Local treatments for metastases of renal cell carcinoma: a systematic review

Saeed Dabestani, Lorenzo Marconi, Fabian Hofmann, Fiona Stewart, Thomas B L Lam, Steven E Canfield, Michael Staehler, Thomas Powles, Börje Ljungberg, Axel Bex

Local treatment of metastases such as metastasectomy or radiotherapy remains controversial in the treatment of metastatic renal cell carcinoma. To investigate the benefits and harms of various local treatments, we did a systematic review of all types of comparative studies on local treatment of metastases from renal cell carcinoma in any organ. Interventions included metastasectomy, radiotherapy modalities, and no local treatment. The results suggest that patients treated with complete metastasectomy have better survival and symptom control (including pain relief in bone metastases) than those treated with either incomplete or no metastasectomy. Nevertheless, the available evidence was marred by high risks of bias and confounding across all studies. Although the findings presented here should be interpreted with caution, they and the identified gaps in knowledge should provide guidance for clinicians and researchers, and directions for further research.

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Department of Urology, Skåne University Hospital, Malmö, Sweden (S Dabestani MD); **Department of Urology, Coimbra University Hospital, Coimbra, Portugal** (L Marconi MD); **Department of Urology, Sunderby Hospital, Sunderby, Sweden** (F Hofmann MD); **Academic Urology Unit, University of Aberdeen, Aberdeen, UK** (F Stewart MSc, T B L Lam MD); **Division of Urology, University of Texas Medical School at Houston, Houston, TX, USA** (S E Canfield MD); **Urologische Klinik, Klinikum der Ludwig-Maximilians Universitaet, Munich, Germany** (M Staehler MD); **Barts Cancer Institute, Queen Mary University of London, St Bartholomew's Hospital, London, UK** (Prof T Powles MD); **Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University, Umeå, Sweden** (Prof B Ljungberg MD); **and Department of Urology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands** (A Bex MD)

Correspondence to:
Dr Axel Bex, Department of Urology, Division of Surgical Oncology, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, Netherlands
a.bex@nki.nl

Introduction

Renal cell carcinoma frequently leads to synchronous or metachronous metastases[1,2] and has an estimated age-standardised mortality in Europe of 2·6%.[3] For synchronous metastatic renal cell carcinoma, cytoreductive nephrectomy in combination with treatment with interferon alfa resulted in a significant improvement in median overall survival compared with treatment with interferon alfa alone.[4] However, in the era of targeted treatment the role of cytoreductive nephrectomy is not well defined. With present targeted drugs, the proportion of patients achieving an objective response has been between 20–40%, but complete responses were reported in only 1–3% of patients.[5–7] Data from a population-based analysis suggest that median overall survival plateaus at 9–40 months, depending on patients' clinical risk scores.[8] Therefore, with the exception of rare but durable responses after high-dose interleukin 2, removal of all synchronous or metachronous lesions, when technically feasible and clinically appropriate, provides the only potentially curative treatment alternative. However, the benefits of local therapeutic options for metastases from renal cell carcinoma are controversial. Despite retrospective data suggesting consistently that complete resection of solitary or oligometastatic metastatic renal cell carcinoma suggests a favourable prognosis independent of race or geographical location,[9] uncertainty exists as to whether this is because of favourable tumour biology, the role of metastasectomy, or both. Less disputed benefits of complete resection include symptom palliation, and delay or withdrawal of systemic treatment, thereby avoiding associated toxicities.

Metastases from renal cell carcinoma are common in lung, bone, liver, and brain, but can occur at any anatomical site.[10,11] Surgical resection is a possible treatment for these metastases, but metastases' accessibility and resectability, and patients' performance and comorbidities have to be taken into account.[12] Radiotherapy modalities can provide valid local non-invasive treatment alternatives to surgery. For brain metastases, these include whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). By contrast with WBRT, SRS delivers highly collimated radiation to a precisely defined target area, minimising the radiation dose to surrounding areas.[13] For other sites, including bone, conventional radiotherapy (CRT) or stereotactic body radiotherapy (SBRT) are options. CRT is fractionated radiotherapy primarily applied to treat painful metastases, whereas SBRT, like SRS, delivers high-dose single-fraction or multi-fraction radiation.[14]

Until now, no systematic review on the outcome of different local treatment options for metastases from renal cell carcinoma has been done, and there is a need to identify potential benefits of such an approach. Therefore, in this systematic review, we aimed to address the question of whether integration of local treatment of metastases into the management of metastatic renal cell carcinoma is beneficial and, if so, what the best treatment modalities are.

