Integrating metastasectomy and stereotactic radiosurgery in the treatment of metastatic renal cell carcinoma

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1. Introduction

In the European Union 60,000 patients are diagnosed annually with renal-cell carcinoma (RCC) [1]. Synchronous metastases are present in up to 30% of patients, with multiple sites affected in 95% [2,3]. Since an additional 40% of those undergoing surgery for localised RCC develop metachronous metastasis, approximately 30,000 patients per year are diagnosed with systemic disease, of which an estimated 7000 have non-clear-cell histology.

In a recent population-based analysis, lung metastasis was most frequent at 45.2%, followed by bone at 29.5%, lymph nodes at 21.8% and liver at 20.3% [4]. Adrenal, brain and other locations had a lower frequency. Moreover, it was found that the proportion of patients with multiple metastatic sites was higher in young patients, 16% and 49% of which had brain and bone metastasis, respectively [4].

2. Rationale of metastasectomy

Selecting appropriate treatment modalities for metastatic RCC remains a challenge. Although objective responses following targeted therapy are frequent, complete remissions occur in only 1–3% [5–7]. Moreover, it has become evident that, despite the most effective drugs in first-line treatment, a ceiling is being reached in median overall survival (OS) which ranges between 9 and 40 months, depending on clinical risk scores [8]. Therefore, together with the occasional durable responses achieved with high-dose interleukin-2, removal of all lesions, when technically feasible, provides the only potentially curative treatment. Traditionally, surgical resection has been the preferred approach (metastasectomy), but recent data on stereotactic radiosurgery (SRS) and ablative techniques indicate that other local non-invasive or less-invasive treatment modalities are a valid alternative to surgery. However, only a minority of patients with mRCC are candidates for metastasectomy. No reliable data exist on the proportion of patients with mRCC who will be eligible for this approach. It has been estimated that only 25% of patients with metachronous metastasis are suitable candidates for resection of metastatic disease [9,10]. For patients with synchronous metastasis a recent study addressed this issue. A whole-nation study on prevalence and potential resectability revealed that 154 patients (16.9%) had synchronous lung metastases [11]. However, only 11 with solitary lesions were deemed eligible for surgical resection, and only one underwent metastasectomy. In addition, patient selection for this approach is difficult because of the heterogeneous course of metastatic RCC. Metastasis may present at diagnosis or within a year after nephrectomy with curative intent, whereas in others disease-free intervals of more than 20 years have been observed with a slow growth of lesions. In few cases spontaneous regression of metastases has been documented, leading to the concepts of immune modulation [12,13].

Currently, prognosis and management of mRCC depend on a number of clinical factors such as performance status, the length of the disease-free interval, synchronous or metachronous metastasis, as well as the burden of metastatic disease and the number and location of sites involved [14]. One of the most commonly used prognostic models, the Memorial Sloan Kettering Cancer Center (MSKCC) risk score, uses Karnofsky performance status, time from diagnosis to treatment, and serum haemoglobin, calcium and lactate dehydrogenase to categorise patients as being at favourable, intermediate or poor risk [15]. After the introduction of targeted therapy the MSKCC risk score remains a valid tool together with the validated Database Consortium (DCM) model to assess the prognosis of patients with comparable concordances of 0.66–0.65 [8,16,17]. Metastasectomy is associated with survival and clinical benefit across these various risk groups [10,18]. In a

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retrospective analysis on 129 patients metastasectomy in the favourable-risk group improved 5-year survival from 36% to 71%, and in the intermediate-risk group from 0% to 38%. When adjusting for risk score, a 2.7-fold increased risk of death remained for patients who did not undergo metastasectomy. Median survival time and 2-year survival rates for low-risk, intermediate-risk and high-risk patients were 76, 25 and 6 months, respectively, suggesting that only patients with a favourable and intermediate risk live long enough to be candidates for metastasectomy. However, MSKCC and DCM scores were primarily developed to assess prognosis in patients receiving systemic therapies. Other clinical factors which may have prognostic value in metastasectomy are recognised.

Patients who are not candidates for metastasectomy are being offered systemic targeted therapy. Following response or substantial downsizing, metastasectomy is occasionally reconsidered in selected individuals to achieve complete resection and even interrupt targeted therapy. This approach is investigational and has not been prospectively studied, but case reports and retrospective series have been published.

A case series described three patients after complete resection of liver, lymph node and vertebral metastases following absence of further progression under treatment with sorafenib and sunitinib [19]. Patients remained disease-free after 16, 24 and 29 months.

