Modified Cancer TNM Classification for Localized Renal Cell Carcinoma based on the Prognostic Analysis of 3748 Cases from a Single Center

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Research

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Abstract

Background The optimal cutoff point for evaluating the prognosis of localized renal cell carcinoma remains unclear. The study aimed to verify the efficacy of tumor diameter in the 2010 AJCC TNM staging system and put forward modification for TNM staging on the prognosis.

Methods 3748 patients with localized renal cell carcinoma were enrolled and grouped according to the 2010 AJCC TNM staging system. COX analysis was used to stratify the prognosis and optimal cutoff point of the tumor diameter in the T1 and T2 prognosis was explored.

Results 3330 (88.9%) were in stage T1 and 418 (11.1%) were in stage T2. The cancer-specific mortality rate was 2.7% (100/3748). Mean follow-up was 49.8 months. The analysis of tumor diameter at 7 cm can greatly determine the prognosis of patients at stages T1 and T2. However, the tumor diameters of 4.5 and 11 cm set as the cutoff points for T1 and T2 subclassifications of patients with LRCC seemed to have better recognition ability than 4 and 10 cm, respectively.

Conclusions The 2010 AJCC TNM stage can greatly predict the prognosis of LRCC in stages T1 and T2. In addition, 4.5 and 11 cm might be optional cutoff points for the tumor diameters for subclassifying stages T1 and T2.

Background

Renal cell carcinoma (RCC) accounts for 2%-3% of malignant tumors and 80%-90% of malignant kidney tumors in adults. The morbidity of RCC increases yearly and varies in different countries or regions ^[1-4]. In 2014, 68 300 new cases of kidney cancer are reported in China, and the morbidity is 4.99 per 100 000. The morbidity of RCC increases significantly compared with the past ^[5-7]. The TNM staging system formulated by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer is widely applied in the clinical treatment of RCC. The TNM staging is closely related to the clinical treatment outcome prediction, treatment options, and tumor-specific mortality ^[1,8-12]. With the progress of clinical research and changes in surgical methods, the TNM staging needs to be continuously revised ^[1, 13, 14]. The single standard for the staging of the localized RCC (LRCC, T1-2N0M0) is the tumor diameter. In the past 20 years, 7 cm is regarded as the staging cutoff point for T1N0M0 (T1) and T2N0M0 (T2), 4 cm serves as the cutoff point for T1aN0M0 (T1a) and T1bN0M0 (T1b), and 10 cm serves as the cutoff point for T2aN0M0 (T2a) and T2bN0M0 (T2b), which are widely applied in clinical treatment. Clinical studies have found that the optimal cutoff point for evaluating the prognosis of LRCC remains unclear ^[1, 15]. This study aimed to verify the efficacy of tumor diameter in the 2010 AJCC TNM staging system and put forward modification for TNM staging on the prognosis.

Methods

Inclusion and exclusion criteria

The data on the diagnosis and treatment of patients with renal carcinoma (4167 cases) diagnosed and operated at the Single Center of Urology Department of the PLA General Hospital from January 2008 to September 2016 were collected and analyzed. The patients were screened in accordance with the inclusion and the screening criteria. The inclusion criteria (Fig. 1) were as follows: (1) confirmed to have LRCC in accordance with the 2010 AJCC TNM staging at T1-2N0M0; (2) received surgical treatment, radical resection, or partial nephrectomy; and (3) had complete medical history and pathological and follow-up data. The exclusion criteria were as follows: (1) imaging examination suggesting the presence of lymph nodes, local or distant metastases, or venous cancer thrombus; (2) complication with other malignant tumors; and (3) metastatic RCC.

Clinical data collection

The collection of clinical data is detailed in the literature^[16]. The pathological TMN staging of renal cell carcinoma recommended by AJCC in 2010^[8] and the grading standard of RCC (G: nuclear grade)^[17, 18] were adopted. According to 1997 WHO recommendation about nuclear grading of RCC which criteria we used, Fuhrman I and Fuhrman II were merged to well differentiated tumor (G1), and Fuhrman III was considered to be intermediate differentiated tumor (G2), and Fuhrman IV was considered to be poorly differentiated or undifferentiated tumor (G3)^[17]. In the event of two Fuhrman ratings, the higher grade was presented. Cancer-specific mortality (CSM) was used as the endpoint of follow-up observation.

