.15(0.59-2.29)	0.665	-	-
pT-stage,□T2	2.56(1.37-4.81)	**0.003**	2.36(1.22-4.56)	**0.011**
RNU approach, Laparoscope	1.14(0.72-1.81)	0.568	-	-
eGFR < 60 (mL/min/1.73 m²)	0.84(0.53-1.32)	0.443	-	-
Cr≥133μmol/l	1.09(0.56-2.14)	0.798	-	-

Methods

Patient population and data collection

UTUC patients who received RNU treatment in Harbin Medical University Cancer Hospital from 2010 to 2020 were identified. Exclusion criteria for this study were: Patients with metastasis before RNU, patients with multiple primary tumors at the same time, and patients receiving any adjuvant or neoadjuvant chemotherapy before surgery were excluded. All pathological specimens were reviewed by experienced urogenital pathologists in our hospital. The study population was limited to patients with high-grade node-negative disease in surgical pathology. Surgical criteria for RNU include regional lymphadenectomy and removal of any other clinically suspicious lesions.

Indicators included in this study: Age, sex, BMI, smoking history, family history of cancer, prior history of bladder cancer, estimated glomerular filtration rate eGFR), pathological tumor stage, tumor site (renal pelvis or ureter), tumor side, tumor size, pathologic lymph node status (PN0-PNx or PN+), multifocality, preoperative hydronephrosis, lymphovascular invasion (LVI), intravesical recurrence (IVR) and surgical type. All patients were followed up at least every 3 to 6 months after RNU. Data on metastatic recurrence were collected from previous medical records of patients in our hospital, and the primary site and date of metastatic recurrence of patients with disease recurrence were confirmed by imaging or biopsy. When diagnosing a recurrence, note if the patient has a recurrence in more than one location. In this study, IVR was not identified as systemic recurrence.

Statistical analyses

All analyses were performed using IBM SPSS Statistical version 26.0(IBM, Armonk, New York, USA) or GraphPad version 9.0. Univariate and multivariate Cox regression analysis were used to evaluate the prognosis of tumor site specific, and to evaluate the relationship between tumor specific time of death and primary site recurrence. Kaplan-Meier and log-rank tests were used to estimate and compare recurrence site-specific survival probabilities. Survival was measured from the date of recurrence to the date of cancer-specific death or last follow-up; If patients did not die from UTUC, they were reviewed at the last follow-up. P values <0.05 were considered statistically significant.

Result

A total of 355 patients met the inclusion and exclusion criteria, and the baseline data of the patients were shown in Table 1. The median age of RNU was 67 years with a median follow-up of 45.2 months. 77 patients (27.1%) in the cohort had metastatic disease recurrence, 273 patients (76.9%) had disease at tumor size≥2cm and 168 patients (47.1%) had disease at pT2-stage or higher. Sex, hydronephrosis, history of bladder cancer, multifocality, tumor size, renal function status, Cr, pT-stage and LVI of patients with and without recurrence were differences in baseline characteristics (Table 1).

Univariate and multivariate cox regression analysis showed that tumor size, pT-stage, and intravesical recurrence (IVR) were independently and significantly associated with an increased risk of metastatic recurrence (all P <0.05)(Table 2).

Primary sites of recurrence of UTUC metastasis in our cohort included liver, bone, brain, lymph node, lung, or multiple sites (a combination of several sites) (Figure 1). Of 77 patients with systemic recurrence, 20 (26%) had multiple recurrences when first diagnosed; Figure1 and Table3 summarize the site-specific median time to recurrence. The median time to multiple site recurrence was significantly shorter than 7.5 months (IQR 2-34 months). Metastatic recurrence in bone, liver, and multiple sites was significantly associated with worse prognosis compared with other sites (Log-rank, P < 0.001; In addition, Cox regression analysis showed that bone (HR = 2.62 [95%CI: 1.80-10.21], P=0.001), liver (hazard ratio [HR] 4.29 [95%CI: 1.80-10.21], P=0.001), and multiple sites (HR = 4.53 [95% CI: 2.13-9.62], P<0.001) were significantly more likely to die from UTUC than patients with lymph node recurrence (Figure 3). Of 77

patients, 38 (49.3%) were eligible for salvage systemic therapy (Good renal function), of which 26 (68.4%) received chemotherapy. 8 (21%) received radiotherapy and 4 (10.6%) received immunotherapy. The statistical significance persisted after salvage treatment. Multivariate analysis of cancer-specific survival was not possible due to the small sample size.