Search strategy and selection criteria

The review was done according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines,[15] and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[16] Studies were identified by searching electronic databases and relevant websites. Sensitive electronic searches were done to identify reports of randomised controlled trials or non-randomised comparative studies of local treatment for metastatic renal cell carcinoma. The search strategy excluded studies published before Jan 1, 2000, and there were no language restrictions. We searched Medline (January, 1946, to Sept 30, 2013), Medline In-Process (from inception up to Sept 30, 2013), Embase (January, 1974, to Sept 30, 2013), Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 8, 2013), and Latin American and Caribbean Center on Health Sciences Information (from January 1967, to Sept 30, 2013). Additional reports were identified through searches of the reference lists of included studies and by

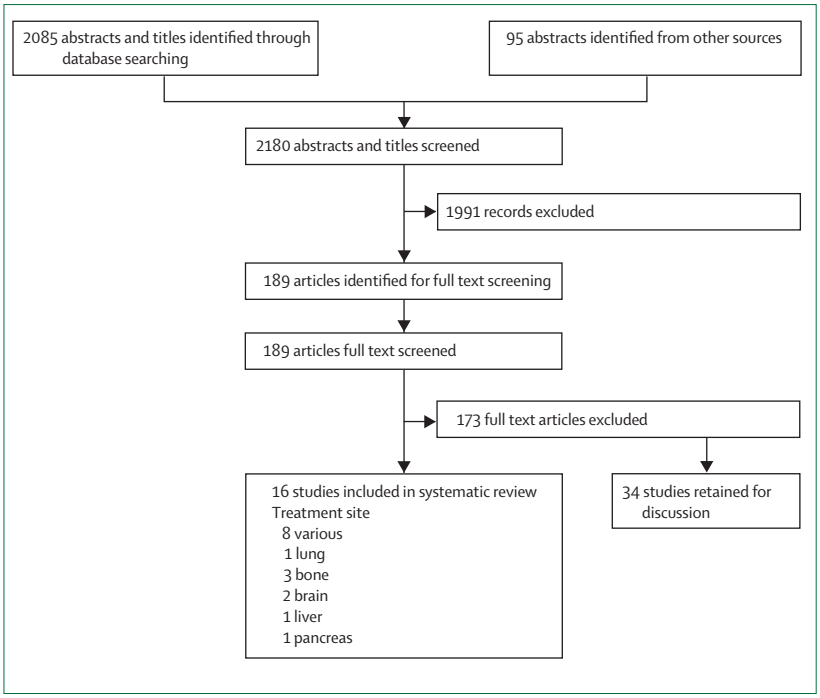

Figure 1: **PRISMA flow diagram**

an expert panel (European Association of Urology Renal Cell Carcinoma Guideline Panel). The search strategy has been described elsewhere;[17] the present Review represents an update of the original search.

Only comparative studies were included, including randomised controlled trials, prospective non-randomised comparative interventional studies, prospective observational studies with a comparator arm, and retrospective comparative studies. Studies with no comparator group (eg, single-arm case series), non-effectiveness studies (eg, prognostication or nomogram studies), reviews, or studies with fewer than ten patients per group were excluded, as were reviews, basic science studies, genetic or epidemiological studies, case series or case reports, studies of local recurrence only, studies of tumour thrombosis of the vena cava, studies of experimental treatments, studies of systemic treatment only, and studies examining only localised treatments for primary kidney cancer. Some of these excluded studies were retained for discussion, to give clinical context as to the relevance and implication of the review findings.

The patient population assessed included patients with metastatic renal cell carcinoma to any organ, except those with synchronous metastases to the ipsilateral adrenal gland or retroperitoneal lymph nodes only. There were no restrictions regarding previous treatment with cytoreductive nephrectomy or systemic or targeted treatment. The types of interventions included metastasectomy with or without intended complete resection of metastases in any organ, WBRT, CRT, SRS, SBRT, CyberKnife radiotherapy, hypofractionated radiotherapy, and no local treatment. The primary outcomes assessed were overall survival, cancer-specific survival, and progression-free survival. Local tumour control, quality of life, symptom control, and adverse events or toxic effects were assessed as secondary outcomes.

