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The spinal distribution of metastatic renal cell carcinoma: Support for locoregional rather than arterial hematogenous mode of early bony dissemination

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Abstract

Background: Quantifying the degree to which spinal involvement of metastatic renal cell carcinoma (mRCC) is a locoregional phenomenon vs. a hematogenous, bone-specific affinity has implications for prognosis and antimetastatic therapy.

Objective: To investigate the distribution of spinal metastasis in mRCC and to explore relationships between clinical factors and patterns of spinal spread.

Methods: Patients with mRCC and spinal involvement from June 2005 to November 2018 were identified. Clinical and biologic features including primary tumor size and degree of spinal and nonbony metastatic involvement were collected. Spinal distributions were evaluated by the permutation test, with the null hypothesis that metastases are distributed uniformly across levels.

Results: One hundred patients with 685 spinal levels involved by mRCC were evaluated. A nonuniform spatial distribution was observed across the cohort ($P < 0.001$); a preponderance of thoracolumbar involvement was noted with the mode at L3. No significant deviation in metastatic distribution from uniform was observed in right- or left-sided tumors, subgroups of distant or local metastases, or histology. Patients with smaller tumors (<4 cm) and local spread had distribution of spinal metastases not significantly different from uniform ($P = 0.292$ and $P = 0.126$, respectively).

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Supplementary materials

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Conflicts of interest

The authors have no disclosures relevant to this study.

Conclusions: These data support a dominant locoregional as opposed to arterial hematogenous mechanism for early spinal dissemination of mRCC. Characterizations of the biologic molecular features contributing to osseous tropism and aggressive tumor biology (as seen in the subset of outlier patients with small tumors who appear to have more uniform spread), have implications for surveillance and are an area of active investigation.

Keywords

Metastatic distribution; Renal cell carcinoma; Spinal metastasis; Spine

1. Introduction

Bony metastasis is a severe and life-limiting complication of cancer, resulting in intractable pain, fractures, and limited mobility and is associated with earlier death in a variety of malignancies including renal cell carcinoma (RCC). Fully one-third of metastatic RCC (mRCC) patients develop bone metastases, and some one-third of these develop neurologic compromise owing to spinal cord or nerve root impingement [1,2]. Survival time is reduced to months in a variety of solid cancers over metastatic patients without bony involvement [2–4]. In addition to contributing to patient suffering and mortality, this disease imposes a significant societal burden: in a Nationwide Inpatient Sample analysis of 144,000 hospitalizations of RCC patients with bone metastasis, 20% involved skeletal-related events, and the cost of these visits increased 203% in inflation-adjusted terms from 1998 to 2010 [5].

Understanding mechanisms of metastasis may allow for development of improved prognostic tools for identifying patients at risk of this devastating complication, and ultimately of antimetastatic therapy. An example of this is the very poor prognosis correlated with acrometastasis in RCC [6]. The pathways involved in bony metastasis have yet to fully elucidated; VEGF and MET receptors have been shown to be expressed on osteoblasts and osteoclasts, regulating their proliferation, migration, and survival. The tyrosine-kinase inhibitor cabozantinib, with activity toward VEGF and MET has been postulated as a mediator of this process, and indeed, the clinical activity of cabozantinib in patients with bone metastases from RCC has been confirmed in a phase III trial [7–9].

One important way to understand this process, and whether there exist clinically meaningful bone-specific processes driving metastasis, is to differentiate the degree to which bony metastasis is a random stochastic event based on relative blood flow patterns, vs. driven by homing or organ-specific colonization ability. For example, the commonality of liver metastases in colon cancer is generally explained by portal drainage patterns, while liver metastases in uveal melanoma are to a large degree seen only with BAP1 mutation [10,11].

Quantifying distribution patterns of spinal metastases from the retroperitoneal space is a unique system for evaluating the degree to which bony distribution is a biologic capacity, vs. a locoregional phenomenon. In the former scenario, a uniform stochastic distribution of metastases would be anticipated across all evaluated bones, whereas in the latter scenario, peak metastatic seeding would present adjacent to the primary tumor mass. In RCC, thoracolumbar oligometastasis has been anecdotally observed to be common but has never

been shown. In this study, we investigated the spatial distribution of metastases across vertebral levels in the first quantitative anatomic study of bone metastases.

