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OBJECTIVE

- To review the clinical characteristics and oncological results in patients submitted to surgical removal of metastasis from renal cell carcinoma (RCC) in atypical sites (atypical metastasis [AM], i.e. metastasis in sites other than the chest, liver, bone, adrenal, brain, kidney, and lymph nodes), compared with patients submitted to metastasectomy due to a lung metastasis (LM).

PATIENTS AND METHODS

- From an institutional database of ≈1800 patients surgically treated for a RCC, we retrospectively identified 37 cases that had undergone metastasectomy for AM and 57 operated for LM.
- Clinicopathological features of the primary RCC and metastasis, and cancer-specific survival (CSS) computed from the time of metastasectomy of patients with AM and LM, were compared.
- A univariate and multivariable analysis applying a Cox regression model was used to evaluate CSS.

RESULTS

- The patients with AM and LM were followed for an average of 40.8 and 50.7

What's known on the subject? and What does the study add?

The interest in metastatic renal cell carcinoma has increased in the last few years, mainly due to the advent of targeted therapies, but metastasectomy remains the sole therapy that can lead to a complete and durable regression, even if only in a minority of patients. The literature reports quite large series of metastasectomies for the most common sites of metastasis, e.g. lung, liver, bone, adrenal and brain, whereas little is known about the management of metastasis in 'atypical' sites.

The prognosis of patients submitted to metastasectomy for a metastasis in an atypical site is equivalent to patients with lung metastasis. The characteristics of the primary tumour in these patients are not indicative, but atypical metastasis (AM) are often located in superficial sites and frequently associated with other metastases. So, physical examination should be included in all follow-up regimens and a complete re-staging should be performed after the diagnosis of an AM.

months from metastasectomy, respectively ($P = 0.372$).

- There were no significant differences in the characteristics of the primary tumour between patients with AM and LM.
- In the cases with AM and LM the diagnosis was simultaneous with that of the primary tumour in 32.4% and 24.6%, ($P = 0.40$) respectively, and, when metachronous, occurred at an average delay of 53.4 and 44.3 months ($P = 0.370$).
- More frequently in the cases with AM other metastases had been diagnosed in the previous medical history (35.2 vs 8.8%, $P = 0.001$) or simultaneously (48.6 vs 8.8%, $P = 0.001$).
- CSS from metastasectomy was affected by the synchronicity in diagnosis between metastasis and primary tumour, and by the

simultaneous presence of other metastases, while the type of metastasis (AM vs LM) did not affect CSS. In fact, metastasectomy in AM was as effective as in LM.

CONCLUSION

- AM are an exceptional presentation of metastatic RCC, but the role of surgery is similar to that of pulmonary metastasis. In these cases, metastasectomy is accepted as possible care, and in AM the CSS after metastasectomy is similar.

KEYWORDS

renal cell carcinoma, metastasis, metastasectomy, targeted therapy

INTRODUCTION

Despite the increase in initial diagnoses from the widespread use of ultrasonography and CT, RCC remains the urological tumour

with the highest mortality rate [1] due to a significant proportion (up to 30%) of patients with metastasis at diagnosis or discovered during follow-up [2–5].

Although the systemic spread of a metastatic tumour excludes a rationale for local treatment, e.g. metastasectomy, this is actually a feasible option for RCC [6,7]. In fact, despite not being supported by a high

level of evidence, over time, this approach has obtained wide consensus both due to the fact that in some cases it allows a prolonged survival and clinical regression of the disease, and because there is a lack of more effective therapeutic alternatives. Even targeted therapies that have recently been introduced into clinical practice, while leading to a significant increase in survival compared with previous therapies [6,8–10], have not replaced the use of metastasectomy due to their limited ability for complete regression of the disease and the need to extend treatment, and the related side-effects, for an unlimited period [6,11–13].

There are published reports on the results of metastasectomy in the most common sites of RCC metastasis (lung, bone, liver, brain and adrenal) [14,15]. However this tumour can, even though unusual, spread to any organ and only single case reports describe metastasectomies in 'atypical' sites.

The present study aimed to assess the clinical characteristics and oncological outcome of surgical removal of metastases occurring in atypical sites by retrospectively reviewing our institutional experience.