Two reviewers (SD and LM) independently screened titles and abstracts of all references identified by the search strategies. Full text copies of all potentially relevant reports were obtained and independently assessed by two reviewers (SD and LM) to identify whether they met the predefined inclusion criteria. Any disagreements were resolved by consensus or arbitration by a third person (TBLL). A data extraction form was developed specifically for the purpose of this assessment to collect information on study design, characteristics of participants, characteristics of interventions, and outcome measures. Two reviewers (SD and LM) independently assessed the risk of bias of individual studies. The standard Cochrane Collaboration risk of bias instrument[16] was used to assess the risk of bias in randomised controlled trials, whereas for non-randomised comparative studies the risk of bias instrument recommended by the Cochrane Non-Randomised Studies Methods Group was used.[16] Additionally, for non-randomised comparative studies, the main confounders for the primary outcomes (ie, survival or tumour response) were identified a priori by the expert panel. The main confounders identified were age, sex, Fuhrman grade, size or volume of metastases, previous treatment before local treatment, performance status, treatment of different sites in the same study, and tumour histology. The confounders were assessed for the following four criteria: first, whether the confounder was considered by the study author; second, the precision of measurement; third, if there was a baseline imbalance between the intervention and comparator group or groups; and finally, the quality of adjustment for imbalance in studies with various treatment sites.[18] A study was regarded as at high risk of bias, if any of the confounders were imbalanced between experimental groups. For outcomes in which the data synthesis involved randomised control trials, or non-randomised comparative studies with low risk of bias, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[19] was used to assess the quality of evidence.

For data analysis, descriptive statistics were used to summarise baseline characteristics. A quantitative synthesis (ie, meta-analysis) was planned for randomised controlled trials only, because of the inherent clinical and methodological heterogeneity present in non-randomised studies. When pooling of data was not done, and where appropriate, results were presented in forest plots to allow a visual comparison of the effects of interventions between studies. Both fixed-effects and random-effects models were used to derive

the appropriate test statistic. For time-to-event data, hazard ratios and 95% CIs obtained directly from studies or indirectly from presented Kaplan-Meier survival curves were used to compare results.[20] In analysing dichotomous outcomes, relative risks with 95% CIs were used, whereas for continuous outcomes, means and SDs or medians and ranges were used to summarise the data, and weighted mean differences and 95% CIs were used to compare interventions. Statistical heterogeneity between studies was assessed by visual inspection of plots of the data, the χ^2 test for heterogeneity, and the I^2 statistic.[21] Analyses were done using Cochrane RevMan version 5.2. If a meta-analysis was not feasible, a narrative synthesis was provided.[22]