Targeted therapy has been discontinued after complete resection of metastatic lesions. A series included six patients after complete resection of residual metastases in the lungs, iliac bone, skin and thyroid following treatment with sunitinib. The patients remained off treatment for 5–19 months [20,21]. The largest study included 22 patients receiving metastasectomy following targeted therapy [22]. Metastasectomy was performed in the retroperitoneum, lung, adrenal, bowel, mediastinum, bone and brain. Consolidative metastasectomy proved feasible with acceptable morbidity, although it resulted in a significant time off targeted therapy and long-term disease-free interval. However, it is not known whether this was primarily due to the complete resection of metastatic disease, which has been identified as an independent factor associated with prolonged survival, or the combination of surgery and targeted therapy.

Ultimately, adequate selection for metastasectomy is of critical importance. If applied appropriately, surgical resection alone or in combination with targeted agents may result in outcome that is superior to systemic therapy alone.

3. General prognostic factors of metastasectomy

The bulk of literature on metastasectomy dates back to the last century, when it was observed that patients with solitary resectable metastasis or multiple metastases restricted to one resectable organ site may have a survival benefit in the absence of effective systemic therapeutic options. In the 1930s there was a report of a patient who survived 23 years following pulmonary metastasectomy [23]. In 1978, one of the first series on metastasectomy in 41 patients with solitary lesions in the lungs, pleura, central nervous system and abdomen was published. In patients with complete surgical resection, the median disease-specific survival was 27 months, with 59% of the patients alive at 3 years [24]. Several authors concluded similar 3-year and 5-year survival after resection of a solitary lesion [25–27] or observed a significant difference in survival in patients with metachronous and synchronous metastasis [28–30].

In a series involving 179 patients the 5-year survival rate after resection of solitary lesions was 22% for synchronous versus 39% for metachronous metastases [31]. In addition, multiple clinical trials from the cytokine era revealed a strong association of outcome and metastatic sites [32,33]. In a retrospective analysis of 101 patients with resection of a total of 152 metastatic lesions at different organ sites [34], median survival was 28 months for the entire series. Survival was improved after resection of lung metastases when compared to other tumour locations and for patients clinically tumour-free after metastasectomy. Again, the time interval between primary tumour resection and metastasectomy correlated positively with survival.

Others have observed similar differences in 5-year survival rates for solitary metastases (56% for lungs, 28% for skin, 20% visceral organs, 18% peripheral bone, 13% brain and 9% axial bone metastases) [31]. One study evaluated 278 mRCC patients to define selection criteria for patients with solitary metastases [35]. On multivariate analysis, factors associated with a favourable outcome were a solitary site and single metastasis, complete resection of the first metastasis, a long disease-free interval and a metachronous presentation. Since then, multiple retrospective series have been published that support these favourable factors [32,36,37] (Table 1).

In a recent retrospective analysis of 109 patients who underwent primary tumour resection and at least one metastasectomy for mRCC, the following additional factors were associated with OS [38]; primary tumour stage $\geqslant$T3 stage, Fuhrman grade $\geqslant$3, non-pulmonary metastases, multi-organ metastases and disease-free interval $\leqslant$12 months were negative pretreatment prognostic factors with an accuracy of 0.87.

As data from Japan suggest, complete metastasectomy is a favourable prognostic factor independent of race or geographical location [39]. No data from prospective randomised trials on metastasectomy for RCC exist, and decision-making relies on retrospective series. It cannot be excluded that the benefit of metastasectomy is due largely to a lead-time bias based on differences in tumour biology. Patients with solitary and oligometastatic disease and a prolonged metachronous interval are more likely to undergo metastasectomy, while those with extensive metastatic burden, rapid progression and reduced performance will probably never be considered for resection. Perhaps not surprisingly, one series found having an aggressive tumour grade to be the only adverse factor for survival [40].

The significance of tumour heterogeneity and aggressiveness should not be underestimated in the interpretation of data which extend the indication for metastasectomy to multiple sites with the aim of achieving complete resection. Complete resection of multiple lesions has been reported as either a resection performed simultaneously at one or more sites or as repeat metastasectomy of asynchronous recurrences after the first resection.

Table 1 – Factors associated with a favourable outcome after metastasectomy, including sterotactic radiosurgery (SRS). General and additional reported site-specific factors for the most common sites.

General[a]	Pulmonary metastasis	Skeletal metastasis	Brain metastasis
Solitary or oligometastatic lesions	<7 Metastases	Peripheral location of metastases	RPA class I: 1. Karnofsky PS >70% 2. Age<65 years 3. Absence of extracranial metastases
Metachronous metastasis and disease-free interval of >2 years	Absence of mediastinal lymph-node metastases	Wide excision	After SRS: >75% decrease of the lesion
Complete resection	Metastases <4 cm	Clear-cell subtype	
Single-organ site	Unilateral lung involvement		
Good performance status (Karnofsky, ECOG, WHO)	Munich I: R0, no risk factor		
MSKCC or DCM good and intermediate risk	Munich II: R0, ⩾1 factor		
Absence of sarcomatoid features	Based on Munich Score risk factors:		
Absence of nodal metastases	1. Pleural infiltration 2. Synchronous disease 3. Retroperitoneal LN 4. Metastases >3 cm 5. Mediastinal/hilar LN 6. Complete resection		

ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; MSKCC, Memorial Sloan Kettering Cancer Center; DCM, Database Consortium model; LN, lymph node.

