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Characterizing the Impact of Lymph Node Metastases on the Survival Outcome for Metastatic Renal Cell Carcinoma Patients Treated with Targeted Therapies

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Abstract

Background: It is unknown whether lymph node metastases (LNM) and their localization negatively affect clinical outcome in metastatic renal cell carcinoma (mRCC) patients.
Objective: To evaluate the clinicopathological features, survival outcome, and treatment response in mRCC patients with LNM versus those without LNM after treatment with targeted therapies (TT).
Design, setting, and participants: Patients ($n = 2996$) were first analyzed without consideration of lymph node (LN) localization or histologic subtype. Additional analyses ($n = 1536$) were performed in subgroups of patients with supradiaphragmatic (SPD) LNM, subdiaphragmatic (SBD) LNM, and patients with LNM in both locations (SPD+/SBD+) without histologic considerations, and then separately in clear cell RCC (ccRCC) and non–clear cell RCC (nccRCC) patients, respectively.
Outcome measurements and statistical analysis: The primary outcome was overall survival (OS) and the secondary outcome was progression-free survival (PFS).
Results and limitations: All patients with LNM had worse PFS ($p = 0.001$) and OS ($p < 0.001$) compared to those without LNM. Compared to patients without LNM (PFS 8.8 mo; OS 25.1 mo), any SBD LNM involvement was associated with worse PFS (SBD, 6.8 mo; $p = 0.003$; SPD+/SBD+, 5.5 mo; $p < 0.001$) and OS (SBD, 16.2 mo; $p < 0.001$; SPD+/SBD+, 11.5 mo; $p < 0.001$). Both SBD and SPD+/SBD+ LNM were retained as independent prognostic factors in multivariate analyses (MVA) for PFS ($p = 0.006$ and

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$p = 0.022$, respectively) and OS (both $p < 0.001$), while SPD LNM was not an independent risk factor. Likewise, in ccRCC, SBD LNM (19.8 mo) and SPD+/SBD+ LNM (12.85 mo) patients had the worst OS. SPD+/SBD+ LNM ($p = 0.006$) and SBD LNM ($p = 0.028$) were independent prognostic factors for OS in MVA, while SPD LNM was not significant ($p = 0.301$). The study is limited by its retrospective design and the lack of pathologic evaluation of LNM in all cases.

Conclusions: The metastatic spread of RCC to SBD lymph nodes is associated with poor prognosis in mRCC patients treated with TT.

Patient summary: The presence of lymph node metastases below the diaphragm is associated with shorter survival outcome when metastatic renal cell carcinoma (mRCC) patients are treated with targeted therapies. Clinical trials should evaluate whether surgical removal of regional lymph nodes at the time of nephrectomy may improve outcomes in high-risk RCC patients.

1. Introduction

Renal cell carcinoma (RCC) is a heterogeneous disease consisting of several tumor types that have their own genetic, molecular, and clinical characteristics. Historical studies in the cytokine era by the University of California Los Angeles (UCLA) and the National Institutes of Health (NIH) described poor prognosis and worse treatment response to interleukin-2 (IL-2) in patients with metastatic involvement of the retroperitoneal lymph nodes [1,2]. Patients with and without retroperitoneal lymph node involvement had median overall survival (OS) times of 8.5 mo and 14.7 mo ($p = 0.0004$), respectively [2]. Pantuck et al [1] reported a better objective response rate in N0M1 compared to N+M1 patients ($p = 0.01$), with survival times of 10.5 mo and 20.4 mo, respectively. The adverse prognostic impact of retroperitoneal lymph node metastases (LNM) on survival outcome in patients with metastatic RCC (mRCC) was confirmed by several other institutions during the cytokine era [3–5]. However, in the era of targeted therapies (TT), the survival outcome for patients with LNM has not yet been well characterized.

RCC preferentially metastasizes via hematogenous routes. Bianchi et al [6] recently described hematogenous metastatic sites in 80% of 11 157 patients with mRCC, while extension of the disease into lymph nodes was described only in 20% of patients. However, the authors did not provide details about the distribution of lymph node localization. The dominant regional LNM sites in RCC are retro- and paracaval, pre- and paraaortic, and interaortocaval lymph nodes in an anatomically intact retroperitoneum [7]. LNM can be unpredictable, and can also occur via direct extension to the thorax, supraclavicular lymph nodes, and iliac lymph nodes [7]. It has not been documented if particular sites of positive lymph node localization have a negative influence on the survival outcome of mRCC patients treated with TT.

Whether retroperitoneal lymph node dissection (LND) improves survival outcome is the subject of ongoing scientific debate. A phase 3 clinical trial (EORTC 30881) demonstrated positive lymph nodes in only 4% of investigated cases having no apparent involvement on computed tomography (CT) imaging. There was no advantage in OS, recurrence-free survival, or progression-free survival (PFS) for RCC patients who underwent LND [8]. The study has been criticized, however, because the majority of patients included had low-stage disease. Moreover, uniform surgical templates were not used for LND [9]. However, retrospective studies have demonstrated that LNM are more prevalent in high-risk patients with high Fuhrman grades, sarcomatoid features, locally advanced tumor stage, tumor size >10 cm, and tumor necrosis [10]. It has been suggested that LND is particularly beneficial in these high-risk patients [11,12]. Trends in the surgical management of RCC that have moved away from open radical surgery with extended LND to laparoscopic and robotic surgery with minimal hilar LND, combined with the negative results of phase 3 studies showing no additional benefit of LND over removal of the primary tumor alone, have decreased enthusiasm for performing extended LND. Therefore, it is common clinical practice to perform LND only in high-risk patients, and with a diagnostic rather than a curative intention [7]. Retrospective studies may be unable to add new insights into the current debate because only a prospective randomized trial with clear inclusion and exclusion criteria would be able to overcome this selection bias. Before planning such trials, however, it is prudent to better understand the impact of LNM and different lymph node localizations on the survival outcome for mRCC patients treated with current state-of-the-art therapies using data from the International mRCC Database Consortium (IMDC).

2. Patients and methods

2.1. Study populations

The IMDC database includes centers from North America (Canada, USA), Europe (Denmark, Greece, Belgium), Asia (Singapore, Japan, South Korea), and New Zealand. Data were collected from August 15, 2008 until December 31, 2013. At the time of analysis, the database contained data on 3405 patients who had received first-line targeted therapies between 2003 and 2013. The final study cohort comprised 2996 patients who were treated with first-line vascular endothelial growth factor (VEGF) inhibitors ($n = 2823$), mammalian target of rapamycin (mTOR) inhibitors ($n = 165$), or a combination of both ($n = 8$) therapies between April 2003 and August 2013. Patients were excluded from the analyses if they had received experimental therapies in first-line treatment ($n = 7$) or if no information was available on their lymph node status ($n = 402$; Fig. 1). Lymph node status was determined according to standard pathologic and CT criteria.