Postoperative follow-up

The median follow-up time was 49.8 months (range: 3-103 months). The follow-up period was three months. The patients were followed up for more than six months at an interval of six months. The follow-up period ended on December 30, 2017. The patient underwent regular reexamination of abdominal ultrasound, pulmonary CT, liver and kidney function, and bone scan when necessary. Local tumor recurrence, distant metastasis, and death were included in the follow-up.

Statistical analysis

All data were analyzed using the SPSS13 and the MedCalc 11.4.2.0 software. All data were expressed as mean $\pm$ standard deviation. The t-test or one-way analysis of variance was used. The counting data was expressed as percentages, and the χ^2 or the Fisher's exact test was used for comparison between groups. The patients were classified in accordance with the 2010 AJCC TNM staging criteria, and CSM was used as the end for clinical observation. The COX regression analysis was used to analyze the predictive value and the difference of the prognosis of LRCC with different tumor diameter cutoff points. The hazard ratio (HR) and 95% confidence interval (CI) were used for risk assessment. $P < 0.05$ was considered statistically significant.

Results

A total of 3748 patients with LRCC were enrolled. The clinical data and characteristics are shown in Table 1. The median follow-up time was 49.8 months (range: 3-103 months). CSM was observed in 100 cases, and the overall mortality rate was 2.7%. A total of 292 cases were totally lost to follow-up, and the loss rate was 7.8%.

Table 1
Clinical and pathological characteristics

Parameters	General characteristics
Patients (n)	3748
Age (year)	52.29 ± 12.37 (0.9–86)
Sex (n, %)	
Men	2699 (72.0%)
Women	1049 (28.0%)
BMI (kg/m²)	25.36 ± 3.43
ASA scores	
I	675 (18.0%)
II	2826 (75.4%)
III	240 (6.4%)
IV	7 (0.2%)
Tumor distribution (n, %)	
Left	1859 (49.6%)
Right	1889 (50.4%)
Tumor diameter (cm)	4.38 ± 2.35 (0.6–23.4)
Surgical strategy (n, %)	
PN partial nephrectomy	1572 (41.9%)
RN radical nephrectomy	2176 (58.1%)
Operation method (n, %)	
Conventional Laparoscopy	3035 (81.0%)
Robot-assisted laparoscopy	474 (12.6%)
Open surgery	239 (6.4%)
Surgery approach	
Transabdominal	532 (14.2%)
Retroperitoneum	3216 (85.5%)

Note: *Nuclear grading according to Fuhrman's classification was performed in only 3276 cases.

Parameters	General characteristics
Histologic type	
Clear cell carcinoma	3353 (89.5%)
Papillary renal cell carcinoma	130 (3.5%)
Chromophobe renal cell carcinoma	158 (4.2%)
Unclassified renal cell carcinoma	107 (2.9%)
Pathological staging (TNM, 2002 AJCC)	
T1aN0M0	2044 (54.5%)
T1bN0M0	1286 (34.3%)
T2aN0M0	312 (8.3%)
T2bN0M0	106 (2.8%)
Nuclear grade* (n, %)	
G1	2929 (89.7%)
G2	312 (9.6%)
G3	26 (0.8%)
Note: *Nuclear grading according to Fuhrman's classification was performed in only 3276 cases.	

Multifactor Cox analysis of the stratified effect of the tumor diameter cutoff point for the 2010 AJCC on TNM staging on the prognosis of LRCC

Results are shown in Table 2. When 7 cm served as the classification cutoff point of stages T1 and T2 (HR = 2.44, CI: 1.45–4.11; P = 0.00), good classification for stages T1 and T2 was achieved. When 4 cm served as the cutoff point of stages T1a and T1b (HR = 1.76, CI: 0.87–3.56; P = 0.12), good classification of stages T1a and T1b was not achieved. When 10 cm served as the cutoff point of stages T2a and T2b (HR = 1.58, CI: 0.69–3.62; P = 0.28), the LRCC prognosis of the two groups was not different. Survival was also strongly associated with tumor size when modeled continuously (HR = 1.71, CI: 1.30–2.25; P = 0.00; Table 2).