[a] Recommendations for lymph node, liver, adrenal, pancreatic and thyroid metastasis and other less frequent sites follow the general factors.

Specifically, asynchronous metastases reflect a more benign course of the disease. In selected cases repeat metastasectomy results in exceptionally long survival lasting more than 10 years [41,42]. In a relatively large study of 141 patients with complete resection of solitary metastases, 5-year survival rates after complete resection of second and third metastases were no different when compared to those of the first metastectomy (46% and 44%, respectively, versus a 43% 5-year OS rate) [35]. This supports data from an early retrospective study on repeat metastasectomy which led to improved survival compared to non-surgical treatment of recurrence after first metastasectomy [43].

Recently a large study analysed survival of patients after complete metastasectomy for multiple synchronous metastases at one or more sites [9]. Of 887 mRCC patients, 125 were identified who underwent complete surgical resection of multiple metastases (two to three or more metastases); 52% had resection at two or more sites, including lungs, bone, viscera and other locations. Patients with multiple non-lung-only metastases had a 5-year survival rate of 32.5% with complete resection versus 12.4% without. After controlling for performance status and disease burden, an almost threefold increased risk of death remained for patients with incomplete resection. A scoring algorithm from the same institution to predict survival for patients with clear-cell mRCC suggests that complete resection of multiple metastases was associated with a 50% decrease in the risk of death [14]. It cannot be ruled out that multiple metastasectomy benefited those patients who would have had a favourable course of disease regardless of surgical intervention. Collectively, these data underscore that careful selection of patients with multiple RCC metastases should be made according to the general prognostic factors (Table 1).

A prominent feature of RCC is its ability to metastasise to any anatomical location. Generally, there is little information on how to treat rare sites. In these circumstances factors associated with a favourable outcome after metastasectomy at more frequent sites should be considered for treatment selection (Table 1). Individual decisions have to be taken for each case.

However, certain metastatic sites are consistent and more frequently observed. This has led to additional information that may guide treatment decisions. Specific management strategies for the most frequent sites will be discussed in detail. In contrast to traditional surgical metastasectomy, stereotactic radiosurgery (SRS) or ablative techniques have been largely applied to certain metastatic sites [44]. Although treatment of RCC metastases with SRS is gaining ground and is likely to be expanded to multiple anatomical regions, most of the experience stems from brain and bone metastasis and will be discussed below. While ablative techniques are minimally invasive and can cause bleeding and thermal damage, cranial and extracranial SRS involves adverse events such as cough, fatigue, skin rash and local pain. Side effects are generally frequent, but mild (grades I–II in 96%) [45].

4. Site-specific strategies

4.1. *Lymph-node metastases*

Data on nodal metastasectomy are difficult to interpret. They are not regarded as distant metastasis (M) in the tumour-node-metastasis (TNM) classification, and often occur in association with further systemic metastatic sites. As a consequence nodal metastasis can manifest as different disease stages and is generally associated with a poor outcome that resembles that of systemic disease in retrospective series [46]. In few studies are locoregional and distant (mostly mediastinal) lymph-node metastases differentiated. There is evidence that resection of isolated nodes may be beneficial in terms of survival.

In fact, isolated lymph-node metastasis is rare. Between 58% and 95% of patients with lymph-node involvement have associated hematogenous metastases [47,48]. Patients with pathological N0 have a 5-year OS of 75%, versus 20% for patients with lymph-node metastases [46,49]. Despite this, patients with single lymph-node metastases and no metastatic disease can potentially be cured by lymph-node dissection (LND) [49].

Regional lymph-node metastases in RCC range from 13% to over 30%. However, the true incidence of solitary nodal metastasis without further systemic disease is unknown. In nephrectomy and autopsy studies single nodal metastases were observed in smaller tumours in 3–4.5% [46,49,50]. At autopsy, anatomical location of lymph-node metastases was unpredictable [51]. The authors found ipsilateral renal hilar lymph-node metastases in 7%, pulmonary hilar lymph-node metastases in 66.2%, retroperitoneal in 36%, para-aortal in 26.8% and supraclavicular in 20.7% [51]. In addition, single metastases in mediastinal, axillary, supraclavicular and iliac lymph nodes without any further metastasis were described [52,53].

