

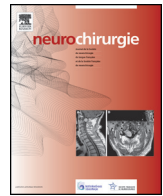


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Original article

Brain metastasis from renal cell carcinoma



Métastases cérébrales de cancer du rein

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ABSTRACT

Background. – Patients with brain metastasis (BM) from renal cell carcinoma (RCC) have a poorly known prognosis due to the rarity of this disease. The aim of our study was to assess the outcome of patients with a BM due to RCC, and to determine the predictive factors for survival.

Methods. – Consecutive patients who underwent treatment between 1997 and 2012 were identified retrospectively from a database ($n = 28$, median age of 57.8 years, sex ratio M/F: 3.7). Main criteria collected concerned survival time. Other data collected were relative to initial histology, clinical findings at the time of BM diagnosis (diagnosis circumstances, KPS), radiological findings and BM characteristics (number, size and localization), treatment of BM (including surgery, stereotactic radiosurgery [SRS], systemic treatments, whole brain radiotherapy [WBRT]) and the outcome of surgery if performed. Statistical analysis of survival was performed using the Kaplan-Meier method.

Results. – Median survival was 13.3 months, 1-year survival was 60.2%, 2-year survival was 16.4%. Univariate analysis showed the existence of intracranial hypertension ($P = 0.01$), other systemic metastasis ($P = 0.049$), the absence of deep metastasis ($P = 0.03$) which are all linked to shorter survival. Age, KPS, initial histology of RCC, number, size, localization, and hemorrhage in BM were not correlated to survival. The median survival in the surgical resection group was 25.3 months versus 8.6 months ($P = 0.02$). The main criteria for the selection of the surgical group were a single BM ($P = 0.04$), and superficial metastasis ($P = 0.02$).

Conclusions. – Three predictive factors for longer survival in BMRCC were the absence of intracranial hypertension, the absence of acute metastasis and the absence of extracranial metastasis. Surgical removal, when possible, seems to benefit patient survival.

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R É S U M É

Introduction. – Les métastases cérébrales (MC) de cancer du rein (CR) sont des atteintes rares dont le pronostic est mal connu. L'objectif est d'analyser la survie chez les patients porteurs de MC de CR et de déterminer les facteurs prédictifs de survie.

Patients et méthodes. – La population est composée d'une série consécutive de 28 patients (âge : 57,8 ; sex-ratio H/F : 3,7) traités pour une MC de CR entre 1997 et 2012. Le recueil rétrospectif de données (histologie du CR, état clinique initial, [circonstances de découverte, score de Karnofsky {KPS}], données radiologiques, traitements [résection chirurgicale, radiochirurgie, thérapies ciblées systémiques et radiothérapie] et survie) a été réalisé. L'analyse statistique de la survie est réalisée par la méthode de Kaplan-Meier.

Résultats. – La survie médiane des patients avec MC est de 13,3 mois, la survie à un an est de 60,2 %, et à 2 ans de 16,4 %. Les variables associées à une survie plus longue sont l'absence d'hypertension intracrânienne ($p = 0,01$), l'absence de métastases systémiques ($p = 0,049$) et l'absence de métastases profondes ($p = 0,03$). L'âge, le KPS, l'histologie des CR, le nombre, la taille, le caractère hémorragique des MC ne sont pas

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significatifs. La survie dans le groupe traité chirurgicalement est de 25,3 mois contre 8,7 mois dans le groupe non traité ($p=0,02$). Les principaux critères de sélection des patients opérés sont l'existence d'une métastase cérébrale unique ($p=0,04$) et l'existence d'une métastase superficielle ($p=0,02$).

Conclusions. – Trois facteurs prédictifs de survie prolongée des MC de CR ont pu être identifiés : l'absence d'hypertension intracrânienne, l'absence de métastases systémiques et l'absence de métastases profondes. Quand la résection chirurgicale est possible, elle semble apporter un gain de survie.

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1. Introduction

Brain metastasis (BM) affects 3.5% [1] to 17% [2] of patients with renal cell carcinoma (RCC). In these patients, median survival varied between 4.1 months [3] and 13.4 months [4] respectively. The armamentarium against these metastases is limited, primarily due to resistance to classical modalities of treatment i.e., chemotherapy [5] and radiotherapy [6]. For these reasons, radiosurgery [7] and surgery have remained an effective conventional treatment proposition [8], despite the resection difficulty related to the vascular nature of the disease [9].

Due to the rarity of the disease, no prospective study has yet been published on this subject. Various prognostic factors have been proposed, including the number of BM [3,10], initial clinical status [10], or the existence of extracerebral metastasis [4]. The most significant prognostic factors isolated in the Radiotherapy and Oncology Group (RTOG) stratification analysis have been used in the form of composite prognostic factor to predict survival and response to radiotherapy and systemic therapy [11]. However, these prognostic factors have been proposed in studies with selective recruitment, based on the access to a surgical, medical or radiotherapy treatment, leading to contradictory results. Thus, much is still needed to enhance our knowledge about the natural history of the BMRCC, the prognostic factors, and the surgical criteria for the resection of BM.