PATIENTS AND METHODS

Since 1983 our institute has been prospectively compiling a database, which includes the clinical, surgical and follow-up data of ≈ 1800 patients who have undergone surgery for RCC. Data were collected after receiving written consent from every patient (as required by Italian law) and under the authorisation of the local Ethics Committee. The histological specimens were evaluated by two skilled uro-pathologists; staging was adapted to the TNM 2002 system [16]; assignment of the histological subtype and grading followed the WHO [17] and Fuhrman' classification [18]. For all patients staging included abdominal CT or MRI and a chest X-ray; in the absence of specific symptoms, a chest CT and a bone scan were indicated in cases of tumours with a clinical staging above second and a brain CT for fourth stage tumours. All patients were followed in a dedicated oncological ambulatory unit with physical examination, blood chemistry analysis and studies of the abdomen (ultrasonography or CT) and chest

(X-ray or CT), in addition to additional tests in cases of specific clinical doubt; upon discovery of metastasis, total-body re-staging was always performed. A metastasectomy was proposed in patients with good performance status and resectable lesions, preferably if localised in a single organ or, when multiple, if the patient could be considered a suitable candidate for multiple metastasectomies or complementary medical treatment.

To date, 349 metastasectomies have been performed in 242 patients.

For this work, we selected a specific population: patients that had undergone surgical removal of an 'atypical' metastasis (AM), defined as a metastasis that is localised in a site other than thoracic (pulmonary, pleural or mediastinal), skeletal, hepatic, adrenal or encephalic were reviewed for this study; direct invasion of organs by the tumour (stage pT4), bilateral renal tumours and lymph node metastases were excluded.

A comparison group was formed of patients that had undergone metastasectomy for a pulmonary metastasis or lung metastasis (LM), considered to be the most typical site for RCC metastasization.

Patients with AM or LM that was not treated surgically and those with associated metastases that had not undergone curative treatment (surgery, radiation therapy or medical treatment) were excluded.

Continuous variables were reported as mean (SD) or median and interquartile range. The Student's *t*-test, the Mann-Whitney *U*-test, Fisher's exact test and the Pearson chi-square test were used to compare continuous and categorical variables, as appropriate.

The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Cancer-specific survival (CSS) was computed from the date of metastasectomy to the last available control, censoring the cases deceased from RCC. Univariable and multivariable Cox regression models addressed time to cancer-specific mortality after metastasectomy. Statistical significance was set at $P < 0.05$. All reported P -values are two sided.

TABLE 1 Sites of AM

Site	Patients, n (%)
Skin	8 (21.62)
Muscles	6 (16.21)
Thyroid	6 (16.21)
Pancreas	4 (10.81)
Testicle	4 (10.81)
Nasopharynx	3 (8.11)
Vagina	2 (5.40)
Omentum	1 (2.70)
Spleen	1 (2.70)
Stomach	1 (2.70)
Breast	1 (2.70)
Total	37 (100)

RESULTS

In 1785 patients with RCC, 37 patients that underwent a metastasectomy for AM (incidence 1.88%, 22 men, 15 women, mean [SD] age at diagnosis of the primary tumour 59.1 [17.5] years; Table 1) and 57 that underwent a metastasectomy for LM (40 men, 17 women, mean age 60.9 [13.2] years) were identified according to inclusion criteria and followed, respectively, for a mean (SD) period of 76.8 (11.4) and 84.0 (8.2) months from diagnosis of the primary tumour ($P = 0.601$) and of 40.8 (9.6) and 50.7 (6.3) months from metastasectomy ($P = 0.372$). In all, 36 patients with a diagnosis of AM that were not treated surgically were excluded.

Table 2 summarises the comparison of the characteristics of the primary RCC in patients with AM and LM, while noting in the former a larger proportion of non-clear cell tumours and with lymph node involvement.

Presentation of the AM and the LM was synchronous with the diagnosis of the primary RCC in 12/37 (32.4%) and in 14/57 patients (24.6%), respectively ($P = 0.40$), while in the remaining cases it occurred at a mean (SD) latency of 53.4 (41.3) and 44.3 (55.7) months, respectively ($P = 0.370$).

During the previous medical history, a metastasis in another organ was detected in 13/37 (35.1%) and 5/57 patients (8.8%) with AM and LM, respectively, while this was simultaneously present at diagnosis of AM or LM in 18/37 (48.6%) and 5/57 (8.8%).

($P=0.001$). In addition to metastasectomy 12 patients, 5/37 with AM (13.5%) and 7/57 with LM (12.3%) underwent medical treatment.

Currently, eight patients with AM at an average of 69 months from metastasectomy and 20 patients with LM at an average of 80 months from metastasectomy are alive and have no evidence of disease; three patients with AM at 114 months from

metastasectomy and one with LM at 81 months from metastasectomy died from causes unrelated to RCC, while 26 patients with AM at 30 months and 36 with LM at 33.5 months from metastasectomy are alive, in progression, or have died from the disease.