In node-positive cases lymph-node dissection was associated with improved survival and a trend towards an improved response to immunotherapy [49]. Patients with regional nodes and distant metastases had significantly inferior survival to those with either condition alone. However, lymph-node status had less impact on survival than primary tumour stage, grade and performance status. [49]. Current guidelines advise that suspicious lymph nodes either at imaging or on palpation should be removed during nephrectomy because LND for clinically positive lymph nodes is associated with improved survival when performed in carefully selected patients [49].

A recent systemic review of the available literature concluded that data from the majority of retrospective non-randomised studies suggest that a possible benefit in terms of OS exists for patients with node-positive disease [54]. In addition, LND at the time of nephrectomy may avoid symptomatic local recurrences. As most clinically suspicious lymph nodes are removed at the time of nephrectomy, few data exist on the management of metachronous regional lymph-node metastases and are often summarised in series reporting on local recurrences [55], but there is a tendency to choose an investigational approach and pre-treat these lesions prior to surgical removal.

Several cases have been reported with downsizing of nodal metastases following tyrosine kinase inhibitors. Subsequent to sunitinib therapy, complete resection of bulky lymph nodes with encasement of the great vessels not amenable to initial excision was performed in a number of patients with clear-cell histology and no evidence of further lesions [56–59]. Downsizing up to 40% was reported following 5–10 cycles. 'Second-look' surgery with complete retroperitoneal LND was feasible in all cases. Despite necrosis, viable clear-cell carcinoma was present in all cases.

4.2. *Thoracic metastases*

Pulmonary, pleural and mediastinal lymph-node metastases occur frequently in RCC and are found simultaneously in 20–35% of patients [60–62]. Lung lesions are most frequent and have a prevalence rate of 74% in autopsy studies [51]. Metastasis is mostly hematogenous, but direct lymphatic drainage from the kidney into the thoracic duct which subsequently drains into the subclavian vein and pulmonary artery has been proposed [63].

There are many retrospective series on resection of pulmonary metastases, but most of the earlier studies were small [33,35,64–67]. Collectively, recent series with larger patient cohorts observed a 5-year survival rate of 37–54% provided that complete resection of solitary or oligometastatic pulmonary metastases was achieved [9,35,60–62,68–74]. Consistent and robust prognostic factors were identified in multivariate analyses (Table 1). Incomplete resection was associated with a poorer 5-year survival of 0–22% [9,35,60,62,71,74,75], as was the number of pulmonary metastases removed [9,35,62,68,69,75]. Thus, median 5-year survival after complete resection of a solitary lesion was 45.6–49 months versus 19–27 months after complete resection of multiple metastases [68,69,75].

In a large study a significantly longer median 5-year survival was observed for patients with fewer than seven pulmonary metastases versus those with more than seven metastases (46.8% versus 14.5%) [62]. Furthermore, the presence of lymph-node metastasis was associated with shorter survival [60–62,74].

Despite complete pulmonary metastasectomy, mediastinal lymph-node metastases decreased median survival from 102 months to 19 months [60] and the median 5-year survival rate from 42.1% to 24.4% [62]. A short disease-free interval after nephrectomy or the presence of synchronous metastasis had a poor outcome [35,62,69,71,74,75]. Disease-free interval of > or <48 months or 23 months were associated with a median 5-year survival rate of 46% versus 26% (69) and 47% versus 24.7%, respectively [62]. The presence of synchronous pulmonary metastasis had a particularly poor outcome, with a median 5-year survival rate after complete pulmonary metastasectomy of 0% versus 43% for patients with metachronous disease [75].

Size of pulmonary metastasis is an additional factor [61,74,76].A median 5-year survival rate of 70% versus 35% was observed after complete resection of metastases either < or >0.5 cm [76]. In an attempt to define a prognostic score, 200 consecutive patients with pulmonary metastases were recently evaluated in a single centre [77]. By multivariate anal-

ysis complete metastasectomy, metastatic size >3 cm, positive lymph-node status of the primary tumour, synchronous metastases, pleural invasion and hilar or mediastinal lymph-node metastases were independent prognostic factors. From these factors the Munich score was developed which discriminates three risk groups with median OS of 90, 31 and 14 months for low, intermediate and high risk, respectively (Table 1).

However, some investigators have found no association with the type of resection and survival [68,73]. SRS or ablative techniques may be an alternative to surgical resection in selected patients [45,78]. In a prospective phase II trial of extracranial SRS given to 82 metastases in mRCC, a total of 63 lung lesions were treated [45]; 50% of the patients were MSKCC favourable-risk and 46.7% intermediate-risk. In 21% of the treated sites total regression was observed after 3–36 months, while another 31% showed regression of >50% after 3–12 months. Median OS was 32 months, suggesting that control and outcome can be achieved similarly to surgical metastasectomy. A recent retrospective analysis including 39 lung lesions suggests that a single fraction equivalent dose (SFED) of $\geqslant$45 Gy is effective for controlling RCC metastases [79].