Table 3 Time to death after recurrence, time to recurrence, and survival probabilities after recurrence for each primary site of metastatic recurrence in patients with high-grade UTUC.

Recurrence site	*Before recurrence*		*After recurrence*	
	Median time to recurrence [IQR] (months)	Median time to cancer-specific death [IQR] (months)	6-month survival probability	1-year survival probability
Lymph nodes	10[3-75]	10[5-26]	80%	46.7%
Lungs	11.5[3-32]	7[3-18]	50%	30%
Liver	15[3-59]	5[2-7]	36.3%	9.1%
Bone	12[2-76]	5.5[2-14]	38.8%	11.1%
Brain	38[9-41]	9[5-24]	66.7%	33.3%
Multiple sites	7.5[2-34]	4[1-11]	20%	5%

IQR = interquartile range

Fig.1. **Distribution of metastatic recurrences by primary site, along with site-specific median time to recurrence and median time to death, in patients with high-grade UTUC. Trecur = median time to recurrence; Tdeath = median time to cancer-specific death after developing recurrence.**

Discussion

At present, only a single-center study and a SEER database based to assess the impact of organ-specific metastasis on the outcome of patients with systemic recurrence after local UTUC treatment[9, 10]. Since there are few studies in this direction, we doubled the sample size for further verification.

In this study, multivariate Cox regression showed that IVR, tumor size, and pT-stage played the role of independent predictors of metastatic disease recurrence after high grade UTUC after RNU. At the same time, it was found that that the liver, bone and multiple site recurrence of patients with UTUC seemed to be related to with rapid onset and poor prognosis. Also, the multiple site recurrence of UTUC patients combined with several sites had the fastest onset and worst prognosis. Lymph node, brain and lung recurrence had a longer onset and better prognosis when compared with other sites. As some previous studies have concluded, analysis of clinical and pathological features suggested that tumor size and

pathological stage can predict recurrence. Evidence has shown that IVR was one of the strongest predictors of metastatic recurrence after RNU. Studies have shown that postoperative prevention of IVR by RNU may reduce the progression rate of muscle-invasive bladder cancer, thus improving the prognosis of patients with UTUC. Studies have shown that postoperative prevention of IVR by RNU may reduce the progression rate of muscle-invasive bladder cancer, thus improving the prognosis of patients with UTUC[11].

It is worth mentioning that, based on our data, LVI did not affect the recurrence of metastatic disease after RNU. However, LVI has been shown to be relevant to poor CSS in UTUC[12]. Also, LVI was not evaluated in a population-based study[11]. The type of surgery was irrelevant to the recurrence of UTUC patients after RNU, even though studies have shown that minimally invasive surgery was superior to open surgery in terms of the prognosis of urinary tract tumors[13].

The role of the site of organ metastasis in predicting patient survival has been gradually revealed in prostate cancer[6], renal cell carcinoma[14], and bladder urothelial carcinoma and other many types of cancer[15]. Liver and bone recurrence has something to do with poor prognosis for a variety of tumors, such as metastatic renal cell carcinoma urothelial, carcinoma of the bladder. Bone recurrence showed a poor prognosis in breast cancer[16], and liver recurrence has a poor prognosis in colorectal cancer[17]. Studies have shown that rapid recurrence of UTUC after RNU[18], in general, has something to do with poorer prognosis, similar to what we found in UTUC. In addition, it has been found that brain recurrence was subtler than other recurrence sites, lymph node recurrence have a higher survival rate, and they may be associated with a relatively better prognosis.

Currently, the therapeutic effects of UTUC metastasis sites are unknown, and details about chemotherapy, radiotherapy, and targeted therapies are lacking. However, different site-specific prognoses suggest that different sites of metastasis may respond in different ways to treatment.

It is believed that UTUC has a relatively low risk of recurrence in lung, brain and lymph nodes and intensive treatment strategies may improve the prognosis, while active treatment for liver, bone and multi-site metastases may have limited benefits for patients. The present study suggests a tendency that the location of organ metastasis in UTUC may influence the outcome of patients with relapse even though it’s not necessarily appropriate to guide clinical treatment decisions. Hence, these findings need to be supported by genetics. Exploring genetic association of recurrence sites of UTUC and the factors determining metastasis at specific sites may also be a great help. Unearthing these underlying mechanisms may help identify targets and treatment options that are beneficial to patients.