Table 2

Statistical significance of the tumor size and the relative risk for cancer-specific mortality (CSM) from localized renal carcinoma by using the 2010 AJCC Edition of the TNM Size Classification and Size Modeled Continuously

Classification	n (no.dead)	Hazard radio	95%CI	P value
The 2010 American Joint Committee on Cancer TNM Classification				
T1aN0M0 $\leq$ 4 cm	244 (18)		Reference	
T1bN0M0 $>$ 4 cm, $\leq$ 7 cm	1286 (39)	1.92	0.9659–3.8363	0.0627
T2aN0M0 $>$ 7 cm, $\leq$ 10 cm	312 (25)	3.59	1.6443–7.8319	0.0013
T2bN0M0 $>$ 10 cm	18 (106)	4.72	1.8395–12.1268	0.0013
The 2010 American Joint Committee on Cancer TNM Classification				
T1N0M0 $\leq$ 7 cm	3330 (57)		Reference	
T2N0M0 $>$ 7 cm	418 (43)	2.44	1.4487–4.1103	0.0008
pT1	3300 (57)			
T1aN0M0 $\leq$ 4 cm	2044 (18)		Reference	
T1bN0M0 $>$ 4 cm, $\leq$ 7 cm	1286 (39)	1.76	0.8685–3.5557	0.1169
pT2	418 (47)			
T2aN0M0 $>$ 7 cm, $\leq$ 10 cm	312 (25)		Reference	
T2bN0M0 $>$ 10 cm	106 (18)	1.58	0.6908–3.6168	0.2783
Size modeled continuously	3748 (100)	1.71	1.3017–2.2541	0.0001

Optimal cutoff point of tumor diameter screened in patients with LRCC at stage T1

A total of 3330 patients with LRCC at stage T1 were selected. The CSM rate, median follow-up time, and tumor diameter were 1.71% (57/3330), 50 months (31–102 months), and 3.75 ± 1.41 cm (0.5–7 cm), respectively. The outcomes of patients with 2010 AJCC stage T1 disease were analyzed according to tumor size using 0.5-cm increments from 2.5 cm to 7.0 cm. Each diameter point was regarded as a special cutoff point, and CSM was used as an observation indicator. The difference of each special cutoff point on the prognosis for patients with LRCC at stage T1 was analyzed using the multifactor COX analysis (Table 3). The CSM of patients with tumor diameter $\leq$ 7 cm, tumor diameter $\leq$ 4.5 cm and $>$ 4.5 cm were 0.9% (22/2400 cases) and 3.8% (35/930 cases), respectively (HR = 2.00, CI: 1.04–3.87; P = 0.04). The CSM of the patients between the two groups was statistically different, suggesting that the tumor diameter of 4.5 cm was the best for substratification of stage T1 compared with other tumor diameter values. This value can be used as the optimal cutoff point for predicting CSM in patients with

stage T1 LRCC. The predictive values of tumor diameters at 4.5 and 4 cm as cutoff points for the CSM of patients with LRCC at stage T1 are shown in Figs. 2A and 2B, respectively.

Table 3

Statistical significance of the CSM rates for patients with stage T1 LRCC that are smaller and larger than the specified cutoff points

Size (cm)	Smaller than size n (no.dead)	Larger than size n (no.dead)	Hazard radio	95%CI	P value
2.5	791 (3)	2539 (54)	3.33	0.7743–14.3212	0.1060
3.0	1205 (12)	2125 (45)	1.367	0.5766–3.2391	0.4781
3.5	1618 (15)	1712 (42)	0.286	0.7081–3.2207	1.5102
4.0	2044 (18)	1286 (39)	0.1169	0.8685–3.5557	1.7573
4.5	2400 (22)	930 (35)	2.0011	1.0351–3.8687	0.0392
5.0	2698 (31)	632 (26)	1.4013	0.7376–2.6623	0.3028
5.5	2909 (34)	421 (23)	1.8221	0.9357–3.5480	0.0776
6.0	3098 (46)	232 (11)	1.7999	0.8463–3.8283	0.1269
Note: The CSM rates of patients with T1N0M0 RCC by 0.5 cm increments between 2.5 and 7 cm are shown in Table 3.					