Isolated mediastinal lymph-node metastasis without pulmonary or other lesions is frequently observed in RCC [80–82]. This may be a consequence of renal lymphatic vessels which always connect to the origin of the thoracic duct, some directly without traversing any retroperitoneal nodes [63]. Resection of isolated mediastinal and intrapulmonary nodal metastases has resulted in DFS of up to 5 years [83,84]. As these lymph nodes are usually not resected at the time of nephrectomy, these series contain mostly metachronous nodal metastases. As already mentioned, concurrent mediastinal lymph-node and lung metastases have a poorer prognosis [60–62]. These studies provide information on the potential prevalence of lymph-node metastases in patients with pulmonary metastatic disease which was 20–35%. With a median OS of <2 years, patients with pulmonary metastases and mediastinal lymph nodes may not be candidates for surgical resection, though match paired analysis suggests a trend towards improved survival [60].

4.3. *Bone*

Bone metastases occur in 16–26% of patients with metastatic RCC and are often symptomatic [15]. The prevalence of solitary bone metastasis may be low. In a series of 94 patients with solitary metastasis, single skeletal secondaries were observed in five patients (5.3%) [35]. Another retrospective series reported a rate of 2.5% [25]. Although prolonged disease-free survival has been reported after surgical resection of single and even multiple bone metastases, the most frequent indication for treatment are symptoms such as pain from nerve-root compression and pathological fractures. External-beam radiotherapy may be equally effective, but no randomised data exist specifically for RCC. As for other metastatic sites, outcome after surgical resection of skeletal solitary or oligometastases has only been evaluated retrospectively. Early reports suggested that patients with solitary bone lesions have a better survival after resection [85]. In a small study analysing bone metastasis from RCC in 13 evaluable patients with solitary lesions, a 5-year survival rate of 55% for the entire cohort was achieved [86].

The 5-year OS rate after resection of solitary bone lesions in other series was 40% [35] and 54%, respectively [87], although numbers were very small. Conversely, a series including 25 patients reported a 5-year survival rate of only 13%, despite wide resection of solitary bone metastasis [88]. A recent series evaluated 125 patients after resection of multiple metastases, including 11 with bone as single site (8.8%) and four (3.2%) with bone and lung involved [9]. The majority (75.2%) had more than three metastases removed. For patients with extrapulmonary sites the 5-year OS rate was 32.5% when complete resection was achieved compared with 12.4% among a matched cohort without complete resection.

One of the largest studies on resection of RCC bone metastases included a literature review. Five-year survival rates were 35.8–55%, comparable to OS observed after resection of lung lesions [86]. Patients with peripheral skeletal location of metastases had a 75% 5-year survival rate. Collectively, metachronous disease with a long disease-free interval, peripheral skeletal location with wide excision and solitary metastases were correlated with longer survival [86]. A further prognostic factor is the presence of a clear-cell histological subtype. Interestingly, the additional presence of pulmonary metastases did not predict early death, some patients surviving for years after complete resection of pulmonary and bone disease [9,89].

Similar predictive factors and survival rates were reported in a number of smaller retrospective series [87,88,90,91]. Because of the retrospective data evaluation, the impact on outcome of resection of RCC bone lesions remains controversial. However, surgical resection of bone lesions to effectively palliate pain and symptoms from spinal cord compression is undisputed.

A randomised prospective trial in patients with bone metastasis from various malignancies, including RCC, demonstrated that immediate decompressive surgery and postoperative radiotherapy are superior to treatment with radiotherapy alone for patients with spinal cord compression [92]. In addition, a prospective non-randomised study demonstrated that spinal surgery was effective in improving quality of life in patients with extradural spinal metastases from various cancers by providing better pain control, enabling patients to regain or maintain mobility, and offering improved sphincter control [93]. Surgery resulted in acceptably low mortality and morbidity rates.

RCC bone metastases are highly destructive vascularised lesions. The risk of life-threatening haemorrhage poses a serious surgical challenge. The largest retrospective study on surgical approach and outcome included a total of 368 RCC bone metastases to the limbs and pelvis [89]. Surgical procedures involved curettage with cementing and/or internal fixation, en-bloc resection with closed nailing or amputation. The 1-and 5-year OS rates were 47% and 11%, respectively. However, 15 patients (5%) died within 4 weeks after surgery due to acute pulmonary or multi-organ failure.

