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Clear Cell Renal Cell Carcinoma: Associations Between CT Features and Patient Survival

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Abstract

OBJECTIVE—The objective of this study was to investigate associations between CT features and survival in patients with clear cell renal cell carcinoma (ccRCC).

MATERIALS AND METHODS—The study included 763 patients with histopathologically confirmed ccRCC who underwent preoperative contrast-enhanced CT between 1999 and 2011. Imaging features, both qualitative (cystic tumor, necrosis, tumor contact with renal sinus, renal vein invasion, peritumoral stranding, and peritumoral neovascularity) and quantitative (maximal tumor diameter and distance from the tumor to the renal sinus), were evaluated. Univariate and multivariable Cox regressions were used to assess associations of imaging features with disease-specific survival (DSS) and disease-specific progression-free survival (PFS).

RESULTS—Greater tumor size and the presence of renal vein invasion on CT were associated with decreased DSS and disease-specific PFS ($p < 0.05$), and the presence of extensive necrosis (more than two-thirds of the tumor volume) was associated with decreased disease-specific PFS ($p < 0.05$); this association remained statistically significant when we controlled for pathologic tumor stage. In contrast, no disease-specific death or progression was seen in patients with purely cystic tumors. Greater distance between the tumor and the renal sinus was not statistically significantly associated with longer survival.

CONCLUSION—In patients with ccRCC, observation of extensive necrosis on CT was statistically significantly associated with decreased disease-specific PFS, whereas greater tumor size and the presence of renal vein invasion on CT were statistically significantly associated with decreased DSS and disease-specific PFS. No disease progression was observed in tumors with a cystic appearance. Therefore, selected CT features could potentially aid in risk assessment for and

counseling of patients with ccRCC and could provide prognostic information beyond the established tumor staging system.

Keywords

CT; diagnostic imaging; outcome assessment; renal cell carcinoma

In recent years, the incidental detection of renal cortical tumors has been increasing [1, 2]. Although surgery remains the reference standard for treatment of these tumors, avoidance of surgery would be desirable for many patients (in particular, elderly patients with existing medical comorbidities and a high risk of experiencing perioperative complications [3]). Thus, there is a great need for a reliable means of assessing the risk posed by a renal tumor, which would not only help in selecting the therapeutic approach but would also be of value in patient counseling. In addition, precise risk assessment could also help in selecting follow-up strategies for patients undergoing surgical resection of the tumor.

A variety of nomograms that combine both clinical and epidemiologic parameters have been developed for this purpose [4]. The imaging information incorporated into these approaches is usually limited to the assessment of tumor stage [4, 5], which itself relies primarily on the assessment of tumor size and the presence of tumor invasion into vascular or surrounding structures—features that have been shown to directly affect patient outcome or the risk of disease progression [6, 7]. However, the commonly observed imaging features of clear cell renal cell carcinoma (ccRCC) are diverse and include features not routinely reported and not included in the determination of tumor stage, such as cystic components, necrosis, peritumoral stranding, and peritumoral neovascularity. Specific genomic mutations, some of which are known to affect patient outcome (e.g., a higher rate of renal vein invasion in tumors with mutations of *KDM5C* and *BAP1* [*BRCA1*-associated protein-1]) have already been shown to have an effect on the appearance of renal cortical tumors on imaging [8, 9]; however, the association between renal tumor imaging features and patient survival has not yet been comprehensively investigated.

We hypothesized that a set of commonly observed imaging features of tumors on preoperative CT examinations could potentially be associated with disease-specific survival (DSS) in patients with ccRCC and thus could be useful for risk assessment for the patient.

Therefore, the purpose of the present study was to investigate associations between CT features and DSS in patients with ccRCC, to identify features that directly affect the prognosis of a patient and that might aid in risk assessment for the individual patient.

Materials and Methods

Patients

This study was HIPAA compliant and was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center. The requirement for informed consent was waived. Radiology and urology databases at Memorial Sloan-Kettering Cancer Center were searched for information from the years 1999 through 2011, to identify patients who matched the following inclusion criteria: resection of histopathologically proven ccRCC at

the institution; CT examination of the abdomen performed less than 180 days before surgery, with application of an IV contrast agent and at least one image acquired during the nephrographic phase; and no evidence of gross distant metastatic disease (M0) at the time that surgery was performed.