Optimal cutoff point of tumor diameter screened in patients with LRCC at the T2N0M0 stage

A total of 418 patients with LRCC at the T2N0M0 stage were selected. The CSM rate, median follow-up time, and tumor diameter were 10.29% (43/418), 33 months (3-102 months), and 9.40 ± 2.36 cm (7.1–23.4 cm). The outcomes of patients with 2010 AJCC stage T2 disease were analyzed according to tumor size using 1-cm increments from 8 cm to 15 cm. Each diameter point was regarded as a special cutoff point, and CSM was used as an observation indicator. The difference of each special cutoff point on the prognosis of patients with LRCC in stage T2 was analyzed using the COX multifactor analysis (Table 3). Table 4 showed the CSM rates of patients at 1 cm increments between 7.1 and 15 cm. The CSM of patients with tumor diameter $> 7, \leq 11$ cm and tumor diameter > 11 cm were 8.1% (29/359 cases) and 23.7% (14/59 cases), respectively (HR = 2.75, CI: 1.14–6.63; P = 0.02). The CSM of the patients in the two groups was statistically different, suggesting that the tumor diameter of 11 cm was the best value for the substratification of stage T1 compared with other tumor diameter values. This value can be used as the optimal cutoff point for predicting CSM in patients with stage T2 LRCC. The predictive values of tumor diameters at 11 and 10 cm as cutoff points for the CSM of patients with stage T2 LRCC are shown in Figs. 3A and 3B, respectively.

Table 4

Statistical significance of the CSM rates for patients with T2 LRCC that are smaller and larger than the specified cutoff points

Size (cm)	Smaller than size n (no.dead)	Larger than size n (no.dead)	Hazard radio	95%CI	P value
8	68 (5)	350 (38)	1.34	0.3933–4.5691	0.6395
9	250 (19)	168 (24)	1.83	0.8342–4.0244	0.1314
10	312 (25)	106 (18)	1.61	0.7066–3.6757	0.2567
11	359 (29)	59 (14)	2.75	1.1408–6.6277	0.0242
12	375 (33)	43 (10)	2.36	0.8668–6.4142	0.0929
13	389 (38)	29 (5)	1.44	0.3312–6.2399	0.6279
14	393 (38)	25 (5)	1.70	0.3876–7.4186	0.4831
15	400 (42)	18 (1)	0	0.0000–0.0000	0.9731
Note: The CSM rates of patients with 2010 AJCC T2N0M0 RCC by 1 cm increments between 8 and 15 cm are shown in Table 4.					

Comparison of the new tumor diameter cutoff point for patients with LRCC at stages T1 and T2 and the differences in tumor diameter cutoff point confirmed in the 2010 AJCC TNM staging on the CSM predictions of patients

Compared with the tumor diameter cutoff points of T1 and T2 subclassification confirmed in the 2010 AJCC TNM staging, the tumor diameters of 4.5 and 11 cm set as the new tumor diameter cutoff points for T1 and T2 subclassifications of patients with LRCC had better recognition ability (Table 5). The survival curves of the two subclassifications are shown in Fig. 4.

Table 5
Comparison of new tumor diameter cutoff point and tumor diameter cutoff point confirmed in 2010 AJCC for patients with LRCC in stages T1 and T2

Classification	n (no.dead)	Hazard ratio	95%CI	P value
2010 The American Joint Committee on Cancer (AJCC) TNM staging				
T1N0M0				
T1aN0M0 ≤ 4 cm	2044 (18)		Reference	
T1bN0M0 > 4 cm, ≤ 7 cm	1286 (39)	1.76	0.87–3.56	0.12
T2N0M0	418 (47)			
T2aN0M0 > 7 cm, ≤ 10 cm	312 (25)		Reference	
T2bN0M0 > 10 cm	106 (18)	1.58	0.69–3.62	0.28
Modified TNM size classification				
T1N0M0				
T1aN0M0 ≤ 4.5 cm	2400 (22)		Reference	
T1bN0M0 > 4.5 cm, ≤ 7 cm	930 (35)	2.00	1.04–3.87	0.04
T2N0M0	204 (11)			
T2aN0M0 > 7 cm, ≤ 11 cm	375 (45)		Reference	
T2bN0M0 > 11 cm	43 (14)	2.75	1.14–6.63	0.02