Regarding palliation, resection of painful RCC bone metastases relieved pain significantly in 91% of patients. A good to excellent functional outcome was achieved in 89%, and 94% with metastatic lesions of the pelvic girdle and lower extrem-

ities were ambulatory [91]. Wider resection reduced the risk of recurrence at the same location and the need for re-intervention [94]. This was a general observation made in bone metastasis from a variety of cancers where wide excision resulted in improved survival and functional outcome compared to laminectomy alone [93].

Surgery for bone lesions should therefore aim at lasting control at the treated site with a durable fixation or reconstruction to prevent re-intervention. As the only randomised trial performed included radiotherapy in both arms, postoperative radiotherapy is advised [92].

Ablative approaches may be an alternative to surgery in selected cases with bulky bone lesions extending to extra-osseous regions [95,96]. As with other extracranial locations, SRS for spinal metastasis of RCC has been shown to be effective in a series of 48 patients with 55 spinal lesions [97]. The 1-year absence of progression rate in the spine was 82.1%. This early series suggests that SRS to spinal metastases is effective in palliating symptoms. At baseline, 23% of patients were pain-free, and this increased to 44% 1 month and 52% 12 months after SRS. In a retrospective study of 24 painful RCC bone lesions a relationship between dose and stable pain relief was observed in patients treated with a dose of 40 Gy in five fractions [98]. Adverse events were absent except one grade 1 skin toxicity. These data suggest that symptomatic and painful RCC skeletal metastases at various anatomical sites can be effectively controlled and palliated by SRS, and prospective non-randomised trials have been initiated.

5. Intra-abdominal organ metastases

5.1. *Liver*

Hepatic metastases are diagnosed in 8–30% of patients with RCC [15]. An autopsy study reported liver metastasis from RCC in 41% [51]. Only in 5% were these metastases solitary metachronous lesion [99]. The simultaneous presence of multiple organ sites explains the paucity of reports on liver metastasectomy either by surgery or by ablative techniques [100]. In addition, in contrast to solitary pulmonary metastases, liver metastases are consistently associated with a poor prognosis [31,32,34].

A few retrospective series with 13–68 patients suggest that surgical resection may be beneficial in terms of survival [99,101–104]. Earlier series reported a median survival following resection of solitary liver metastasis of 16–48 months with 5-year survival rates of 8–38.9% [99,101,102,104]. Factors associated with a good prognosis were disease-free interval longer than 6–24 months, performance status and completeness of resection. A large retrospective series analysed the outcome of 88 patients with liver as the only metastatic site [103]. Sixty-eight patients underwent metastasectomy compared to 20 who refused. The median 5-year OS rate after metastasectomy was 62.2% versus 29.3% in the control. In both cohorts 79% received systemic therapy, which suggests that liver metastasectomy may be appropriate for carefully selected patients. Patients with high-grade RCC and synchronous metastases did not benefit from hepatic metastasectomy. Furthermore, metastasectomy is associated with significant morbidity of 20.1% [103]. One series even reported a mortality rate of 31% [99]. In contrast, a contemporary multi-institutional analysis of 43 patients reported a low morbidity and near-zero mortality [105]. Three-year OS was 62.1% with a median recurrence-free survival of 15.5 months. However, recurrence occurs in up to 50% after liver resection [101,105]. Morbidity, mortality and recurrence need to be balanced against a potential benefit when selecting patients. It may be that surgery of small lesions is not superior to the use of ablative techniques in this setting which have been applied effectively [106]. SRS has been applied in a few patients with liver metastasis.

In a Swedish single-centre prospective study including multiple sites three liver lesions were treated successfully [45]. A retrospective analysis of SRS to RCC and melanoma metastases revealed that liver lesions treated with SRS with a SFED of $\geqslant$45 Gy had a local control rate at 24 months of 100% [79].

5.2. *Adrenal metastases*

Adrenal metastasis has been found in 3.1–5.7% in nephrectomy series [107–109]. In up to 23% of adrenal lesions simultaneous metastasis at other sites were present. Adrenal metastasis generally has a poor prognosis despite complete resection of solitary ipsilateral metastases at the time of nephrectomy. It is unknown whether this is directly due to the adrenal involvement or a consequence of an often concomitant advanced locoregional tumour stage. In 347 patients with advanced stage disease (T3-4N0-1M0-1) adrenal metastases occurred in 8.1% [109]. Among 56 patients with adrenal metastases, 82% had pT3 tumours [108]. Presence of distant metastases, vascular invasion within the primary tumour and multifocal growth of renal-cell cancer within the tumour-bearing kidney were identified as independent predictors of adrenal metastases [110].