2. Methods

Following institutional review board approval, an institutional database was queried to identify consecutive patients with a pathologic diagnosis of RCC and spinal metastatic involvement from June 2005 to November 2018 at a tertiary care center. Patients included were treatment-naïve, with de novo spinal metastases. Patient consent was not required as data was de-identified and collected in a retrospective fashion. A blinded radiologist examined the first cross-sectional imaging obtained involving the spine and scored each spinal level for absence or presence of disease. Clinical and biologic features including primary tumor size, histology, laterality, and degree of spinal and nonbony metastatic involvement (including regional lymph node and distant deposits) were retrieved from medical records. Patients with RCC without spinal involvement as well as patients with more than one malignancy were excluded. Likewise, patients with limited imaging data (only including central or only peripheral levels) were excluded, as they biased the analysis due to lack of coverage. These included 3 patients whose imaging covered C1–T11, T10–L5, and T7–S5. Data from remaining patients ($n = 100$) are presented and analysis was performed using by-level proportions with metastatic involvement among patients with imaging data at the given level. Data in the figures are presented in a normalized fashion to aid with visual interpretation.

2.1. Statistical analysis

Test for uniformity: Spinal metastatic distributions were evaluated by a permutation test, with the null hypothesis that rate spinal metastases are equal across all levels examined. Specifically, let X_j patients has a metastasis at level j among n_j who had imaging on k-th level, j = 1,..29 consecutively ordered matching C1–C7, T1–T12, L1–L5, S1–S5. Let p_j be proportion of patients with metastasis at j-th level, estimated by $\hat{p}_j = X_j/n_j$. Let $\bar{p} = \sum_{j=1}^{29} \hat{p}_j/29$ be the average observed metastasis rate per level. We define test statistic as $T = \sum_{j=1}^{29} (\hat{p}_j - \bar{p})^2$. The null hypotheses is that $p_1 = \ldots = p_{29}$. To generate the distribution of the proposed test statistic under the null hypothesis we use data specific number of metastases per patient observed in our study, defined M_i, i = 1,.., 100. Note that at most one metastasis per patient per level is counted, i.e., if multiple lesions are observed per level they are counted as 1. For each patient, at iteration b, we randomly allocate M_i metastases to levels 1,..,29 with equal probability. We then calculated the observed $\hat{p}_j^b$ and the corresponding test statistic T^b. After repeating this for b = 1 1000 times we obtain the distribution of the test statistic under the null, and the P value is defined as $\sum_{b=1}^{1000} \frac{1(T^b > T)}{1000}$. The advantage of the proposed test is that it takes into account the variation in the observed number of metastases across patient. All analyses were performed in the R platform v3.6.1. Statistical significance was assumed at $P \leq 0.05$.

3. Results

One hundred patients with 685 spinal levels involved by mRCC were evaluated. Baseline clinical characteristics are presented in Table 1. Demographic and histologic features of this cohort demonstrated a preponderance of men (68%) and clear cell histologic subtype (71%). Sixty-two patients (62%) were imaged with MRI, 32 (32%) with CT, 3 (3%) with PET/CT, 2 (2%) with bone scan, and 1 (1%) with CT + MRI. Imaging capturing the entire length of the spine (C1–S5) was obtained in 67 patients (67%); the number of spinal levels involved across the cohort is detailed in Supplementary Table 1.

Median tumor size was 8 cm (range 1.2–17.2 cm). With respect to locations of metastatic involvement, 71 patients (71%) were noted to have extra-osseous metastatic spread, and 29 patients (29%) had spine-only disease, with or without local retroperitoneal lymph node involvement. Thirty-five patients (35%) had metastatic involvement in only one vertebral level; 32 patients (32%) had involvement in 2 to 5 vertebral levels, and 33 patients (33%) had metastatic involvement in greater than 5 vertebral levels.

A heat map demonstrating the percentage of vertebral levels involved with metastatic RCC across all scanned vertebral levels is presented in Fig. 1, and a patient-level depiction of metastasis distribution is included in Supplementary Fig. 1. A nonuniform distribution of metastases by level was observed across the cohort ($P < 0.001$); a preponderance of thoracolumbar involvement was noted with the mode occurring at L3. Metastatic distribution was significantly nonuniform for right- or left-sided tumors, as well as for clear cell or nonclear cell renal cell histology ($P < 0.001$). Similar results were seen for patients with different number of levels involved with metastatic disease (1 level, $P = 0.008$; 2–5 levels, $P = 0.004$; >5 levels, $P < 0.001$; Fig. 2) and patients with both distant and local as well as distant only spread (both $P < 0.001$), while hypothesis of uniformity could not be rejected for patients with local spread ($P = 0.126$). Tumors <4 cm demonstrated distribution not significantly different from uniform ($P = 0.292$), unlike tumors 4 to 7 cm and >7 cm (both $P < 0.001$; Fig. 3). Note, however, the 2 groups were uniform distribution cannot be rejected are relatively small, with $n = 12$ patients each. We further explored the differences in uniformity between patients categorized into 3 groups: patients with spine-only disease, patients with spine and other bony (nonspinal) disease, and patients with spine and distant soft tissue metastases, finding no significant difference in uniformity between these 3 groups.