	Site of treatment	Interventions	Age (years; mean [SD] or median [range or IQR])	Performance status (as stated by author)	Follow-up (months; mean [SD] or median [range])	Tumour grade (% Fuhrman ≥3)	Tumour histology (% clear-cell carcinoma)	Metastatic burden	Treatment before or after intervention	Outcomes measured
Amiraliev et al (2012);[23] Russia; retrospective comparative study (abstract only); 1998–2010	Lung	Complete MTS (n=90), immuno-therapy (interferon alfa; n=41), or targeted therapy (sunitinib and sorafenib; n=21)	NR	NR	NR	NR	NR	NR	NR	OS
Alt et al (2011);[12] USA; retrospective comparative study; 1976–2006	Various (39% lung only; 40% lung + various)	Complete (n=125) or incomplete MTS (n=762)	Complete: 62 (range 41–85) Incomplete: 62 (range 21–92)	ECOG 0–1: complete 89·3%, incomplete 81·0%	Complete: 37·2 (range 0·0–334·4) Incomplete: 31·2 (range 0·0–182·4)	76·9%	90·2%	≥3 metastases: complete 75%, incomplete 92%	Previous CN or RN. Received SysT: complete 28·0%, incomplete 48·5%	OS, CSS
Petralia et al (2010);[24] Italy and Austria; retrospective comparative study (abstract only); 1984–2006	Various (% lung NR)	Complete MTS (n=35), or incomplete MTS, no MTS, or Adj SysT (n=143)	60 (range 27–87)	NR	21 (range 1–235)	56·2%	NR	NR	Previous CN or RN. Incomplete MTS, no MTS, or Adj SysT: 21% received Adj SysT	CSS for MTS *vs* the 3 other groups
Staehler et al (2010);[25] Germany; retrospective comparative study; 1995–2006	Liver	Complete MTS (n=68) or no MTS (refused surgery; n=20)	58 (range 17–78)	MSKCC score ≥ inter-mediate: complete MTS 94%, no MTS 95%	26 (range 1–187)	Complete MTS: 28% No MTS: 0%	Complete MTS: 88% No MTS: 55%	≥2 metastases: complete MTS 62%, no MTS 70%	Previous CN. Received Adj SysT: complete MTS 81%, no MTS 80%	OS
Staehler et al (2009);[26] Germany; retrospective comparative study (abstract only); 1995–2006	Various (67% lung)	Complete MTS (n=183) or no MTS (refused surgery; n=57)	NR	NR	26 (range 1–187)	NR	NR	NR	Previous CN or RN	OS
Eggener et al (2008);[27] USA; retrospective comparative study; 1989–2007	Various (64% lung)	MTS (91% complete MTS; n=44) or no MTS (n=85)	61·7 (IQR 52·7–70·8)	KS ≥80: 106 (82%)	NR	NR	80%	1 metastases: MTS 100%, no MTS NR	Previous RN in 123 patients (95%). 6 (5%) had a partial nephrectomy	OS
Zerbi et al (2008);[28] Italy; retrospective comparative study; 1998–2006	Pancreas	Complete (n=23) or no MTS (n=13)	Complete MTS: 64·0 (SD NR) No MTS: 65·9 (SD NR)	NR	31 (range 12–98)	NR	NR	≥2 metastases: complete MTS 17·4%, no MTS 46·1%	Previous RN. Received Adj SysT: complete MTS 35%, no MTS 100%	OS
Brinkmann et al (2007);[29] Germany; prospective comparative study; 1997–2004	Various (85% lung)	Complete (n=18) or no MTS (n=16)	Complete MTS: 61 (range 43–75) No MTS: 64 (range 39–76)	ECOG 0–1: complete MTS 78%, no MTS 81%	NR	NR	NR	>50% with 2 or more organ systems with metastases	100% received neo-Adj SysT. Previous CN: complete MTS 94%, no MTS 75%	CSS
Kwak et al (2007);[30] South Korea; retrospective comparative study; 1990–2004	Various (48% lung)	Complete (n=21) or no MTS (n=41)	Complete MTS: 60 (range 38–79) No MTS: 61 (range 31–79)	ECOG 0–1: complete MTS 100%, no MTS 44%	Complete MTS: 36·5 (range 4·0–182·7) No MTS: 8·4 (range 0·9–63·7)	Complete MTS: 61·9% No MTS: 56·1%	Complete MTS: 85·7% No MTS: 78·0%	≥2 metastases: complete MTS 33·3%, no MTS 70·7%	Previous CN	OS

(Table 1 continues on next page)