The majority of radiographically or clinically apparent ipsilateral adrenal metastases are resected at the time of nephrectomy. Isolated, synchronous contralateral and metachronous ipsilateral or contralateral adrenal metastases are rare, and little is known about their management. They are often included in series on the management of local recurrences [55,111,112]. Survival with locally recurrent renal-cell carcinoma is poor, with a 5-year survival rate of 28% [111]. Patients after surgical resection had an improved 5-year survival rate of 51% compared to 18% treated with systemic therapy and 13% with observation alone.

Contralateral adrenal involvement, either synchronous or metachronous, is rare. In one autopsy series of patients after nephrectomy for RCC it was observed in 0.7% [51]. A small series on the outcome of 11 patients after surgery for metastatic RCC in the contralateral adrenal gland reported that synchronous contralateral adrenal metastasis occurred in two patients. The mean (median, range) time to contralateral adrenal metastasis after nephrectomy for nine patients was 5.2 (6.1, 0.8–9.2) years. All patients had adrenalectomy. Despite resection, most patients in this study died from RCC after a median of 3.7 (range 0.2–10) years after adrenalectomy for contralateral adrenal metastasis [113]. Collectively, not more than 60 cases are described in the literature [114–116]. Survival ranges from 8 to

70 months, and factors associated with outcome are uncertain. Some observed an association of survival with a metachronous interval of >18 months [115]. In summary, adrenalectomy for isolated metachronous ipsilateral and contralateral adrenal metastasis is recommended because it is associated with long-term survival in individual patients. Ablative percutaneous techniques may be an alternative to open or laparoscopic adrenalectomy [117].

5.3. *Pancreatic metastases*

Pancreatic metastases of RCC are relatively infrequent but have been described in 411 patients in 170 publications [118]. A systematic literature search reported the clinical outcome of pancreatic RCC metastases [118]. Of the metastases, 321 were treated surgically and 73 non-surgically. In the metastasectomy group 65.3% of the lesions were solitary and symptomatic in 57.4%. Following metastasectomy, 2-year and 5-year disease-free survival was 76% and 57%, respectively. Interestingly, the 2- and 5-year OS rates were 80.6% and 72.6%. Further extrapancreatic disease had no impact on OS in the metastasectomy group. Surprisingly, the time to pancreatic metastasis and the number of pancreatic lesions were not associated with a worse outcome. As expected, patients with unresected pancreatic disease had a significantly shorter 2- and 5-year overall survival rate of 41% and 14%, respectively. These data suggest that metastasectomy may be beneficial in patients in whom the pancreas is the only metastatic site and who are fit enough to undergo pancreatic surgery. In-hospital mortality after pancreatic metastasectomy was 2.8%, and a significant number of patients underwent extensive surgery (pancreaticoduodenectomy in 35.8% and total pancreatectomy in 19.9%). In view of the retrospective quality of the data and the significant surgical morbidity, patients with a short time to pancreatic metastasis following nephrectomy may be best treated with systemic therapy first.

5.4. *Brain metastases*

Brain metastasis is observed in 2–17% of patients with RCC, and is readily diagnosed by symptoms in more than 80% of cases [119–121]. If left untreated, median survival is poor (3.2 months) [122]. After the introduction of SRT, indications for craniotomy have been largely abandoned except for lesions >2–3 cm, rapid onset of symptoms and in cases of large lesions with midline shift [123–125]. Because of their relative paucity, therapeutic strategies for RCC brain metastases have often been evaluated together with cerebral lesions of various primary tumours. Generally, selection of patients for therapy of brain metastases, regardless of the primary tumour site, involves assessment of performance status, extracranial tumour load and the course of the disease, as summarised in the Radiation Therapy Oncology Group (RTOG) recursive partition analysis (RPA) [126]. Unfortunately, the majority (70–80%) of patients with RCC brain lesions belong to RPA class II – Karnofsky score (KS) >70%, further extracranial metastases – who have a poor median survival of 4.2 months [124,127].

In another study, including 4295 patients, significant prognostic factors for RCC brain metastasis were KS performance status and number of brain metastases [128]. Those with a KS of 90–100% and a single brain metastasis had a median OS of 14.8 months versus 3.3 months for those with a KS <70% and more than three metastases. Others have confirmed these observations [125].

An early retrospective series of whole-brain radiation therapy (WBRT) observed survival of patients with single brain metastases from RCC of 4.4 months only, which suggested that aggressive surgical treatment would be superior [129]. A prospective randomised trial of surgery and WBRT versus WBRT alone was in favour of the combination, although only few of the 63 patients with brain metastases had RCC [130,131].