The search identified a total of 827 patients. Of these, 64 patients were excluded for the following reasons: presence of bilateral tumors on CT ($n = 35$), prior nephrectomy of the contralateral kidney ($n = 21$), contralateral recurrence ($n = 6$), polycystic kidney disease ($n = 1$), and the simultaneous appearance of lung cancer and visible metastatic disease on CT ($n = 1$). Patients who underwent nephrectomy or who had bilateral tumors or contralateral recurrence were excluded, to ensure that potential disease progression would be caused by the measured tumor and not by a second or previous tumor with a potentially differing set of features on CT. The final cohort therefore consisted of 763 patients.

Patient characteristics and survival data were collected from the electronic medical records system at Memorial Sloan-Kettering Cancer Center. The mean interval between CT examination and surgery was 42 days (range, 0–169 days).

Image Analysis

Two radiologists, one with 10 years of experience in genitourinary imaging and one participating in a dedicated fellowship on genitourinary imaging, evaluated imaging studies in consensus with the use of commercial PACS software (Aquarius Intuition, Terarecon). To allow optimal assessment of tumor size, the maximal tumor diameter (expressed in millimeters) was measured in the orientation or multiplanar reformation in which it was largest. In addition, the presence or absence of the following imaging features was assessed: presence of cystic tumor (no solid component) or solid tumor parts, necrosis (comprising none to one-third of the tumor volume, one-third to two-thirds of the tumor volume, or more than two-thirds of the tumor volume, as determined by visual assessment), the relationship of the tumor to the renal sinus (defined as no contact, contact but no gross invasion, or gross invasion of the renal sinus), gross renal vein invasion, peritumoral stranding, and peritumoral neovascularity (see Figs. 1A–1F, for examples of these features). If there was no gross invasion of the tumor into the renal sinus, the distance from the tumor to the renal sinus was measured (in millimeters) in the plane or reformation in which it was shortest.

Statistical Methods

Two survival outcomes were examined: DSS, which was defined as the time between the date when surgery was performed and the date of either the last follow-up or death due to disease, and disease-specific PFS, which was defined as the time between the date of surgery and the date of disease progression, death due to disease, or the last follow-up. Cause-specific Cox regression that censored patients who died of other cancers was used to examine univariate associations between CT features and each survival outcome, where the cause-specific hazard ratio (HR) was estimated by censoring patients who died of other cancers. Multivariable cause-specific Cox regression was then performed to include CT features that were statistically significant in the univariate analysis. Backward elimination analysis was used to select independent CT features that were associated with each outcome.

Subgroup analyses were also separately performed for tumors with a maximum length of 4 cm or less, those longer than 4 cm but no more than 7 cm, and those longer than 7 cm. The cumulative incidence function for disease-specific death and for disease-specific death or progression was estimated, treating death caused by other cancers as a competing risk [10, 11].

A test for which $p < 0.05$ was considered to denote statistical significance. All statistical analyses were performed using software packages SAS (version 9.2, SAS Institute) and R (version 2.13, The R Foundation for Statistical Computing).

Results

Patient and Tumor Characteristics

Table 1 illustrates patient and tumor characteristics as well as the frequency of the presence of each CT feature. For the 763 patients included in this study, tumors were staged as follows: 53.3% (407) had pT1a tumors, 16.5% (126) had pT1b, 3% (23) had pT2a, 1% (8) had pT2b, 9.3% (71) had pT3a, 16.1% (123) had pT3b, 0.1% (1) had pT3c, and 0.5% (4) had pT4. The N stage was reported as pN0 for 29.6% (226) of patients, as pNx for 70.1% (535) of patients, and as pN+ for 0.3% (2) of patients.

At the last follow-up, 93 patients had died, with 79 of them dying of ccRCC. Another 29 patients were alive even though their disease had progressed. With a median follow-up of 56.1 months (range, 0.2–161.4 months), the median DSS and the median disease-specific PFS were not reached.

Associations Between CT Features and Patient Survival

All investigated CT features were statistically significantly associated with DSS and disease-specific PFS in univariate analysis ($p < 0.05$), with the exception of cystic tumor appearance. No disease progression or disease-specific death was noted among patients with purely cystic tumors (Table 2).