Analysis of CSS, calculated from the time of metastasectomy (Table 3) showed that the factors with a statistically significant

negative impact were the synchronous presentation of metastasis with the primary tumour (Fig. 1, $P=0.014$) and the simultaneous presence of multiple metastases (Fig. 2, $P=0.003$), while atypical localisation compared with pulmonary localisation did not have any impact (Fig. 3, log-rank test $P=0.626$).

DISCUSSION

Despite the progressive increase of initial diagnosis, the mortality rate for RCC has not decreased in parallel [1–6], both due to the probable overtreatment of small and biologically indolent masses, as well as the still significant proportion of masses that are highly aggressive and have the ability to metastasise at diagnosis or after radical surgical treatment of the primary tumour [1–6].

At present metastasectomy has gained a wide consensus because of the possibility of extending survival, even if it lacks a solid

TABLE 2 Features of primary RCC in patients with AM and LM

Variable	AM	LM	<i>P</i>
Symptomatic at diagnosis, n/N (%)	25/37 (67.56)	37/57 (64.91)	0.827
Mean (SD) diameter, cm	8.9 (3.4)	7.9 (3.0)	0.128
Clear cell histology, n/N (%)	33/37 (89.2)	57/57 (100)	0.022
Extracapsular, n/N (%)	15/37 (40.54)	26/57 (45.61)	0.675
Venous invasion, %	32.4	25.0	0.43
pN+, %	10.8	1.8	0.059
G3–G4, %	70.3	64.2	0.51
Multifocality, %	8.1	5.3	0.54

TABLE 3 Analysis of CSS from metastasectomy

Factor	Univariable analysis		Multivariable analysis	
	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)
Primary RCC	0.434	1.607 (0.490–5.273)	–	–
	0.157	1.067 (0.975–1.167)	–	–
	0.218	2.115 (0.643–6.960)	–	–
	0.215	0.643 (0.320–1.292)	–	–
Metastasis	0.627	1.183 (0.600–2.333)	–	–
	0.017	2.287 (1.157–4.521)	0.059	1.969 (0.976–3.974)
	0.981	0.990 (0.411–2.381)	–	–
	0.005	3.268 (1.417–7.539)	0.020	2.770 (1.172–6.549)
	0.243	2.020 (0.620–6.582)	–	–

FIG. 1. Kaplan–Mayer curves estimating CSS in metachronous and synchronous metastasis.

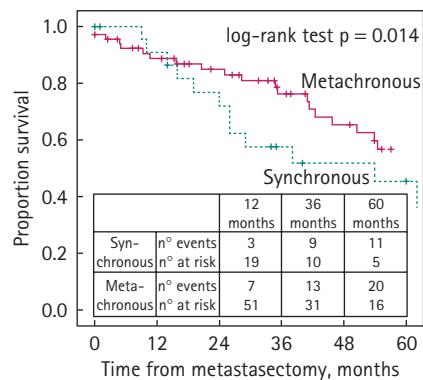


FIG. 2. Kaplan–Mayer curve estimating CSS in single and multiple metastases.

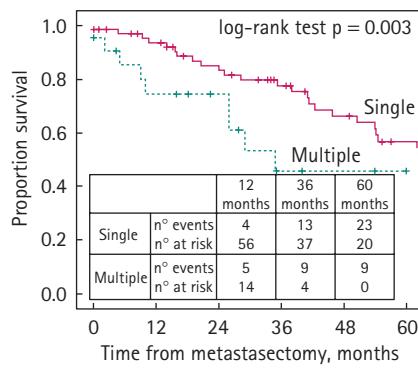
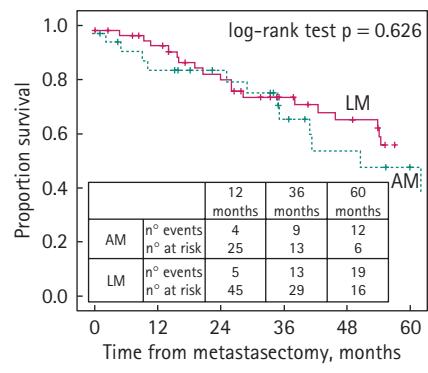


FIG. 3. Kaplan–Mayer curve estimating CSS in patients with LM and AM.



biological rationale to support it and has low levels of evidence (3) and grades of recommendation (B). Furthermore, selection of the ideal candidate for metastasectomy is still poorly defined and is generally reserved for patients with a good performance status and lesions that are technically resectable [6]. Thus, metastasectomy was mainly supported by the lack of effective immunotherapy [19]. Now, in the contemporary era of targeted therapies, the need to extend treatment indefinitely, with the associated side-effects and economic costs, and the extremely low rate of complete regression [20] can still justify the use of metastasectomy. This type of surgery is generally burdened by a low rate of morbidity and is not technically complex.

