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ORIGINAL PAPER

The role of surgery in clinical management of patients with metastatic papillary renal cell carcinoma

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Abstract
Objectives Patients with metastatic papillary renal cell carcinoma (RCC) show special clinical behavior compared to patients with other histologic subtypes of RCC. This study aimed to assess the relevance of surgical and systemic options used in treatment of these patients prior to the recent era of targeted therapies.
Methods Retrospectively, we assessed clinical data of 61 patients with metastatic papillary RCC who were treated at eight centers in Germany.
Results Median follow-up was 20 (range 1–114) months and median age at time of diagnosis was 62 (range 24–85) years. Men were affected predominantly (50/61; 82%). Twenty-one patients (34%) showed metastases at time of diagnosis. In the remaining 40 patients, median time to development of metastases was 30.4 (range 3–143; mean 16.5) months. Sites of metastases were lung (37; 61%), bone (24; 38%), liver (20; 33%), lymph nodes (24; 38%), and local recurrence (17; 28%). Others sites of disease were brain metastases (6 patients/10%), peritoneal carcinosis (5 patients/8%), and others. A surgical approach with potentially curative intention was performed primarily in 11 patients (18%). 31 patients received an immuno- (interferon-$\alpha \pm$ interleukin-2) or immunochemotherapy as first line treatment for metastatic disease. Overall, 42/61 patients (69%) received systemic therapy. Supportive care

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only was performed in 12 patients (20%) because of poor performance status. Median overall survival after diagnosis of metastatic disease was longer than 48 months in patients with tumor resection ($n = 11$) compared to 13.0 ± 4.3 months 95% CI 4.5–21.5 ($n = 42$) months in patients without surgical approach.

Conclusions Complete resection of metastases represents a valid option in management of patients with relapsing or metastatic papillary RCC.

Keywords Papillary renal cell carcinoma · Metastases · Immunotherapy · Prognosis · Survival

Introduction

Renal cell carcinoma (RCC) accounts for 3% of all human malignancies (Gieseg et al. 2002). The clear cell histologic subtype represents the most common histologic feature, with a frequency of 65–80% of adult renal neoplasms, whereas papillary RCC accounts for approximately 7–14% of renal epithelial tumors (Reuter and Presti Jr 2000). Recently, studies using current histological subtyping in RCC have identified histology as an important prognostic factor for survival (Beck et al. 2004; Cheville et al. 2003; Gutbjartsson et al. 2005; Ficarra et al. 2005). Each of the malignant histological subtypes is associated with distinct predominant chromosomal abnormalities (Junker et al. 2003). It was demonstrated several years ago that, in conventional clear cell RCC, originating from the proximal convoluted tubules, a deletion or partial deletion of chromosome 3p is characteristic, and mutation of the von-Hippel-Lindau gene occurs exclusively in this type (Gnarra et al. 1994). In papillary RCC, which probably originates from the proximal convoluted tubules, trisomy of chromosomes is often seen, including trisomy of chromosomes 7 and 17 (Renshaw and Fletcher 1997). After nephrectomy for a localized tumor, papillary histology seems to predict a favorable prognosis compared to the clear cell subtype (Kattan et al. 2001). In the metastatic setting, however, papillary RCC seems to be characterized by poor prognosis and resistance to systemic therapy (Beck et al. 2004; Mai et al. 2001; Motzer et al. 2002; Motzer and Russo 2000). The aim of this retrospective trial was to assess the relevance of surgical and systemic options used in treatment of these patients prior to the recent era of targeted therapies.

Methods

We performed a retrospective analysis of clinical features, treatment outcome, and survival of 61 patients, who were treated for metastatic papillary RCC at eight German centers. The survey assessed all patients who were treated at the centers with diagnosis of metastatic papillary RCC between November 1994 and March 2005. All patients had pathologic findings of papillary RCC or, in case of mixed histology, at least predominantly papillary RCC and clinical evaluation of metastases or local recurrences, including follow-up data. In all cases, papillary subtype of renal cancer was primarily diagnosed by tumor nephrectomy.

In patients who were eligible for surgical approaches with potentially curative character metastasectomy was performed. In these patients survival was assessed from the time of surgery. The remaining patients were recommended to receive systemic therapy. In these patients overall survival was assessed from time of starting systemic treatment. Systemic treatment included cytokines [interferon-α (IFN-α), interleukin-2 (IL-2)], cytokine combinations, conventional chemotherapy [Gemcitabine, Capecitabine, Cisplatin, Vinblastine (Vbl), 5-fluorouracile (5-FU)], or combined immunochemotherapy.