4. Discussion

In 1940, Oliver Batson described a large, valveless, venous network connecting the internal vertebral venous plexuses to the deep pelvic plexuses, purported to explain some degree of metastatic spread, vs. the widespread belief at the time that lymphatic drainage was the predominant metastatic route [12]. Ever since, this route has been suggested to be relevant in cases of thoracolumbar metastasis, particularly in cases of oligometastasis, but has never been shown to be the predominant mode of spinal spread [13,14]. Understanding this process with additional precision has basic biologic and potentially therapeutic implications. For example, the identification of RANKL-mediated osteoclast activation within the bone

metastatic microenvironment has led to the successful adoption of RANK-directed therapy (denosumab and others) in several malignancies [15–18].

More importantly, the degree to which there exists bone specific capillary vs. venous extravasation this may allow for understanding whether there exist vascular bed-specific signaling. Furthermore, identification of tumor-specific predictors of additional metastasis and of survival would allow for treatment stratification. For example, many authors continue to advocate aggressive (and relatively morbid) surgical resection of solitary spine metastases specifically in the thoracolumbar junction on the basis of presumed favorable biology given the theoretical advantage of improved local control, despite effective radiation paradigms across histologies [19,20]. Surgical treatment of nonspinal bone metastases is also relied upon given poor radiosensitivity, and indeed aggressive surgery continues to be a mainstay for solitary disease in some centers [21,22].

In this study, we demonstrate a nonuniform distribution of RCC bone metastases centered at the upper/mid-lumbar spine immediately adjacent to the level of the kidneys, with a mode at L3, concordant with the hypothesis that RCC spread to the spine (and indeed early bony events) is largely driven by a locoregional mode of spread and not a random stochastic distribution to all bones within the body.

Furthermore, patients with spinal metastasis and clinical features associated with aggressive metastatic phenotypes demonstrated more equal rates of metastases across distribution of levels, suggesting inherent biologic features predisposing these tumors to widespread systemic dissemination through the whole-body circulation. These phenotypes included those with distant extraosseous spread and greater numbers of vertebral levels involved. In addition, we found support for our hypothesis that those with small primary tumor size (<4 cm) would paradoxically also have more equal rates of spread of metastases in the spinal distribution reflecting more aggressive metastatic capacity, as these tumors rarely metastasize [23]. Those harboring metastogenic cell populations despite their small size would thus be predicted to have aggressive metastatic capacity not reflecting the locoregional phenotype described above. The 4 cm cutoff is based on several series demonstrating differential survival and metastatic potential, resulting in the 2002 revision to RCC TNM guidelines [24–30].

This study demonstrates that spinal bony involvement in RCC is predominantly a function of distance from the kidneys and suggests that a circulating tumor concentration gradient biases metastatic deposit rates. This is concordant with the theory of the valveless Batson plexus acting as a conduit for spread from the retroperitoneal space to the vertebral column. Arterial spread, reflecting poor tumor deposit settling within locoregional compartments, would be predicted to be randomly distributed throughout spinal levels given this would involve admixture and random circulation of these metastogenic populations through the body. Future studies are geared towards an outlier analysis to define the molecular features that facilitate metastasis distant to the thoracolumbar junction.

An important limitation in our study design is its retrospective nature, and critically, that these data are captured at a single time point along each patient’s metastatic course. In other

words, patients who have spine-only disease may progress to extra-spinal or soft tissue/visceral sites of metastases.