Discussion

The TNM staging of LRCC is still the most important determinant of disease recurrence and death ^[19], and the tumor diameter is the standard for the TNM staging of LRCC. In 1987, the tumor diameter cutoff point for LRCC prognosis is first located at 2.5 cm ^[20]. In 1997, on the basis of the survival rate of RCC, epidemiological characteristics, and research observations, 2.5 cm is changed to 7 cm as the cutoff point to judge the prognosis of LRCC ^[21]. With the support of follow-up research and a large number of reviews and other evidence-based medicine, 4 cm is further determined as the optimal cutoff point for judging the prognosis of LRCC in T1, which is further divided into T1a and T1b. Based on these values, ≤ 4 cm is selected as the surgical selection criterion for partial nephrectomy ^[22–24]. In 2010, AJCC has revised the TNM staging of RCC. On the basis of the original determination, 10 cm is used as the cutoff point for the tumor diameter of T2a and T2b in stage T2. In the past 10 years, 7 cm is used as the cutoff point for the classification of stages T1 and T2, whereas 4 cm is used as the T1a and T1b cutoff point, and 10 cm is used as the T2a and T2b cutoff point, which is widely used clinically. However, with a large number of clinical observations, these optimal cutoff points for evaluating the prognosis of LRCC are questioned by various studies ^[1, 14, 15] and needed to be constantly revised on the basis of big data. For example, Hafez

et al. [25] have analyzed a group of patients undergoing selective partial nephrectomy. The tumor-specific mortality of patients with RCC with 4 cm tumor diameter is higher than that of patients at stage T1b. Elmore et al. [26] have analyzed the survival and tumor recurrence of patients with RCC undergoing radical nephrectomy. The analysis has revealed that the difference between stages I and II cannot be stratified when the threshold value of stages I and II in TNM in 1997 is 7 cm. Patients with tumor measurement range between 5.1 and 7.0 cm have shown the same survival rate as patients with the disease at stage II. Therefore, 7 cm is evidently a high cutoff point. Similarly, Waalke et al. [15] have confirmed that the diameter cutoff point of 10 cm, as the standard of T2 subclassification, cannot independently predict tumor-specific mortality in patients with RCC. Many scholars have successively put forward proposals to modify the TMN staging criteria for RCC, and several cutoff points for tumor diameter are proposed to stratify the prognosis of LRCC on the basis of the analysis of the clinical data of large samples. A range of tumor diameter cutoff points from 4.5 cm to 5.5 cm is recommended in most studies [25–28]. The 2019 EAU guidelines on RCC [1] have clearly proposed that 4 cm is not the best choice as a cutoff value to subclassify T1 tumors, and the size stratification value of T2 tumors is also widely questioned. In 2011, Waalkes et al. [15] have analyzed 5122 patients with RCC undergoing surgery from three centers in Germany. In accordance with the 2010 AJC TNM classification, 579 patients are divided into stages T2a (445, 76.9%) and T2b (134, 23.1%). The Kaplan-Meier curve has shown no significant difference in CSS (cancer specific survive) between T2a and T2b patients, which have 5-year CSS of 79.0% and 74.1%, respectively ($P = 0.38$). Therefore, tumor diameter 10 cm, as cutoff point for the prognosis of RCC during stage II, should be revised as necessary.

In this research, the multifactor COX analysis is used to analyze the stratification effect of the 2010 AJCC TNM on the prognosis of LRCC. Results show that the tumor diameter at 7 cm ($HR = 2.44$, $CI: 1.45–4.11$; $P = 0.00$) can achieve the classification of the prognosis of patients with RCC at stages T1 and T2. However, 4 ($HR = 1.76$, $CI: 0.87–3.56$; $P = 0.12$) and 10 ($HR = 1.58$, $CI: 0.69–3.62$; $P = 0.28$) cm cannot achieve the classification of the expected prognosis for the subclassification of stages T1 and T2. Therefore, patients with RCC at stages T1 and T2 are separately analyzed to screen for the tumor cutoff points for the new tumor staging subclassification. Further analysis has confirmed that the cutoff point of T1 tumor diameter is 4.5 cm ($HR = 2.00$, $CI: 1.04–3.87$; $P = 0.04$) and the cutoff point of the T2 tumor is 11 cm ($HR = 2.75$, $CI: 1.14–6.63$; $P = 0.02$). Our research results and the existing literature reports share the common understanding on the 4 and 10 cm as the optimal cutoff points for T1 and T2 subclassification. These two cutoff points are somewhat controversial for the prognosis of LRCC [1, 15, 23]. However, the optimal cutoff point of the tumor diameter redetermined using different studies is somewhat different. Researchers believe that this finding is closely related to various factors, such as tumor heterogeneity, race, genes, diagnosis and treatment levels, and changes in survival environment and economic levels. Our research is targeted at the Chinese population and is an important supplement to the TNM of RCC.