Survival rates were calculated according to the Kaplan–Meier method. Survival times were compared using the log rank test. Statistical analyses were performed using the SPSS software package 17.0.

Results

Median follow-up was 20 (range 1–114) months. Fifty of 61 patients (82%) were males and 11 (18%) were females. At time of diagnosis median age was 62 (range 24–85) years. In 21 patients (34%) metastatic disease was assessed already at time of diagnosis. In the remaining 40 patients the median interval from nephrectomy to development of metastatic disease was 30.4 (range 3–143, mean: 16.5) months. The most common sites of metastases were lung, bone, liver, local recurrences, and lymph nodes in different locations (Table 1).

Eleven of 61 patients (18%) had primary surgery of metastases (lung 2, local recurrence/lymph nodes 7, liver 1, brain 1). In 31 patients (51%) metastatic disease was primarily treated with immunotherapy (IFN-α ± IL-2) and immunochemotherapy (IFN-α + Vbl. or IFN-α + IL-2 + 5-FU), respectively. Seven patients received primarily various conventional chemotherapy regimens or radiation therapy. Supportive care only was given in 12 patients (20%) because of poor performance status.

Characteristics of the primarily surgically treated patients are summarized in Table 2. Complete removal of metastasis (R0 resection) was achieved in nine cases (82%) out of the primarily surgically treated patients. Within a medium follow-up of 29 months, 9 of the 11 patients (82%) showed progressive disease and underwent further therapy.

Table 1 Metastatic sites in 61 patients with papillary RCC compared to reported series of metastatic clear cell RCC

Metastatic site	61 patients with papillary RCC		Escudier et al. 2007; $n = 903$	Motzer et al. 2007; $n = 750$
	n	%	%	%
Lung	37	61	77	78
Bone	24	38	n.a.	30
Liver	20	33	26	25
Local recurrence	17	28	n.a.	n.a.
Lymph node (different locations)	24	38	n.a.	55
Brain	6	10	Excluded from study	Excluded from study
Peritoneum	5	8	n.a.	n.a.

Overall, 42/61 patients. (69%) received an interferon- or interleukin-based immunotherapy; most patients (25/42) had at least two different treatment schedules. Five out of 42 patients (11.4%) achieved an objective response. Median survival from time of beginning systemic therapy in $n = 42$ patients was 13.0 ± 4.3 months (95% CI 4.5–21.5). In 7 of the 31 patients with primary immunotherapy cytokines had to be stopped early because of decreased performance status.

A total of 46/61 patients (75.4%) died within follow-up time. In the Kaplan–Meier-analysis median survival from time of diagnosing metastatic disease or local recurrence was assessed to be 13 ± 1.5 months (95% CI 9.9–16) for the whole group, whereas patients with primary surgical resection of local recurrence/metastases showed a median survival time of more than 48 months ($n = 11$). Survival data for different treatment groups are shown in Table 3 and Figure 1.

Discussion

Meanwhile, it is well accepted that papillary RCC represents a subtype of renal cancer with different behavior compared to the clear cell subtype. In our series the pattern of metastatic disease showed more local recurrences than it is typically known for renal cancer (Ljungberg et al. 2007). It is unclear if these local recurrences are caused by lymph node involvement or represent extranodal tumor growth in the fossa renalis.

This is the first report giving survival data of surgically treated patients with metastatic papillary RCC in the literature. Ronnen et al. (2006) from the Motzer group described surgical resection only for two patients, which could mean that these patients had no evidence of disease during follow-up. In our series the median overall survival time of the 11 patients with primarily surgical treatment of metastatic disease was longer than 48 months. This reflects complete resection of metastases (histopathologically confirmed R0-resection) as the only potentially curative option for patients with metastatic papillary RCC. Nevertheless, resection of metastases led to long-lasting freedom from disease in only two out of 11 patients. Whereas local tumor control rate reached 78% (7/9 patients) after complete resection, 5/9 patients developed new metastases in different locations leading to subsequent therapies. On one hand there is a clear bias in comparing survival date from patients with primary surgical versus systemic treatment, as the non metastases resected patients had a more advanced disease with primary unresectable metastases. On the other hand, our data demonstrate that resection of metastases can lead to long disease-free survival or be even curative. Besides that the presented data could lead to the suggestion that minimization of the tumor burden can improve outcome under systemic therapy in papillary RCC. Recently presented data support such theories. Barbastefano et al. presented analogous data at ASCO 2009 in terms of targeted therapy following tumor nephrectomy in patients with primary metastatic clear cell RCC. Reduction in tumor burden of more than 90% was associated with prolonged response to systemic therapy. (Barbastefano et al. 2009)

Until the availability of targeted agents it has been a common practice to offer immunotherapy as the first line approach to patients with metastatic RCC, regardless of the histopathological subtype of renal cancer.