RCC can metastasise to virtually any location, but it commonly spreads to the lung, bone, liver, brain and adrenal gland. Therefore, the literature reports clinical studies of metastasectomy performed in these sites, with a fair number, ≈ 200 cases, of these being in the lung [21–30].

In contrast, publications on the management and surgical treatment of AM sites are few, usually just limited to case reports, with the exception of a literature review on a period of >50 years, which included 321 cases of pancreatic metastasectomies and a multicentre study that collated 45 thyroid metastasectomies from 15 German institutions [29,30].

The aim of the present study was to characterise patients that underwent metastasectomy for RCC metastasis occurring in an atypical site, defined as non-localised in the thorax, bone, liver, brain and adrenal. A comparison group was compiled of patients that had undergone metastasectomy for the most typical RCC metastasis, i.e. LM.

The choice of considering only patients that underwent metastasectomy guaranteed a sure histological diagnosis in all cases. Furthermore, a selection was therefore made of only those patients with good performance status and lesions that were surgically resectable and not disseminated, thus making the comparison groups uniform for extent of the disease.

In our experience, AM were found in 15% of the cases that underwent metastasectomy

(37/242 patients), they were located in different anatomical sites, and diagnosed either simultaneously to the primary tumour or after a long interval. The characteristics of the primary tumour in these cases did not prove to be significantly different compared with those cases with LM and, therefore, it is not possible to provide indications for specific follow-up for the diagnosis of an AM. However, careful examination of the teguments, the neck and the genitals is recommended in all patients to allow, without additional costs, identification of all atypical presentations with 'superficial' localisation; abdominal investigations, performed as routine, would allow for diagnosis of the remaining AM.

In particular, the cases with AM presented more frequently than other metastasis, either simultaneously or occurring during their previous clinical history (25/37 [67.6%] vs 9/57 [15.8%]), therefore, once an AM is diagnosed, a full re-staging is mandatory.

The experience reported in the present study confirms that metastasectomy is a valid therapeutic option in metastatic RCC: a total of 32/94 patients (34%) are, in fact, alive or deceased from causes unrelated to the RCC, at a considerable time after metastasectomy. The factors that had a significantly negative influence on CSS from metastasectomy were the simultaneous presence of multiple metastases ($P = 0.020$, hazard ratio [HR] 2.770) and, to a lesser extent, the synchronous diagnosis of metastasis compared with that of the primary tumour ($P = 0.059$, HR 1.969). In the cases where these two conditions were absent, the median estimated survival rate from metastasectomy was extremely satisfactory (104 months, 95% CI 48.9–160.4). The lack of influence of a medical history of previous metastases, confirms the opportunity to repeat the metastasectomy, when possible, as also previously noted by van der Poel *et al.* [28].

The atypical localisation per se had no prognostic impact, with a survival rate comparable with cases with LM. It should be noted that the latter were diagnosed as asymptomatic in almost all cases after the results of routine thoracic examinations, while the diagnosis of AM was often reached due to the presence of a clinically significant and often symptomatic lesion. The limited numbers do not allow for

statistical analysis, but as with the small number of other reported experiences [31,32], both pancreatic and thyroid localisation showed better survival rates, with a proportion of patients with no evidence of disease of almost 50%, which could possibly indicate a *relatively* low biological aggressiveness.

In the present study, there was no beneficial effect from the association of medical therapy with metastasectomy, but this information should be reviewed considering that these therapies were mainly interleukin 2/interferon, as the study period was largely before the targeted therapies era. The few data coming from American tertiary academic institutions about the role of metastasectomy after targeted therapy are encouraging, but still too preliminary to provide conclusive advice [33].

The present study is subject to some limitations. It is a retrospective analysis, although of a prospectively compiled database; it is limited numerically, single-centred and takes place over an extended period: the rarity of the disease in question would require a multi-centre study to overcome these limitations.

In conclusion, the data from the present study showed that metastasectomy can be effective in the treatment of a metastasis from RCC localised in an atypical site, especially when there are no other simultaneous metastases. Nevertheless, the high rate of recurrences make the advent of an effective systemic therapy of paramount importance.

CONFLICT OF INTEREST

None declared.

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Abbreviations: AM, atypical metastasis; CSS, cancer-specific survival; HR, hazard ratio; LM, lung metastasis.