	Site of treatment	Interventions	Age (years; mean [SD] or median [range])	Performance status (as stated by author)	Follow-up (months; mean [SD] or median [range])	Tumour grade (% Fuhrman ≥3)	Tumour histology (% clear-cell carcinoma)	Metastatic burden	Treatment before or after intervention	Outcomes measured
(Continued from previous page)										
Russo et al (2007);[31] USA; retrospective comparative study; 1989–2003	Various (48% lung)	Complete MTS (n=61), or no or incomplete MTS (n=30)	61 (IQR 52–68)	KS ≥80: complete MTS 89%, no or incomplete MTS 84%	43 (range NR)	NR	Complete MTS: 90%. No or incomplete MTS: 97%	≥2 metastases: complete MTS 28·0%, no or incomplete MTS 53·0%	Previous CN	OS
Lee et al (2006);[32] South Korea; retrospective comparative study; 1999–2003	Various (63% lung)	MTS (45% complete MTS) + SysT (n=20) or no MTS + SysT (n=37)	58 (range 31–77)	Participants with ECOG 0–1: MTS + SysT 100%, no MTS + SysT 79%	NR	NR	NR	≥2 metastases: MTS + SysT 75%, no MTS + SysT 95%	Previous RN or CN. 100% received Adj SysT	CSS, PFS
Zelefsky et al (2012);[33] USA; retrospective comparative study; 2004–10	Bone (various locations)	Single-dose (n=59) or hypofractionated IGRT (n=46)	NR	NR	12 (range 1–48)	NR	NR	Pelvic or spine metastases: single-dose IGRT 85%, hypofractionated IGRT 67%	NR	Local PFS
Hunter et al (2012);[34] USA; retrospective comparative study; 2002–10	Bone (spine C1 to sacrum)	Single-dose SBRT (n=76) or CRT (n=34)	SBRT: 57 (range 41–80) CRT: 62 (range 43–81)	Median KS: SBRT 80 (range 50–90), CRT 70 (20–100)	4·3 (range 0·2–38·0)	NR	NR	Multiple sites treated: SBRT 59%, CRT 24%	Prior radiation to spine: SBRT 16%, CRT 18% Palliative surgery: SBRT 0%, CRT 23%	Symptom control
Fuchs et al (2005);[35] Switzerland; retrospective comparative study; 1976–99	Bone (various locations)	MTS or local stabilisation (n=33), or non-surgical treatment (n=27)	Mean 67 (range 38–85)	NR	21 (range 1–76)	26·7%	NR	Participants with appendicular metastases: MTS or local stabilisation 73%, non-surgical treatment 78%	No treatment 15%, CN 60% or RN 25%. 20% of all patients received SysT	CSS
Fokas et al (2010);[36] Germany; retrospective comparative study; 1996–2006	Brain	SRS (n=51), WBRT (n=20), or SRS + WBRT (n=17)	≥63 years: SRS 59%, WBRT 80%, SRS + WBRT 48%	RPA I: SRS 33%, WBRT 5%, SRS + WBRT 17%	NR (range 9–95)	NR	NR	≥2 metastases: SRS 17·6%, WBRT 100%, SRS + WBRT 100%	No treatment or RN or CN for all participants Salvage therapy=surgical resection	OS, symptom control
Ikushima et al (2000);[37] Japan; retrospective comparative study; 1983–98	Brain	FSRT (n=10), MTS + CRT (n=11), or CRT alone (n=12)	≥60 years: FSRT 10%, MTS + CRT 18%, CRT 8·3%	ECOG 0–1: FSRT 100%, MTS + CRT 82%, CRT 50%	5·2 (range 0·5–68·0)	NR	NR	>1 metastases: FSRT 10%, MTS + CRT 36%, CRT 50%. Extracranial metastases: FSRT 90%, MTS + CRT 82%, CRT 100%	No treatment, RN, or CN for all participants	CSS, local control

Adj=adjuvant. CN=cytoreductive nephrectomy. CRT=conventional radiotherapy. CSS=cancer-specific survival. ECOG=Eastern Cooperative Oncology Group performance status. FSRT=fractionated stereotactic radiotherapy. IGRT=image-guided radiotherapy. KS=Karnofsky performance status. MSKCC=Memorial Sloan Kettering Cancer Center. MTS=metastasectomy. NR=not reported. OS=overall survival. PFS=progression-free survival. RN=radical nephrectomy. RPA=recursive partition analysis. SBRT=single-fraction high-dose stereotactic body radiation therapy. SRS=stereotactic radiosurgery. SysT=systemic therapy. WBRT=whole-brain radiotherapy.

Table 1: **Baseline characteristics of all included studies**

Findings

The literature search identified 2180 studies, 189 of which were selected for full-text screening (figure 1). Six articles in languages other than English were translated. 16 studies reporting on 2350 patients were eligible for final inclusion. Of studies not meeting the inclusion criteria, 34 were retained for discussion.