Our study has several limitations. First, the present study is a retrospective one with a sample from a single institution, prone to selection bias. Second, it lacks standardization of the remedial systemic care patients receive (often the physician empirically decides on chemotherapy, immunotherapy, or radiation). Third, surgical techniques vary from patient to patient. (we did not select patients from the same group of physicians because of the rarity of UTUC) Nevertheless, this is one of the largest single-center studies to investigate the effect of organ-specific metastasis on the outcome of UTUC in the presence of the rarity

of UTUC. In the future, collaboration between multi-institutional research teams will be particularly crucial in order to better understand this phenomenon.

Conclusion

Approximately 21.7% of these patients with advanced UTUC treated with RNU suffered from systemic recurrence. Besides, IVR is a predictor of metastatic recurrence in this population, and prevention of IVR after RNU may be conducive to improving the prognosis of patients with UTUC. It's noteworthy that results showed that the recurrence of liver, bone and multiple sites of UTUC was relatively fast and the prognosis was poor, while the recurrence of lung, brain and lymph nodes of UTUC was relatively slow and the prognosis was hidden. In addition, these findings in our study are of paramount values for the specific treatment plans for recurrence sites as it is, meanwhile, critical to investigate the genetic association of UTUC and elucidate the underlying mechanisms of metastasis recurrence.

Declarations

Authors contribution *Jianing Gao* and *Dexin Ding* contributed to protocol/project development, data collection, data analysis and manuscript writing/editing

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Conflict of interest No

Ethical standards We affirm that all authors have complied with the principles of the journal of *UROLOGIA INTERNATIONALIS* regarding ethical responsibilities of authors and compliance with ethical standards.