However, when including only preoperatively available CT features in multivariable analysis, only the maximum tumor length and the presence of renal vein invasion remained statistically significantly associated with shorter DSS and disease-specific PFS. Although the presence of necrosis as a categorical variable with three categories (none to one-third of the tumor volume, one-third to two-thirds of the tumor volume, or more than two-thirds of the tumor volume) was not statistically significantly associated with survival outcomes in univariate analysis, the presence of extensive necrosis (more than two-thirds of the tumor volume) compared with no extensive necrosis (less than two-thirds of the tumor volume) was statistically significantly associated with a shorter disease-specific PFS in univariate analysis as well as in multivariable analysis (HR, 1.69 [95% CI, 1.03–2.76]; $p = 0.037$) (Table 3) that controlled for maximal tumor diameter and the presence of renal vein invasion. These associations remained statistically significant when we additionally controlled for pathologic tumor stage in the multivariable model (except for the influence of greater tumor size on DSS), showing the effect of these CT features on patient survival beyond the established tumor staging. Although visible renal vein invasion was statistically

significantly associated with shorter DSS and disease-specific PFS, extensive necrosis was associated with shorter disease-specific PFS only (HR, 1.66 [95% CI, 1.02–2.72]; $p = 0.042$) (Table 3 and Figs. 2A–2F).

In analyzing subgroups of patients on the basis of maximal tumor size (≤ 4 cm, > 4 cm but ≤ 7 cm, or > 7 cm), only the presence of gross renal vein invasion in tumors measuring larger than 4 but no more than 7 cm was still statistically significantly associated with shorter DSS, and only gross renal vein invasion in tumors larger than 4 cm but no more than 7 cm and in tumors larger than 7 cm was still statistically significantly associated with shorter disease-specific PFS in multivariable analyses (Table 4). When we also included the pathologic stage in this model, none of the CT parameters affected patient survival more than tumor stage (Table 4).

The minimal distance from the tumor to renal sinus fat was measured in 299 patients in whom no gross invasion of the renal sinus was seen. However, a longer distance was not statistically significantly associated with DSS (HR, 0.96 [95% CI, 0.88–1.05]; $p = 0.398$) or disease-specific PFS (HR, 0.96 [95% CI, 0.89–1.04]; $p = 0.323$).

Discussion

The imaging features of ccRCC are diverse. Some of these features (i.e., tumor size, vascular invasion, and invasion of the surrounding structures) are established factors in local staging of ccRCC, whereas others (i.e., cystic tumors, extensive necrosis, contact between the tumor and the renal sinus, peritumoral stranding, and neovascularity) are not part of staging but may potentially affect patient outcome. The identification of such additional independent prognostic markers during routine imaging would be of considerable clinical value, because it could help in assessing the risk of disease progression and would be of value in patient counseling.

Greater tumor size and the presence of renal vein invasion are known strong predictors of decreased disease-specific outcome [6, 12], which confirms the importance of these features for both the TNM staging system and previously published nomograms for risk assessment [4, 5, 13]. In the present study, greater tumor size and visible renal vein invasion were also associated with shorter patient survival. However, we also found this association to remain statistically significant even when we controlled for pathologic tumor stage. This finding indicates that these CT features provide additional prognostic information beyond the established staging system; this information might reflect distinct differences in patient survival within the same T stage. For example, patients with stage T3a ccRCC resulting from muscular venous branch invasion, as determined by histopathologic findings, might still have a better outcome than patients who had stage T3a ccRCC and renal vein invasion clearly visible on CT. These findings could easily expand on the current staging system because CT is routinely performed for these patients.

When we stratified our data by tumor size and included only CT features in the multivariable model, the presence of gross renal vein invasion also remained a strong indicator of an elevated risk for disease progression, albeit only for tumors larger than 4 cm; this is probably

because renal vein invasion is very rarely seen in tumors 4 cm or smaller (e.g., it was noted only in two patients in the present study). When we also control for pathologic stage in the multivariable model and analyze the data separately on the basis of tumor size, associations between CT features and survival did not remain statistically significant, potentially also because of small sample size. Therefore, future studies are needed to create a detailed subgroup analysis.