Progression free and overall survival following nephrectomy for locally confirmed papillary RCC seems to be better than that for those patients with the clear cell type (Cheville et al. 2003). The papillary subtype of RCC represents only 7–14% of all RCCs (Reuter and Presti Jr 2000). Since patients with metastatic disease of this type are rarely seen in daily practice, experience with this tumor type is limited. In addition, there are two subtypes of the papillary RCC, which again are characterized by different clinical behavior (Jiang et al. 1998). It is an important drawback of this retrospective study that there was no possibility to distinguish type 1 and type 2 papillary RCC. The patients were treated at outstanding centers specialized in attending to

Table 2 Characteristics of patients with primary surgical therapeutic approach to metastatic papillary RCC

Age at time of metastatic desease (years)	Time from tumor nephrectomy to diagnosis of metastatic disease (months)	Localisation of metastasi(e)s	Complete resection (R0)?	Recurrence in the same location?	Recurrence in different location	Subsequent therapy(ies)	Survival
56	8	Liver	Yes	No	No	No	32+
68	46	Lung	Yes	No	Lung (different location); adrenal gland	Surgery	22+
65	25	Local recurrence/lymph node	No	Minimal residual disease	No	ICT; Interferon + Interleukin-2	28+
62	37	Lung	Yes	No	Retroperitoneum, Lung (different location)	Radiation; Interleukin-2 (Inhalation); ICT	38
24	0	Lymph node (supraclavicular)	Yes	No	Systemic progression	ICT; radiation; Gemcitabine + Cisplatin	18
51	7	Local recurrence/lymph node	Yes	No	Bone, abdominal wall	Surgery	12
33	54	Local recurrence/lymph node	Yes	n.a.	n.a.	ICT; Gemcitabine + Interferon	42+
55	62	Local recurrence/lymph node	Yes	Yes	Bone	Surgery; radiation	64+
62	5	Brain	Yes	No	No	Adjuvant radiation	13
77	4	Local recurrence/lymph node	No	Rapid progression despite of systemic therapy		Interferon; Bevacizumab; radiation	8+
65	7	Local recurrence/lymph node	Yes	No	Peritoneal carcinosis	Interferon	15

ICT Immunochemotherapy (Interleukin-2 + Interferon + 5-Fluorouracil)

Table 3 In Kaplan–Meier analysis assessed data on overall survival of the 61 patients with metastatic papillary renal cell carcinoma

Patient subgroup	*n*	Median survival	95% CI
Entire group	61	13.0 ± 1.5 months	9.9–16.0 months
Primarily surgical therapy of metastatic disease	11	Not reached	
Primarily immuno (chemo) therapy of metastatic disease	31	13.0 ± 2.9 months	7.2–18.7 months
No specific tumor therapy; best supportive care only	12	5.0 ± 1.3 months	2.7–7.3 months

Seven patients with different primary therapy (conventional chemotherapy, radiation) were excluded from analysis. Median follow-up was 20 months

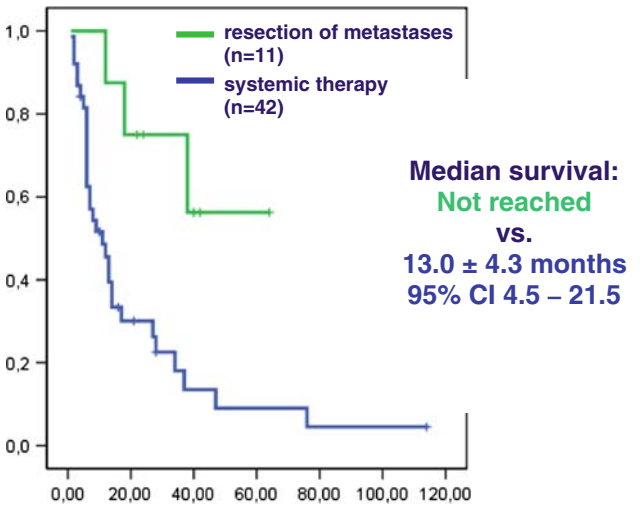

Fig. 1 Kaplan–Meier analysis of overall survival in patients with metastatic papillary renal cell carcinoma according to the used therapy for metastatic disease (resection of metastases versus immuno (chemo) therapy)