5. Conclusions

This analysis of bony distribution across spinal levels in bone-metastatic RCC supports the concept of a dominant locoregional mode of bone spread—in concordance with the theory of the Batson plexus serving as a conduit between the retroperitoneum and adjacent vertebral column—as opposed to stochastic studding of bones from an arterially diluted, hematogenous pool of tumor cells circulating throughout the body. Outlier analysis on metastatic deposits distant to the thoracolumbar junction, with diffuse spread to many bony levels, and those emanating from otherwise low-risk primary tumors, are being studied to characterize biologic molecular features contributing to aggressive osteo-tropic biology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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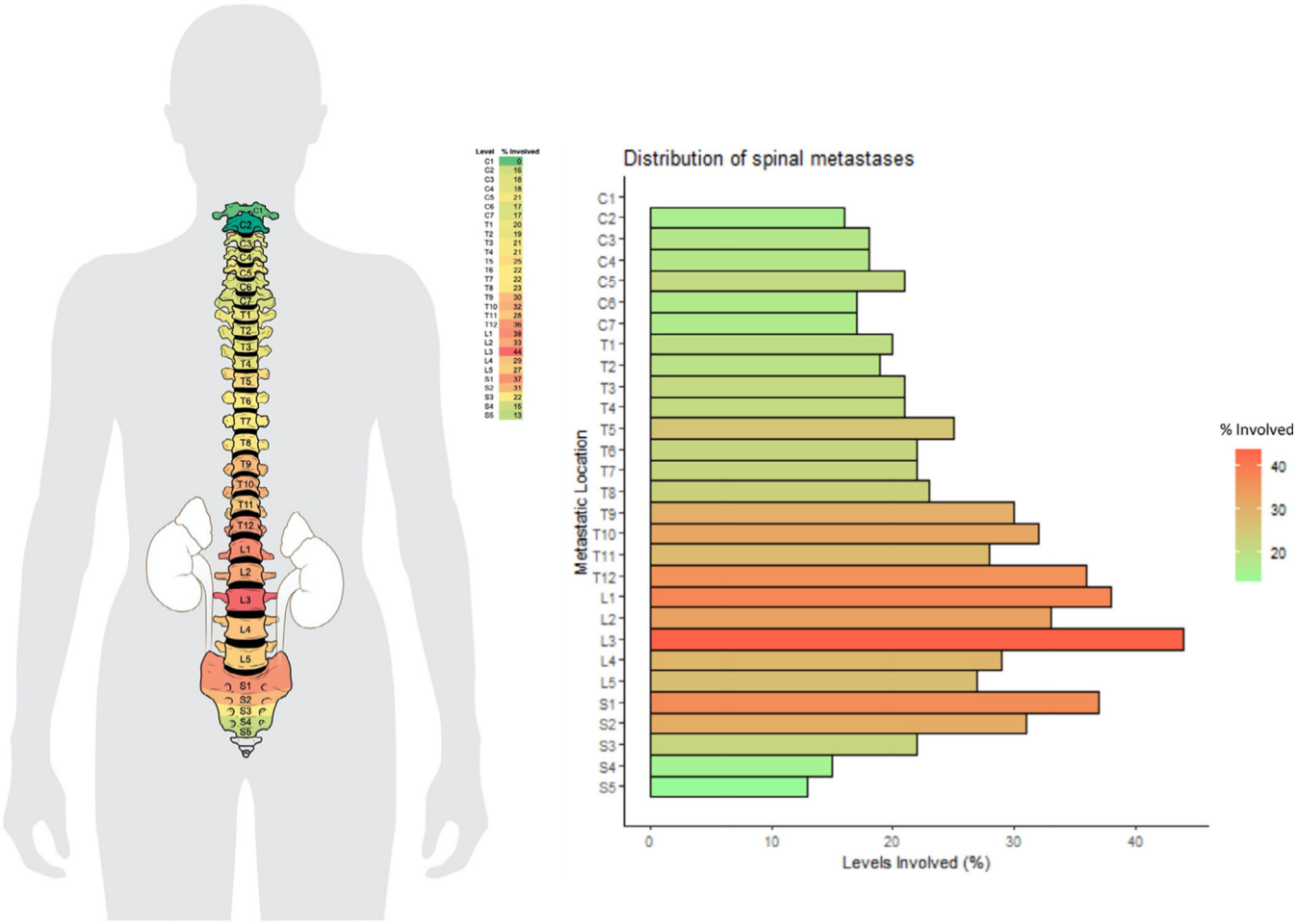

Fig. 1.

Heat map demonstrating the percentage of vertebral levels involved with metastatic renal cell carcinoma across all scanned vertebral level, and distribution of spinal metastasis across all patients (n = 100; mode = L3; $p < 0.001$).