The presence of extensive necrosis on CT studies was associated with decreased disease-specific PFS after adjusting for tumor size, the presence of renal vein invasion, and pathologic stage, thus providing additional value to prognostic assessment beyond tumor stage. This finding expands on the results of prior studies. For example, an association between the presence of necrosis on imaging and increased tumor aggressiveness (i.e., a higher Fuhrman grade for ccRCC) has previously been reported [14, 15]. To our knowledge, the first evidence supporting our hypothesis was published by Raj et al. [13], who incorporated the presence of necrosis on imaging into a preoperative nomogram. In the present study, we were able to further expand on these results by providing a homogeneous patient cohort with histopathologically confirmed ccRCC and by having all imaging studies centrally reviewed by two radiologists, rather than by relying on the evaluation of radiologic reports; reliance on radiologic reports does not guarantee consistent reporting, because the radiologist may not mention the presence of necrosis in every case, particularly when the cases have been collected over a large time span of up to 35 years and from two different institutions [13].

Our results also align with a preliminary analysis of 68 patients with ccRCC by Beddy et al. [15], which also found an association between the presence of necrosis and decreased survival and which, in addition, showed that the presence of necrosis was associated with a lower percentage of tumor cells with clear cytoplasm on histopathologic examination. Our analysis of the presence of necrosis within subgroups of patients, as based on tumor size, was limited because of the small number of patients with disease-specific events.

Of interest, we did not see any disease-specific progression or death among patients with purely cystic tumors. This is perhaps because these tumors belong to the distinct subgroup of multilocular cystic ccRCC, a rare, low-grade tumor that is known to have a favorable prognosis [16, 17] and that has been shown to have a distinct genomic makeup. Tumors in this subgroup lack mutations in *SETD2*, *KDM5C*, and *BAP1* [8], which are known to be negative prognostic factors when found in solid tumors [18, 19]. The findings of Karlo et al. [8], who also noted an association between a higher rate of renal vein invasion and mutations in *KDM5C* and *BAP1*, align well with the decreased survival rate noted for patients with renal vein invasion. However, in a recent investigation, The Cancer Genome Atlas–Renal Cell Carcinoma Imaging Research Group [20] did not find an association between the presence of necrosis on CT and a specific genomic mutation of the tumor. Given the fact that the presence of extensive necrosis had a significant effect on patient survival in our study, this discrepancy highlights the urgent need for further investigations in this field.

Although we found that tumor size, renal vein invasion, and extensive necrosis could be useful in risk assessment performed for patients with ccRCC who underwent surgery, and

although we observed that cystic tumor appearance seemed to be associated with a favorable prognosis, the other features that were investigated (i.e., tumor contact with the renal sinus, peritumoral stranding, and neovascularity) were of no additive value in multivariable analysis, even though they were statistically significantly associated with patient survival in univariate analysis. This probably occurred because these features are directly related to increasing tumor size, which, for example, increases the risk of renal sinus invasion and also induces peritumoral neovascularity to accommodate the increasing demand of the growing tumor for blood supply. In addition, a discrepancy between the presence of renal sinus or muscular venous branch invasion on histopathologic examination and its visibility on imaging has been reported [21]. In patients without gross sinus invasion, a greater distance between the tumor and the renal sinus is known to be associated with a decreasing probability of muscular venous branch invasion [22]; however, in our study, we did not find a statistically significant association between a longer distance and DSS or disease-specific PFS. The fact that we assessed the maximal tumor diameter with the use of the 3D reformation on which it was found to be largest, thereby obtaining the most accurate measurement possible, might have brought out the dominant influence of tumor size on survival.

In the present study, we focused on CT so that we could recruit the largest patient cohort possible; however, assessment of the same qualitative imaging features is possible on both routine CT and MRI examinations and does not require dedicated MRI sequences or extensive additional analyses. Because virtually every patient with a renal mass undergoes imaging before surgery, incorporating the prognostic imaging features that we identified into existing nomograms and, thus, clinical practice could easily lead to more accurate risk stratification for patients with newly diagnosed renal masses.

We acknowledge the limitations of our study. First, we restricted ourselves to the assessment of ccRCC and required all patients in the study to have undergone surgical resection of the tumor, thereby causing a selection bias toward patients deemed eligible for surgery. In addition, although reliance on precise diagnosis based on histopathologic analysis of the surgical specimen allowed us to obtain a homogeneous patient cohort, such a precise diagnosis is not available in the preoperative setting. Future studies are therefore needed to evaluate whether CT findings are also of value for other RCC subtypes, such as papillary or chromophobe RCC, and for renal cortical tumors more generally. However, a previous report indicated that it is indeed possible to differentiate ccRCC from other more indolent tumors by use of routine multiphase CT [23]. Second, although qualitatively assessed features can be directly applied in routine clinical practice, potential differences in interpretation between readers still need to be investigated. However, other studies have shown good interreader agreement for qualitatively assessed CT features [8]. Finally, we did not include the presence of suspicious lymphatic nodes in our analysis, because only two patients in our cohort had proven lymph node metastases at the time of surgery, and because the benefit of retroperitoneal lymph node dissection is still controversial [24], particularly in our patient cohort, most of whom had pT1–pT2 tumors.