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Figures

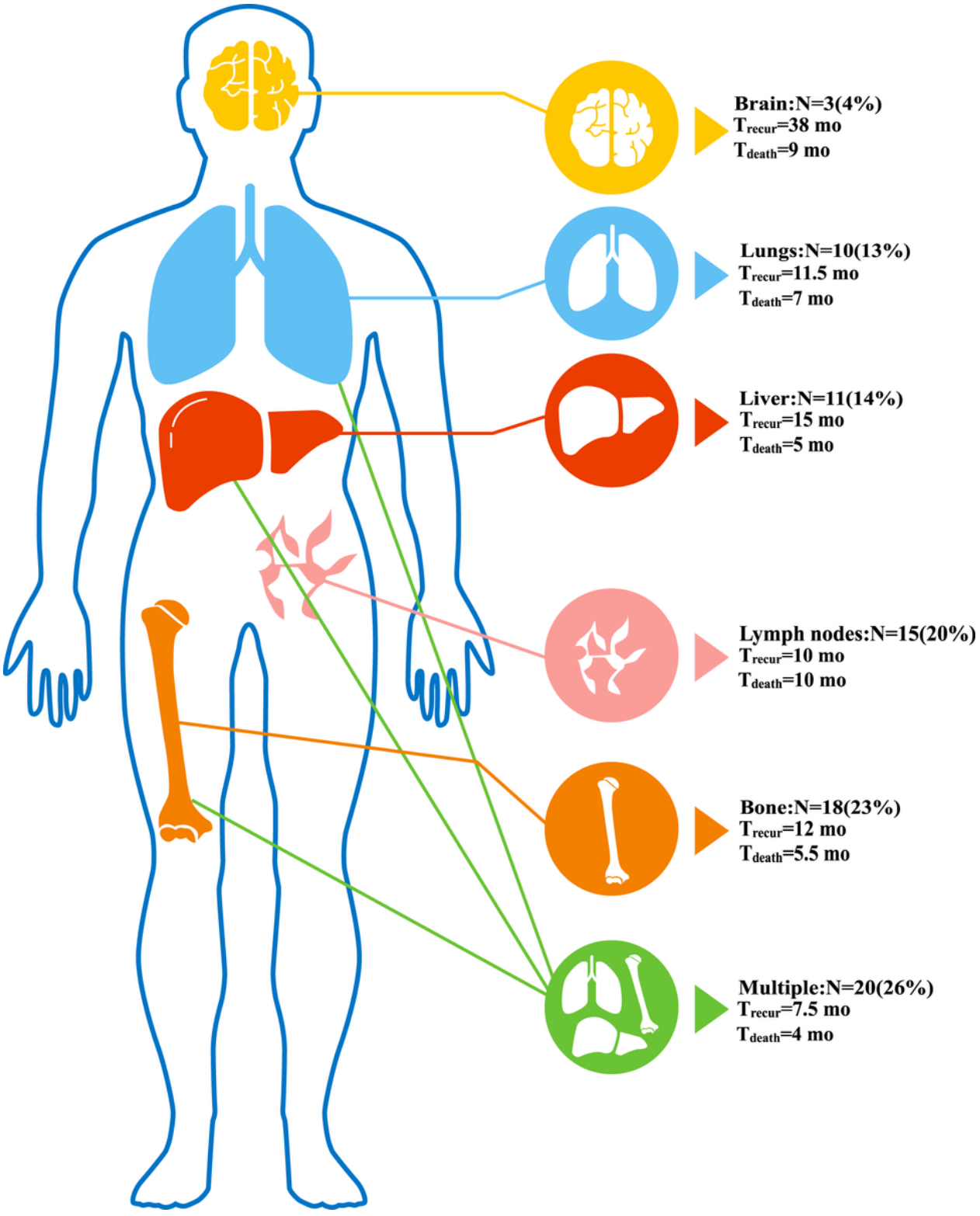

Figure 1

Distribution of metastatic recurrences by primary site, along with site-specific median time to recurrence and median time to death, in patients with high-grade UTUC. Trecur = median time to recurrence; Tdeath = median time to cancer-specific death after developing recurrence.