The aim of this study was to attempt to determine the outcome of a series of consecutive patients with BM from RCC, as well as the prognostic factors of survival, while analyzing the factors that led to surgical treatment for these patients.

2. Patients and methods

This retrospective longitudinal and observational study included all the consecutive patients who presented with a brain metastasis due to renal cell carcinoma between 1997 and 2012, collected from a computerized database. Exclusion criteria were the incomplete availability of the histological, clinical or radiological data at the time of inclusion.

Our primary objective was to attempt to determine the median survival of BMRCC patients. Secondary objectives were the analysis of the prognostic factors affecting survival and the decision concerning surgical treatment.

The primary endpoint was survival time, defined as the delay between clinical diagnosis and death. Secondary endpoints were organized into 5 categories: diagnostic circumstances, BM characteristics, RCC histology, prognostic score, and treatments.

The diagnostic circumstances included the initial symptomatology: epilepsy, intracranial hypertension (ICH) and focal deficit, and the Karnofsky Performance Status (KPS [12]).

The BM characteristics were the number, size (maximum diameter on T1 gadolinium weighed sequence MRI), location (supratentorial, infratentorial, superficial or deep), hemorrhage, and delay of RCC diagnosis (synchronous or metachronous).

The RCC histology included the T grade ranked from 1 to 4 according to the locoregional and general extension of the RCC, and the Fuhrman grade ranked 1 to 4 according to nuclear size,

irregularity and nucleolar prominence in the malignant cells and describing the severity of the cytologic malignancy [13].

The prognostic index used to stratify our population was the Disease Specific Graded Prognostic Assessment for RCC (DS-GPA [11]), taking into account 2 prognostic factors: KPS and the number of intracranial metastasis. The score ranges from 0 to 4, 0 being the worst prognostic score and 4 the best prognostic score.

Treatments included surgical resection, whole brain radiotherapy (WBRT), systemic targeted treatments (sunitinib, sorafenib, temsirolimus or interferon), stereotactic radio surgery (SRS), a combination of treatments, or a conservative treatment.

Quantitative variables (age, number and size of BM, median survival and median delay to BM) were considered as continuous variables with normal distribution, and were expressed as median \pm standard deviation (S.D.). Qualitative variables (sex ratio, KPS ≥ 70 , location of BM, DS-GPA, initial T grade ≥ 3 , Fuhrman grade ≥ 3 , extracranial metastasis, type of treatments) were expressed in proportion to a confidence interval at 95%. Survival from BM onset was calculated using the Kaplan-Meier method and groups were compared with the log-rank test. The surviving patients were censored at the end of the follow-up period.

To find patterns in the surgical decision to treat a BM, we compared patients who did not undergo surgery with patients who underwent surgery. Comparison was performed on all the variables described previously, using Fisher's exact test.

All statistical tests were performed using SPSS 20 (SPSS, Inc., Chicago, IL). Tests were considered statistically significant if $P < 0.05$.

3. Results

3.1. Population

Patient characteristics are outlined in Table 1. Our population included 28 patients with 56 BM (median age: 57.8 ± 8.86 years; range: 41–76 years; sex ratio M/F: 3.7) treated for BMRCC.

At the time of the diagnosis, 26 patients (92.8 \pm 9.3%) exhibited symptoms associated to their BM and 2 patients were asymptomatic (7.2 \pm 9.3%), the discovery of the BM was fortuitous on a brain-imaging follow-up to their cancer. ICH was the only symptom in 6 patients (out of 18 patients with ICH), and was related to a hydrocephalus in 3 cases, an acute hemorrhage in 2 patients, and size, number and edema associated to the BM in the 13 other patients. A neurological deficit was the only sign in 6 patients (out of 18 with a neurological deficit). The deficits presented were motor deficits in 9 patients, a sensory deficit in 2 patients, aphasia in 3 patients, visual impairment in 2 patients, cerebellar ataxia in 3 patients, and frontal lobe disorder in 1 patient. One patient also had a neuroendocrine disorder due to the location of the metastasis in the hypothalamus. Only one patient had an isolated epilepsy that led to the diagnosis of BM.

All the patients had an MRI. Brain imaging showed a single metastasis in 13 patients (47.4 \pm 18.5%), 2 BM in 6 patients (21.4 \pm 15.5%), 3 BM in 7 patients (25 \pm 16.04%) and 5 BM in 2 patients (10.7 \pm 9.3%) totaling 56 BM, an average of 2 ± 1.16 brain metastasis per patient. The mean size of the BM was 16 ± 9.9 mm.

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