In conclusion, we found that tumor size, the presence of gross renal vein invasion, and the presence of extensive necrosis affected outcome for patients with ccRCC who underwent

surgery and provided additive prognostic information beyond pathologic tumor stage. In contrast, we found no disease-specific progression in patients with tumors of purely cystic appearance. Thus, reporting of these CT features might allow more accurate risk stratification in patients with ccRCC.

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Fig. 1. Examples of CT features of clear cell renal cell carcinoma (ccRCC)

A, 48-year-old man with ccRCC with cystic tumor appearance.

B, 50-year-old woman with ccRCC with extensive necrosis.

C, 69-year-old woman with ccRCC with contact between tumor and renal sinus without unequivocal invasion on imaging.

D, 58-year-old man with ccRCC with gross renal vein invasion.

E, 79-year-old man with ccRCC with peritumoral stranding.

F, 64-year-old man with ccRCC with peritumoral neovascularization.

A

B

C

D

Fig. 2. Associations between disease-specific death and disease-specific progression of patients with clear cell renal cell carcinoma (ccRCC) and CT features of ccRCC

A–F, Graphs show cumulative incidence curves for disease-specific death in different tumor size groups (**A**), disease-specific progression in patients in different tumor size groups (**B**), disease-specific death in patients with or without gross renal vein invasion on imaging (**C**), disease-specific progression in groups with or without presence of gross renal vein invasion on imaging (**D**), disease-specific death in patients with or without presence of extensive necrosis on imaging (**E**), and disease-specific progression in patients with or without presence of extensive necrosis on imaging (**F**).

TABLE 1

Patient and Tumor Characteristics and Frequencies of CT Features

Characteristic	Value ^a
Age (y)	
Mean $\pm$ SD	59 $\pm$ 12
Range	22–87
Maximum tumor length (mm)	
Mean $\pm$ SD	47.6 $\pm$ 26.6
Range	6–201
Sex	
Female	268 (35)
Male	495 (65)
Maximum tumor length	
4 cm	362 (47)
> 4 but $\leq$ 7 cm	285 (37)
> 7 cm	116 (15)
Cystic tumor	
Solid tumor parts present	747 (98)
Purely cystic tumor	16 (2)
Necrosis	
No extensive necrosis	687 (90)
Extensive necrosis	76 (10)
Contact with renal sinus	
No contact	131 (17)
Contact but no gross invasion	168 (22)
Invasion	464 (61)
Renal vein invasion	
No	689 (90)
Yes	74 (10)
Peritumoral stranding	
No	482 (63)
Yes	281 (37)
Peritumoral neovascularity	
No	418 (55)
Yes	345 (45)

Note—Except where otherwise indicated, data are the no. (%) of patients. A total of 763 patients were evaluated.

^aNot all percentages total 100%, because of rounding.

TABLE 2
Associations Between CT Features and Survival Outcomes for 763 Patients, According to Univariate Analysis

Feature	n	DSS		Disease-Specific PFS	
		Cause-Specific HR (95% CI)	p	Cause-Specific HR (95% CI)	p
Maximum tumor length	362	1	< 0.001	1	< 0.001
4 cm	285	1.51 (0.88–2.59)		1.86 (1.15–3.00)	
> 4 but < 7 cm	116	3.62 (2.10–6.23)		5.20 (3.24–8.35)	
> 7 cm			0.011		< 0.001
Cystic	747				
Solid tumor parts present	16	NE		NE	
Purely cystic tumor	687	1		1	
Necrosis	76	2.07 (1.18–3.64)		2.51 (1.57–4.00)	
No extensive necrosis	131	1	0.047	1	0.001
Extensive necrosis	168	1.08 (0.46–2.52)		1.04 (0.48–2.26)	
Contact with renal sinus	464	1.94 (0.96–3.92)		2.36 (1.26–4.43)	
No contact	689	1	< 0.001	1	< 0.001
Contact but no gross invasion	74	3.92 (2.31–6.65)	4.65 (3.00–7.20)		
Invasion			0.046		< 0.001
Renal vein invasion	482	1		1	
No	281	1.57 (1.01–2.45)		2.10 (1.44–3.06)	
Yes	418	1.62 (1.04–2.53)	0.032	2.20 (1.50–3.24)	< 0.001
Peritumoral stranding	345				
No					
Yes					
Peritumoral neovascularity					
No					
Yes					

Note—No disease-specific death or progression was seen in patients with purely cystic tumors.