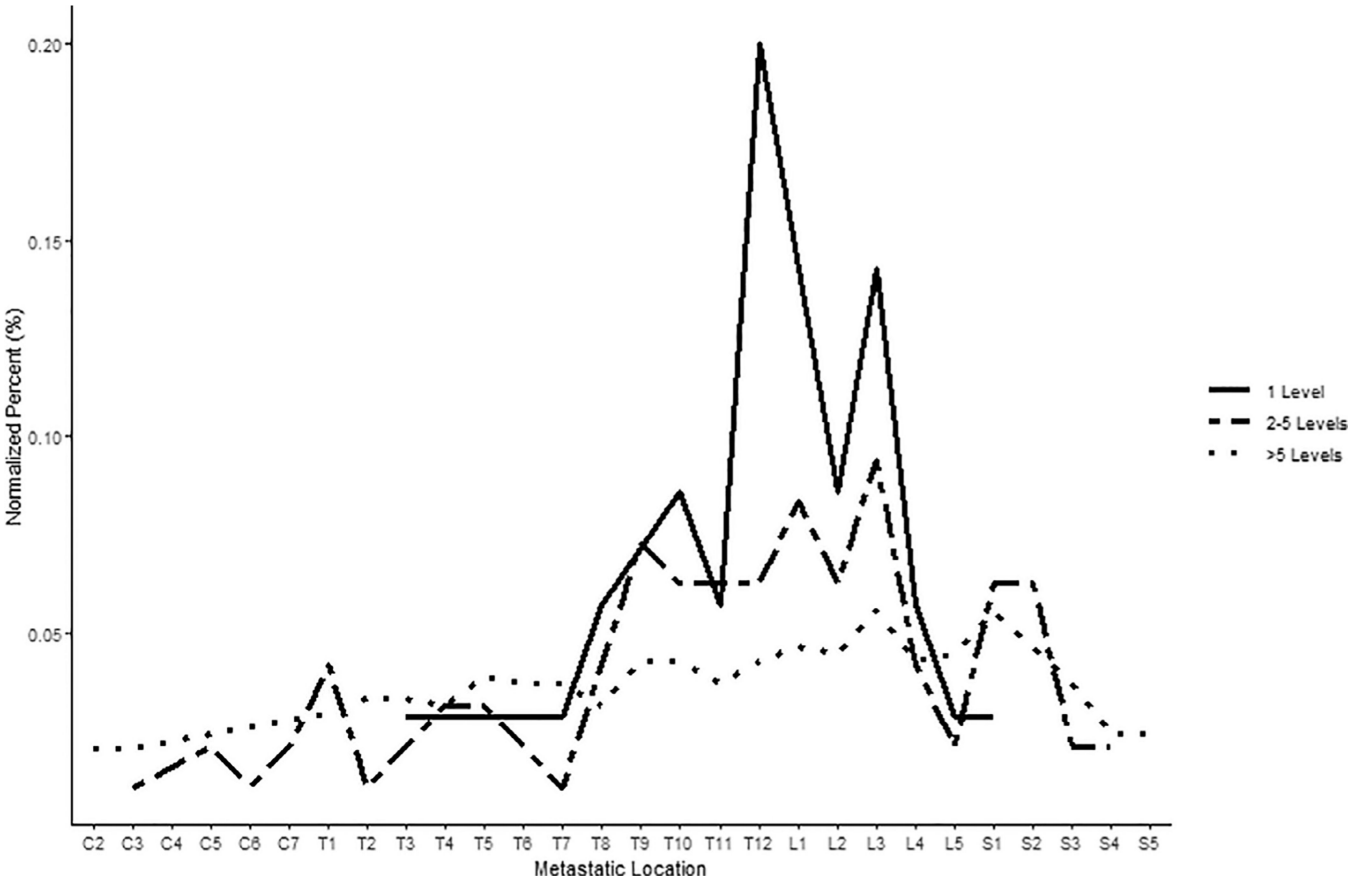

Fig. 2.

Differences in spinal metastatic distribution by number of vertebral levels involved with metastatic renal cell carcinoma. Metastatic distribution was significantly non-uniform across all groups (1 level involved, $p = 0.008$; 2–5 levels involved, $p = 0.004$; >5 levels involved, $p < 0.001$).