For patients with extracranial progressive disease WBRT seemed sufficient. In a further study, craniotomy with resection of brain metastases in 50 patients with RCC again proved superior to WBRT, with a median overall survival of 12.6 months [132]. However, the addition of postoperative WBRT did not result in a survival difference. Currently, WBRT is regarded an adequate choice for patients with a poor performance and multiple lesions in whom palliative control of symptoms is the principal aim. In contrast to WBRT, SRS can provide effective local control comparable to surgery, even when multiple lesions and recurrent metastases are present [133].

Experience with SRS in the treatment of brain lesions exceeds that at extracranial sites. This is because SRS has been applied relatively early after its introduction to brain metastases as ‘gamma knife’ or ‘radiosurgery’ with the first series on RCC published in 1998 [134]. In one of the larger series, 85 patients with 376 brain metastases from RCC underwent SRS [124]. The median tumour volume was 1.2 cm (range: 0.1–14.2 cm) although 65% had multiple brain lesions. Median OS was 11.1 months after SRS with a local tumour control rate of 94%. Most patients (78%) died because of systemic progression. RTOG RPA classes I, II and III survived for 24.2 months, 9.2 months and 7.5 months, respectively. Another SRS series of 69 patients observed a median survival of 13 months in patients without and 5 months in those with active extracranial disease [135].

In a recent retrospective analysis 46 patients with 99 brain lesions were treated by SRS [136]. A single brain metastasis was treated in 56.5%. Local tumour control was achieved in 84.7%. Median OS was 10 months, but increased to 18 months for those with a >75% decrease in metastasis volume. It has been argued that survival rates after SRS are inferior to those after craniotomy, but the size of the retrospective series involving patients with RCC brain metastases, and the fact that more patients with a long metachronous interval and fewer brain metastases were candidates for craniotomy [132,137], do not allow a direct comparison.

5.5. *Thyroid metastases*

The thyroid gland is infrequently involved, and the first cases were reported in the 1940s [138]. The largest retrospective study evaluated 45 resections of solitary thyroid metastases at 15 different centres [139]. The 5-year overall survival rate was 51%. Prognosis was significantly poorer in patients >70 years of age, but no other factors were established. There was a striking coincidence of thyroid and pancreatic metastases (31%).

Another group reported on seven patients with solitary RCC metastases in the thyroid and a median OS after thyroidectomy of 38.1 months [140]. In a clinicopathological study of 36 cases, 64% had documented previous evidence of RCC as

Table 2 – Median overall survival and 5-year survival rates after surgical complete resection or stereotactic radiosurgery (SRS) of solitary or oligo metastasis at various sites.

Metastatic site	Patient numbers	Median OS	5-Year survival rates (%)
Pulmonary	48–200	Munich I: 90 months Munich II: 31 months Munich III: 14 months After SRS: 32 months[a]	37.2–54
Liver	31–68	Not reported	38.9–62.2
Bone	9–38	Not reported	40–55
Brain	11–138	RPA I: 14.8 months RPA II: 4.2 months After SRS: RPA I: 24.2 months RPA II: 9.2 months	12–18
Adrenal (ipsi- and contralateral)	5–30	8–70 months	51–100
Pancreas	321 (review)	Not reported	57
Thyroid	7–45	38.1 months	51

RPA, recursive partition analysis.
[a] 97% Memorial Sloan Kettering Cancer Center (MSKCC) favourable and intermediate.

long as 21.8 years before the thyroid lesion developed (mean, 9.4 years). After a mean follow-up of 9.1 years, 36% were alive or had died without evidence of disease [141].

6. Conclusion

Only few and selected patients, especially those with solitary metastases at single-organ sites, may benefit from metastasectomy. Consistently, survival benefit and even cure have been reported after complete surgical resection and SRS (Table 2). However, available data specifically related to RCC are from retrospective non-randomised studies. Therefore it remains unresolved whether the observed survival benefit is a consequence of surgical intervention or a selection of patients with more benign tumour biology who, owing to a mild clinical course, were considered for metastasectomy.

The best outcome has been observed after resection of metachronous solitary or oligometastases in the lung, but similar survival rates were reported for other sites, including liver, pancreas, bone and even multiple sites, provided that complete resection was achieved.

Despite consistent prognostic factors associated with a favourable outcome following metastasectomy, no general therapeutic guideline can be given. Careful patient selection is paramount, and the decision to resect metastases has to be taken for each site and each individual patient. Performance status, risk profiles, patient preference and alternative techniques to achieve local control, such as SRS or ablation, will have to be considered. After the introduction of targeted therapy, more patients with metastatic RCC may become candidates for complete surgical resection; pretreatment and multimodality concepts integrating medical and surgical treatments are being investigated.

7. Conflict of interest statements

A.B. has taken part in advisory boards of Pfizer, Bayer, GSK and Novartis. A.B. is the PI of the EORTC SURTIME trial which is in part supported by an educational grant from Pfizer.

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