DSS = disease-specific survival, PFS = progression-free survival, HR = hazard ratio, NE = not estimable.

TABLE 3

Associations Between CT Features and Survival Outcomes in a Multivariate Analysis Including Only CT Parameters and in a Multivariate Analysis Including CT Parameters and Pathologic Stage

Variables Assessed	DSS		Disease-Specific PFS	
	Cause-Specific HR (95% CI)	<i>p</i>	Cause-Specific HR (95% CI)	<i>p</i>
CT parameters alone				
Maximum tumor length		0.032		0.001
4 cm	Reference		Reference	
> 4 but < 7 cm	1.43 (0.83–2.46)		1.64 (1.01–2.67)	
> 7 cm	2.43 (1.25–4.71)		3.04 (1.70–5.43)	
Renal vein invasion		0.012		0.001
No	Reference		Reference	
Yes	2.32 (1.20–4.49)		2.45 (1.44–4.16)	
Necrosis		NS		0.037
No extensive necrosis			Reference	
Extensive necrosis			1.69 (1.03–2.76)	
CT parameters and pathologic stage		NS		0.026
Maximum tumor length				
4 cm			Reference	
> 4 but < 7 cm			1.41 (0.85–2.34)	
> 7 cm			2.51 (1.28–4.91)	
Pathologic stage		0.001		0.001
1	Reference		Reference	
2	0.58 (0.14–2.46)		0.61 (0.21–1.71)	
3 and 4	2.48 (1.47–4.16)		2.06 (1.24–3.44)	
Renal vein invasion		0.007		0.023
No	Reference		Reference	
Yes	2.33 (1.26–4.30)		1.86 (1.09–3.18)	
Necrosis		NS		0.042
No extensive necrosis			Reference	
Extensive necrosis			1.66 (1.02–2.72)	

Note—Parameters not significantly affecting patient outcome are not shown.

DSS = disease-specific survival, PFS = progression-free survival, HR = hazard ratio, NS = not significant and not included in the multivariable model.

TABLE 4

Subgroup Analyses, Stratified by Size, for a Multivariate Analysis Including CT Parameters Only and for a Multivariate Analysis Including CT Parameters and Pathologic Stage

Variables Assessed	DSS		Disease-Specific PFS	
	Cause-Specific HR (95% CI)	<i>p</i>	Cause-Specific HR (95% CI)	<i>p</i>
CT parameters alone				
Maximum tumor length ≤ 4 cm (<i>n</i> = 362)	No significant CT feature		No significant CT feature	
Maximum tumor length > 4 but ≤ 7 cm (<i>n</i> = 285)				
Renal vein invasion				
No	Reference	0.032	Reference	0.036
Yes	3.28 (1.11–9.55)		2.75 (1.07–7.10)	
Maximum tumor length > 7 cm (<i>n</i> = 116)				
Renal vein invasion				
No	No significant CT feature		Reference	0.024
Yes			2.05 (1.10–3.84)	
CT parameters and pathologic stage				
Maximum tumor length ≤ 4 cm (<i>n</i> = 362)				
Pathologic stage		0.031		0.012
1 and 2	Reference		Reference	
3 and 4	2.94 (1.10–7.83)		3.17 (1.29–7.79)	
Maximum tumor length > 4 but ≤ 7 cm (<i>n</i> = 285)				
Pathologic stage		0.041		0.034
1 and 2	Reference		Reference	
3 and 4	2.22 (1.03–4.77)		2.02 (1.06–3.86)	
Maximum tumor length > 7 cm (<i>n</i> = 116)				
Pathologic stage		0.038		0.005
1 and 2	Reference		Reference	
3 and 4	2.83 (1.06–7.57)		3.31 (1.45–7.56)	

Note—DSS = disease-specific survival, PFS = progression-free survival, HR = hazard ratio, NS = not significant and not included in the multivariable model.