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Original article

Effect of glandular metastases on overall survival of patients with metastatic clear cell renal cell carcinoma in the antiangiogenic therapy era

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Abstract

Background: Glandular metastases (GMs) (pancreas, breast, parotid, thyroid, or contralateral adrenal) are rare in metastatic clear cell renal cell carcinoma (mccRCC).

In a multicenter study we have assessed outcome from mccRCC with or without GMs.

Patients and methods: Patients with mccRCC and GM or non-GM (NGM) at first presentation of mccRCC, treated at 9 European centers (5 French, 3 UK, and 1 Belgian centers) between January 2004 and October 2013, were retrospectively analyzed. Association between overall survival (OS) and site of metastases was assessed using the log-rank test for univariate analysis and the chi-square test for multivariable Cox regression.

Results: In all, 138 patients with GM mccRCC and 420 with NGM mccRCC were included; 37.2% patients with GM had Memorial Sloan-Kettering Cancer Center (MSKCC)-favorable risk vs. 18% NGM patients; 10.7% patients with GM had MSKCC-poor risk vs. 27% NGM patients ($P < 0.0001$). Median interval from metastases to treatment was 4.2 months (range: 0–221.3 mo). Median OS was 61.5 months (51.4–81.6 mo) for GM and 37.4 months (31.3–42 mo) for NGM (hazard ratio [HR] = 1.7; 95% CI = 1.3–2.2, $P < 0.001$).

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In univariate OS analysis, age, delay between initial diagnosis and metastases, MSKCC, bone/lung metastases, and GM or NGM group were significant parameters ($P < 0.001$). In multivariate analysis, adjusted according to MSKCC risk group, NGM vs. GM was a strong prognostic factor (HR = 1.4; 95% CI = 1.0–1.8, $P = 0.026$); bone or liver metastases were also significant (HR = 1.3; 95% CI = 1.1–1.7, $P < 0.02$; HR = 1.4; 95% CI = 1.1–1.7, $P < 0.02$, respectively). Even in patients without bone or liver metastases, GM status was significant (HR = 1.8; 95% CI = 1.2–2.7, $P < 0.004$).

Conclusions: This large retrospective study shows that the presence of at least 1 GM site in development of mccRCC was associated with a significantly longer OS. The presence of GMs vs. NGM disease was an independent prognostic factor for survival irrespective of the presence or absence of bone or liver metastases. This finding could affect daily practice in which patients with mccRCC and GMs should receive more aggressive treatment with a potential for long-term survival.

The causal mechanisms for this improved prognosis in GM mccRCC would be evaluated in translational studies.

Keywords: Kidney cancer; Clear cell renal carcinoma; Prognosis factors; Glandular metastases; Survival outcome; Targeted therapies; Antiangiogenic therapy

1. Introduction

Renal cell carcinoma (RCC) accounts for 3% of adult malignancies and is the most common malignancy in the kidney. More than two-thirds of the patients are diagnosed with localized disease. Approximately 20% to 30% of all patients undergoing nephrectomy for clinically localized disease develop metastatic disease. Approximately 20% to 30% of the patients diagnosed with RCC already have metastatic disease at presentation [1,2]. In metastatic clear cell RCC (mccRCC), despite new targeted therapies, prognosis remains poor and 5-year life expectancy is less than 20% [3]. The most common sites of metastatic disease include lung (45%), bone (30%), lymph node (22%), liver (20%), and brain (8%) [4]. Adrenal metastasis occurred in 9%, but few data are available concerning other glandular metastatic sites such as pancreas, breast, thyroid, and parotid. These various metastatic sites that we considered as glandular metastases (GMs) are infrequent sites of metastasis. However, kidney cancer is the most frequent tumor that metastasizes to these sites and the evolution is frequently indolent [5].

Recent advances in understanding the molecular biology of RCC have led to the development of new targeted agents, which have been proven active in progression-free and survival improvement. Some prognostic factors have been identified and combined to develop prognostic models. The most widely used is the Memorial Sloan-Kettering Cancer Center (MSKCC) score. More recently, the International Metastatic Kidney Cancer Database Consortium developed a new score [6,7]. All of these scores were based on biological parameters, time from nephrectomy, and Karnofsky performance status. In addition to these scores, it appears that the metastatic site may also have an effect on survival. Recently the International Kidney Cancer Working Group identified that bone or liver metastases confer a significantly poorer overall survival (OS) than other metastatic sites do [8].

GMs, particularly pancreatic and adrenal metastases, are often associated with good survival in the literature, although the studies are based on heterogeneous patient populations [9,10]. The aim of this study was to evaluate the effect of GMs in mccRCC on OS in patients treated with targeted therapies, the current standard of care.

2. Materiel and methods

2.1. Population

A retrospective study was performed in 5 centers in France, 1 in Belgium, and 3 in the UK. Only patients who had been treated with at least 1 targeted therapy (anti-VEGF, TKI-VEGFR, or mTOR inhibitor) for mccRCC in each institution between January 2004 and October 2013 were considered for analysis. Patients treated by surgery alone, immunotherapy alone, or without treatment of mccRCC were excluded from this analysis. Of the centers, 3 identified patients with mccRCC with or without GM, whereas 6 of the centers contributed only to patients with glandular metastatic RCC. Glandular metastatic sites were defined as pancreas, breast, parotid, thyroid, and adrenal gland (contralateral to the primary tumor). Patients excluded from the study were those with ipsilateral adrenal metastases and those whose metastatic disease was treated by metastasectomy alone.

The following patient characteristics at the time of metastatic disease were collected: prognostic factors by MSKCC classification, sites of metastases (based on radiological and pathological data), local and systemic treatments for metastatic disease, and survival data. Based on recent published data we evaluated the prognostic effect of bone and liver metastases in patients with GMs at diagnosis and NGM [8].

2.2. Statistical analysis

Baseline patient and disease characteristics were summarized using descriptive analysis. Differences between patients with GM and NGM were assessed using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. OS was defined as the time between the date of first diagnosis of metastases and the date of death from any cause. We were able to set the date of point since the diagnosis of the first metastases