Reasonable and effective classification suggestions are initiated for the long-term prognosis of patients with RCC at stages T1 and T2 in this research, which provide important reference data for the updating of

the T staging system. Based on the results of this study, the indication for partial nephrectomy of LRCC patients can be increased from 4 cm to 4.5 cm. This increase can change the conservative clinical status when 4 cm is regarded as the gold standard for partial nephrectomy and avoid blindly expanding the indication of partial nephrectomy, thereby corresponding to the actual clinical requirements.

This study has certain limitations. First, the median follow-up is 49.8 months (3-103 months). A longer clinical follow-up observation is required for the results to be more convincing. Second, our conclusion is based on a retrospective analysis of the follow-up observations of patients with RCC undergoing surgery in a single center. Verification through the use of multiple centers or other large prospective studies is needed to support our conclusions and provide a theoretical basis for redefining the TNM stage of LRCC.

Conclusions

The 2010 AJCC TNM stage can greatly predict the prognosis of LRCC in stages T1 and T2. In addition, 4.5 and 11 cm might be optional cutoff points for the tumor diameters for subclassifying stages T1 and T2.

Abbreviations

RCC
Renal cell carcinoma
LRCC
Localized renal cell carcinoma
AJCC
American Joint Committee on Cancer
HR
Hazard ratio
CI
Confidence interval
CSM
Cancer-specific mortality

Declarations

Ethics approval

This study was conducted according to the ethical guidelines of the Helsinki Declaration and approved by the Ethics Committee of Chinese People's Liberation Army General Hospital.

Consent to participate

Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

The publication of this study has been approved by all authors.

Availability of data and material

The data used during the study are available from the corresponding author upon request and may only be provided with restrictions (e.g. anonymized data).

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Authors' contributions

Qiang Wang: Design of the work, revising the paper and final approval of the version to be published

Ye Tian: Design of the work and revising the paper

Jian Zhang: Drafting the paper and statistical analysis

Xiaoli Li: Drafting the paper and statistical analysis

Jun Lin: Drafting the paper and statistical analysis

Zhijia Liu: Acquisition of data, analysis and interpretation of data

Changqing Chen: Analysis and interpretation of data

Yu Tao: Analysis and interpretation of data

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Conflicts of interest

The authors declare no conflict of interest.

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Figures

Patients in PLA General Hospital diagnosed between Jan, 2008-Sept, 2016 with malignant RCC who underwent operative management (n = 4167)

Figure 1

The inclusion criteria

Patients in PLA General Hospital diagnosed between Jan, 2008-Sept, 2016 with malignant RCC who underwent operative management (n = 4167)

Figure 1

The inclusion criteria

Figure 2

Predictive value of tumor diameters at 4.5 and 4 cm as cutoff points for the CSM of patients with LRCC in stage T1

Figure 2

Predictive value of tumor diameters at 4.5 and 4 cm as cutoff points for the CSM of patients with LRCC in stage T1

Figure 3

Predictive value of tumor diameters at 11 and 10 cm as cutoff points for the CSM of LRCC patients in stage T2

Figure 3

Predictive value of tumor diameters at 11 and 10 cm as cutoff points for the CSM of LRCC patients in stage T2

Figure 4

Survival curve of patients with LRCC at stages T1 and T2 after the adjustments of tumor diameter cutoff points and confirmed by 2010 AJCC TNM

Figure 4

Survival curve of patients with LRCC at stages T1 and T2 after the adjustments of tumor diameter cutoff points and confirmed by 2010 AJCC TNM