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Original article

The independent oncological role for cytoreductive nephrectomy in metastatic renal cell carcinoma: Prognostic features in the era of targeted therapies

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Abstract

Objectives: To describe the effects of cytoreductive nephrectomy (CN) on the natural course of metastatic renal cell carcinoma (mRCC). CN appears to stabilize metastatic lesions in mRCC in a subgroup of patients and we hypothesize that systemic treatment might be deferred in these patients with stable disease after CN.

Subjects and methods: Overall, 45 patients with mRCC who underwent CN and subsequent oncologic follow-up were included in this retrospective, single-center analysis. After CN, patients were followed at least every 3 months with clinical evaluation, contrast-enhanced computerized tomography scan of chest and abdomen, with additional imaging if needed. At 3 months, patients were radiographically evaluated and categorized into nonresponders (death or progression) or responders (stable disease or remission). Kaplan-Meier and Cox proportional hazards regression statistics were used to describe prognostic factors for overall survival (OS) and systemic therapy–free survival (STFS).

Results: Median OS was 31(3–121) months. Further, 24 (53.3%) and 21 (46.7%) patients were classified as responders and nonresponders at 3 months, respectively. Responders had a significant better 2-year OS compared with nonresponders (81.7% vs. 26.5%, $P = 0.005$). Responders also had a better 2-year STFS (40.3% vs. 6.3%, $P = 0.005$). On Cox regression analysis, worse OS was found to be associated with low preoperative hemoglobin levels, the absence of postoperative radiographical response, and the presence of non–clear cell pathology. The presence of postoperative radiographical response, normal preoperative lactate dehydrogenase levels, the presence of a single metastasis, and performing metastasis-directed therapy was found to be associated with a longer systemic therapy-free period.

Conclusion: A beneficial oncologic response is observed in approximately half of the patients undergoing CN. Absence of radiographic progression at 3 months is an important marker for OS and STFS. Therefore, systemic treatment might be postponed in selected patients.

Keywords: Renal cell carcinoma; Metastasis; Nephrectomy; Cytoreductive surgery

1. Introduction

In Europe, renal cell carcinoma (RCC) is currently the sixth most common malignancy [1]. These tumors are

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nowadays more often diagnosed in an earlier stage for which curative treatment is possible [2]. Nevertheless, up to 30% of patients are diagnosed with metastatic RCC (mRCC) at presentation [2]. Median overall survival (OS) of mRCC is only 9 to 29 months, despite the introduction of novel systemic therapies [3–5].

Cytoreductive nephrectomy (CN) combined with systemic treatment has shown to benefit OS compared with systemic treatment alone [5,6]. CN, combined with complete resection of metastatic lesion(s), has been reported to substantially prolong survival in a subset of patients [7]. Although novel systemic therapies such as tyrosine kinase inhibitors (TKIs) and inhibitors of mammalian target of rapamycine (mTOR) have improved survival compared with immunotherapy, toxicity is still substantial [8,9]. The true role of CN in this era of targeted therapies would be revealed by the SURTIME (NCT1099423) and CARMENA (NCT00930033) trials, but not until the end of 2016 [10,11]. Awaiting these results, we aim to report real-world data on these patients, regarding OS, clinical outcome, and the start of systemic therapy.

2. Materials and methods

2.1. Patient selection

A retrospective surgical database was scanned for nephrectomies performed between April 2005 and April 2015 at a single tertiary center. Pediatric tumors, non-malignant pathologies and non-RCC malignancies were filtered out. Overall, 51 adults with synchronous mRCC who underwent a CN were retained. A patient was excluded from the analysis because of synchronous transitional cell carcinoma and 6 patients did not meet the minimum 3-month follow-up requirement, resulting in 45 included subjects (Fig. 1).

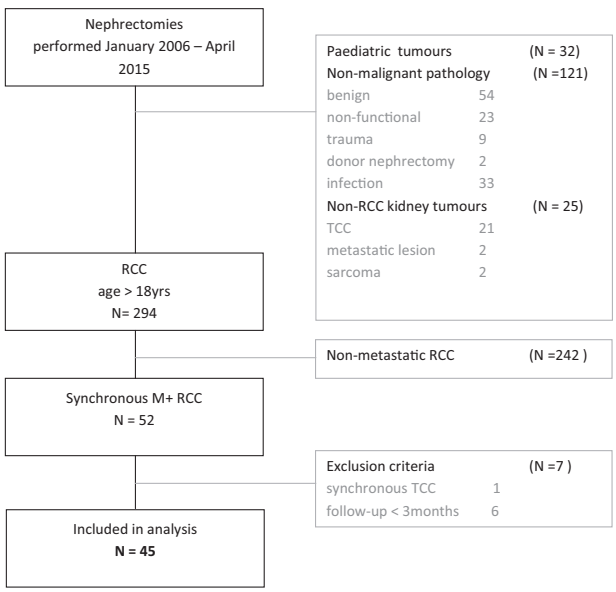

Fig. 1. Patient selection flow-chart. M+: metastatic disease; TCC: transitional cell carcinoma.

2.2. Patient population

Preoperative radiographic staging included at least contrast-enhanced computerized tomography (CT) of chest and abdomen. Other imaging was performed if clinically indicated. Cytroreductive nephrectomy was performed open, by retroperitoneoscopy, by laparoscopy, and transperitoneal robot-assisted in 33 (73%), 4 (9%), 3 (7%), and 5 (11%) patients, respectively. Choice of technique was dictated by tumor extent, tumor location, and surgeon's preference. Resection specimens were processed by a pathologist with specific interest in urologic malignancies (M.P.) and classified according to the TNM classification. Other histological factors included for this analysis were Fuhrman grade, RCC subtypes, and sarcomatoid features. Preoperative laboratory values (hemoglobin, calcium level, platelet count, neutrophil count, and lactate dehydrogenase [LDH]) were retrieved. Abnormal biochemistry was defined as a hemoglobin level below the lower limit of normal (LLN), a calcium level exceeding the upper limit of normal (ULN), a platelet count exceeding 374 × 10E3/µl, a neutrophil count higher than the ULN, or a LDH exceeding 1.5 times ULN in analogy to the Heng et al. [5] and MSKCC [12] prognostic criteria (Table 1).

Owing to the retrospective nature of this study, baseline patient characteristics, such as performance status and the presence of localized symptoms could not be retrieved for all patients and were thus not included into this analysis.

After CN, patients were followed up at least every 3 months with clinical evaluation, contrast-enhanced CT of chest, and abdomen and additional imaging, when indicated. Radiographic progression was defined as one or more of the following: (1) progression of bone metastases (new bone metastases or 2 or more additional bone metastases) on bone scan, CT or magnetic resonance imaging. (2) Progression of soft tissue metastases according to RECIST 1.1 criteria. (3) Development of at least one new visceral or soft tissue metastasis. Complete response or remission was defined as complete disappearance of all extranodal lesions and reduction of nodal lesions to a size of <10 mm. Partial response required a minimal size reduction of 30% in a lesion, without other signs of progressive disease. Patients with stable disease did not meet the qualifying characteristics of progression or response [13].

When deemed possible, solitary or oligometastatic lesions were treated by metastasectomy or stereotactic body radiation therapy (SBRT). Systemic therapy was started at time of extended radiographic progression (based on RECIST 1.1 guideline, clinical judgment, and after multidisciplinary discussion) or symptomatic disease or both. In cases with minimal progression, systemic therapy was delayed after multidisciplinary discussion. Patients who received adjuvant therapy electively outside of these