patients with metastatic disease. Typically, radical nephrectomy had been performed earlier at different hospitals. In most cases there was no tumor tissue available for further histologic or genetic investigations. Diagnosis of papillary RCC was given by several pathologists at different treatment sites. Missing central and independent review could be one reason for the surprising high objective response rate of more than 10% in this cohort of patients with metastatic papillary RCC, which is in contrast with published data by others. In a series of 22 patients with metastatic papillary RCC no objective response after immunochemotherapy with IFN-α, IL-2 and 5-FU was seen (Herrmann et al. 2007).

There are some publications in the literature which deal with the prognosis of patients with metastatic papillary RCC. Motzer et al. reported in 2002 on 18 patients with metastatic papillary RCC. Six of these patients received immunotherapy. In this series the median overall survival time of patients with papillary RCC was 5.5 months (95% CI 4–12 months) (Motzer et al. 2002). In a more recent publication the Motzer group reported on patients with papillary RCC again (Ronnen et al. 2006). There could be some overlapping of this 38 patient group with the first-mentioned series. 5 (13%) patients received supportive care only, 2 (5%) received surgical resection only, and 1 (3%) patient received unknown therapy. Forty-four systemic treatments were given to the remaining 30 patients. Only one patient was observed to have a partial response to systemic therapy with sunitinib, a tyrosine kinase inhibitor. The median overall survival time of the entire group was 8 months (95% CI 5–12 months). Survival data depending on supportive care only, surgical, or systemic anticancer therapy are not given. Looking at our data on patients under systemic therapy, the reported data of the Motzer group seem to be comparable with our results because of widely overlapping 95% confidence intervals (5–12 months versus 9.9–16 months).

At present, immunotherapeutic options in systemic treatment of metastatic RCC have widely been replaced by so-called targeted therapies with tyrosine kinase inhibitors or mTOR-inhibitors. In clear cell RCC targeted therapy represents the standard of care for patients with unresectable metastatic disease. But until now, no specific trials have been reported to evaluate the efficacy of novel targeted drugs in the different subtypes of metastatic non-clear cell RCC (Schrader et al. 2008). Therefore, only limited data are available, especially in terms of overall survival. Choueiri et al. reported on 53 patients with non-clear cell RCC under treatment with the tyrosine kinase inhibitors sorafenib and sunitinib. The number of patients with papillary and chromophobe histologies was 41 (77%) and 12 (23%), respectively. Response rate, progression-free survival (PFS) time, and overall survival time for the entire cohort were 10%, 8.6 months, and 19.6 months, respectively. Two of 41 papillary RCC patients (4.8%) achieved a response (both patients were treated with sunitinib). PFS for the whole papillary RCC cohort was 7.6 months. Sunitinib-treated papillary RCC patients had a PFS of 11.9 months compared with 5.1 months for sorafenib-treated patients ($p = 0.001$). Data on overall survival of papillary RCC patients are not given (Choueiri et al. 2008). Recently Dutcher et al. published data from a subgroup analysis of a prospective randomized trial in poor risk RCC patients. 10 patients with papillary-only features in histology experienced a median overall survival of 10.9 months (95% CI 7.8–15.1 months) on treatment with the mTOR-inhibitor temsirolimus, which led to a relative risk reduction with a hazard ration of 0.5 (95% CI 0.27–0.94) in comparison to 10 patients with identical histologic features, who were treated with interferon-α (median survival

5.1 months, 95% CI 3.2–11.3 months) (Dutcher et al. 2009).

Conclusions

Metastatic papillary RCC is characterized by resistance to systemic therapy and poor survival, even despite recently developed targeted therapies. Patients with metastatic papillary RCC develop local recurrences more often after radical nephrectomy for localized tumor than those with clear cell RCC. Despite the given bias of a retrospective analysis, our results demonstrate that resection of metastases is the only potentially curative option, which should be offered to all patients with the chance of complete removal of metastases (R0-resection).

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