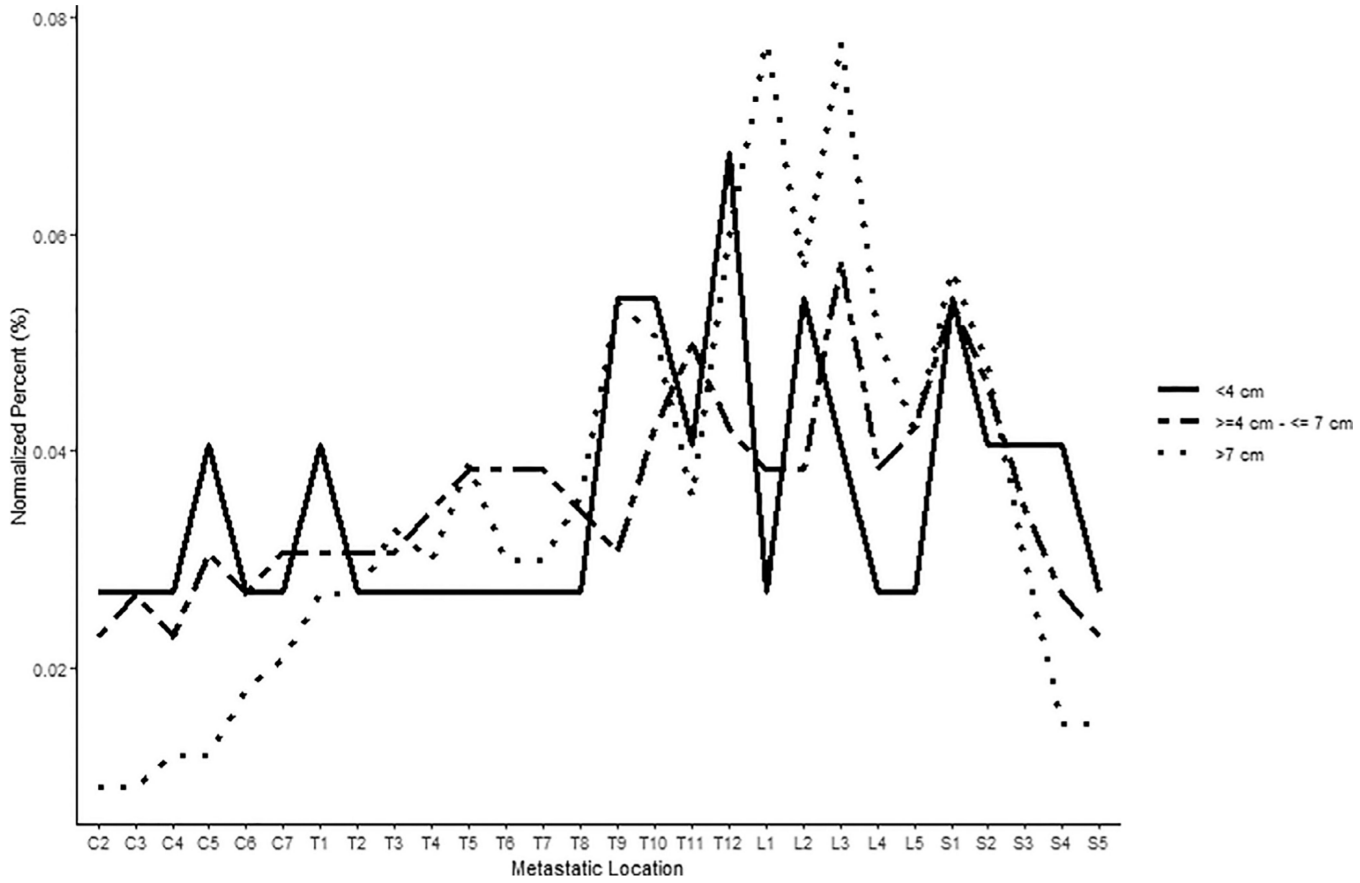

Fig. 3.

Differences in spinal metastatic distribution by tumor size. Tumors <4 cm demonstrated spinal distribution not significantly different from uniform ($p = 0.292$), while tumors 4–7 cm and >7cm displayed significantly non-uniform distributions (both $p < 0.001$).

Table 1

Baseline and clinical characteristics[a]

	***N* = 100**
Sex	
Male	68 (68%)
Female	32 (32%)
Histology	
Clear cell RCC	71 (71%)
Clear cell RCC with sarcomatoid features	12 (12%)
Chromophobe RCC	15 (15%)
Collecting duct RCC	1 (1.0%)
Unclassified RCC	1 (1.0%)
Age at diagnosis (years)	57 (19, 85)
Laterality	
Left	55 (55%)
Right	45 (45%)
Tumor size (cm)	8.0 (1.2, 17.2)
Unknown	5
Metastatic site	
Distant	28 (28%)
Distant + regional lymph nodes	43 (43%)
Regional lymph nodes only	12 (12%)
Spine only	17 (17%)

RCC = renal cell carcinoma.

[a]Statistics presented: *n* (%); median (minimum, maximum).