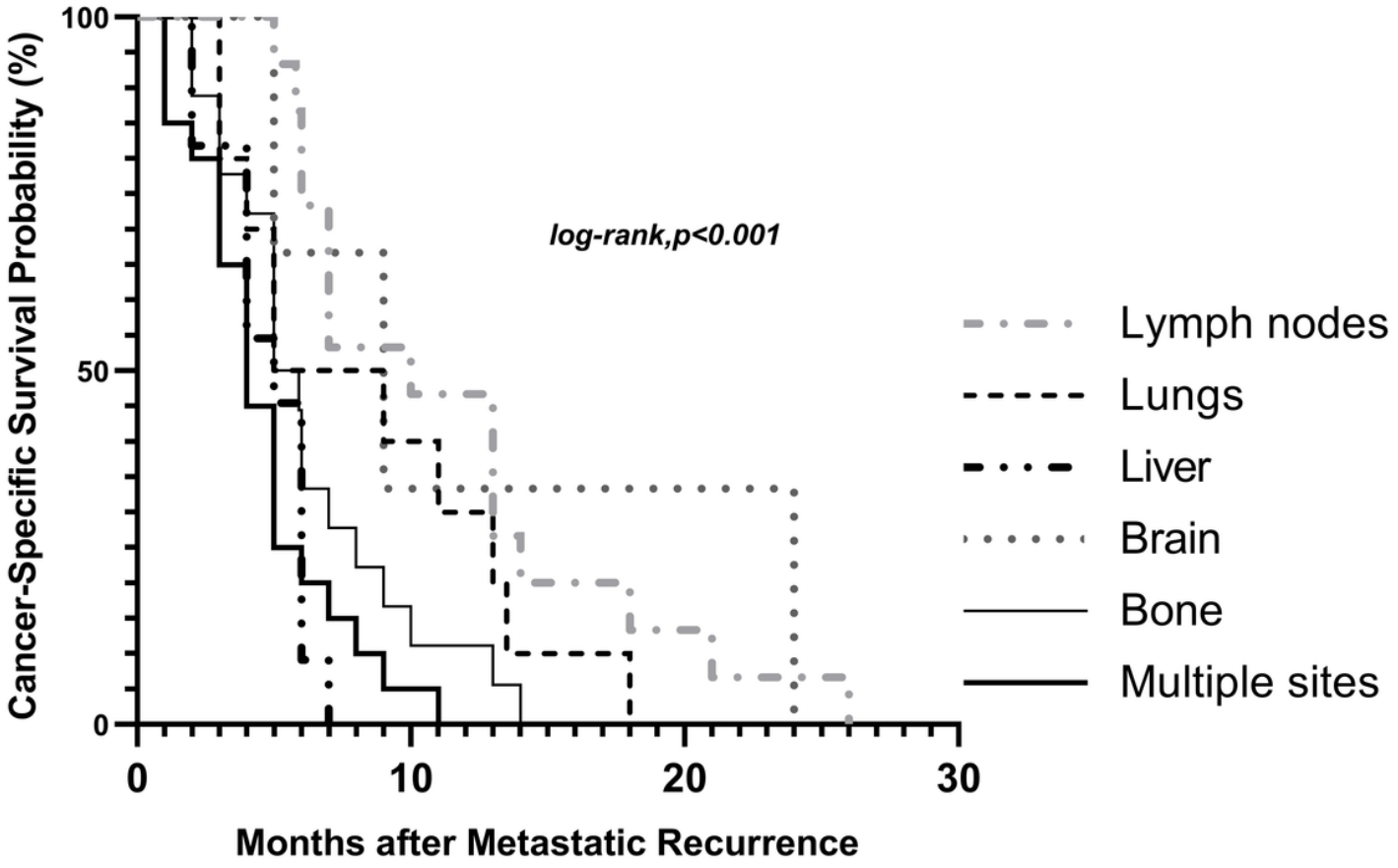

Figure 2

Kaplan-Meier plot of CSS after recurrence by primary site of recurrence in patients with high-grade UTUC.

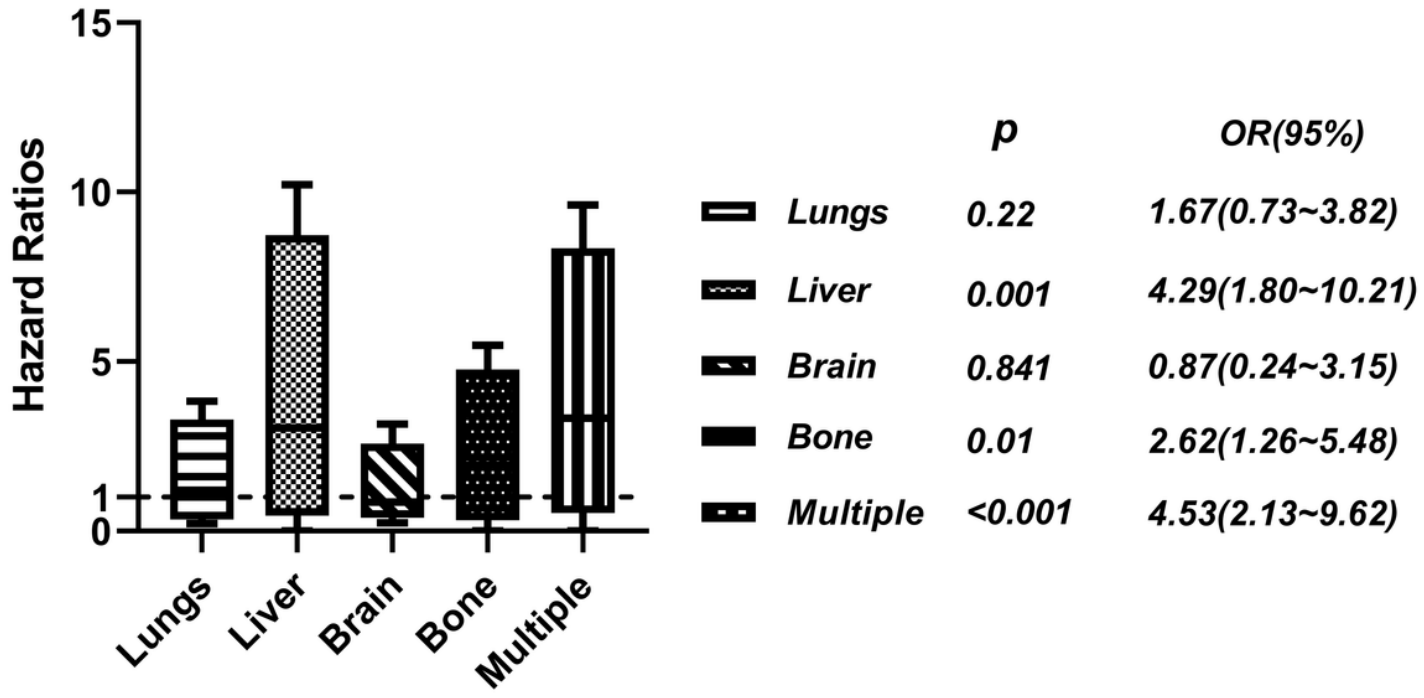

Figure 3

Forest plot showing hazard ratios of CSS for different primary sites of metastatic recurrence compared to lymph nodes in patients with high-grade UTUC.