All 16 included studies were retrospective comparative studies (table 1). No randomised controlled trials or prospective non-randomised comparative studies were identified. Eight studies assessed local treatments of metastases from renal cell carcinoma in various organs,[12,24,26,27,29–32] of which the most common sites were lung, bone, liver, and brain, and less common sites were pancreas, adrenal gland, lymph nodes, thyroid gland, spleen, ethmoid sinus, and skin (table 1). Other studies also assessed local treatments for metastases from renal cell carcinoma in bone (including the vertebrae),[33–35] the brain,[36,37] liver,[25] lung,[23] and

	Comparator	Outcome	p value
Amiraliev et al (2012)[23] (abstract only; lung)			
Immunotherapy (interferon alfa; n=41)	Complete metastasectomy (n=90)	Median OS 18·0 *vs* 36·3 months	<0·05
Targeted therapy (sunitinib + sorafenib; n=21)	Complete metastasectomy (n=90)	Median OS 30·4 *vs* 36·3 months	<0·05
Notes	Three-arm study. Not reported if systemic therapy was given to metastasectomy group		
Alt et al (2011)[12] (various: 39% lung only, 40% lung + various)			
Incomplete metastasectomy (n=762)	Complete metastasectomy (n=125)	Median OS 15·6 *vs* 48·0 months, adjusted HR 2·61 (95% CI 1·99–3·42). Median CSS 15·6 *vs* 57·6 months, adjusted HR 2·91 (2·17–3·90)	OS <0·001; CSS <0·001
Notes	Type of systemic therapy not specified in study. 43·7% of all patients also received radiation therapy for ≥1 metastases		
Petralia et al (2010)[24] (abstract only; various [% lung NR])			
Incomplete metastasectomy, no metastasectomy, or systemic therapy (n=143)	Complete metastasectomy (n=35)	Median CSS 14 *vs* 30 months, adjusted HR 1·71 (95% CI 1·09–2·69)	0·02
Notes	Type of systemic therapy given not specified in study		
Staehler et al (2010)[25] (liver)			
No metastasectomy (refused surgery; n=20)	Complete metastasectomy (n=68)	Median OS 27 *vs* 142 months, adjusted HR 2·23 (95% CI 1·05–4·72)	0·003
Notes	Adjuvant systemic therapy was interferon alfa, interleukin 2, or both. 6% of patients received multikinase inhibitors		
Staehler et al (2009)[26] (abstract only; various [67% lung])			
No metastasectomy (refused surgery; n=183)	Complete metastasectomy (n=57)	Mean OS at 5 years 35·3% (SD 9·2) *vs* 57·8% (5·9) Median OS 55·5 *vs* 122·0 months, adjusted HR 2·14 (95% CI 1·44–3·17)	Mean OS <0·001; median OS <0·001
Notes	Author contacted to get study data. Median OS and OS HR based on statistical analysis of acquired data. Not reported if systemic therapy was given		
Eggener et al (2008)[27] (various [64% lung])			
No metastasectomy (n=85)	Metastasectomy (91% complete; n=44)	Median OS 21 *vs* 45 months, adjusted HR 2·70 (95% CI 1·6–4·5)	<0·001
Notes	Not reported if systemic therapy was given		
Zerbi et al (2008)[28] (pancreas)			
No metastasectomy (n=13)	Complete metastasectomy (n=23)	OS at 2 years 59% *vs* 95% (p value NR); OS at 5 years 47% *vs* 88% (p value NR). Median survival for complete metastasectomy not reached; median survival for no metastasectomy 27 months (95% CI 17·5–50·2)	Median survival 0·0263
Notes	Adjuvant systemic therapy was interferon alfa, interleukin 2, or both. 5·5% of patients also received thalidomide		
Brinkmann et al (2007)[29] (various [85% lung])			
No metastasectomy (n=18)	Complete metastasectomy (n=16)	Median CSS 50 (range 18–104) *vs* 58 months (9–104)	0·223
Notes	Neoadjuvant systemic therapy was a combination of interferon alfa, interleukin 2, and flourouracil		
Kwak et al (2007)[30] (various [48% lung])			
No metastasectomy (n=41)	Complete metastasectomy (n=21)	Median OS 8·4 *vs* 36·5 months, adjusted HR 2·57 (95% CI 1·21–5·44)	<0·001
Notes	Study only included patients who had not received any immunotherapy		
Russo et al (2007)[31] (various [48% lung])			
No metastasectomy or incomplete metastasectomy (n=30)	Complete metastasectomy (n=61)	Median OS 12 *vs* 30 months	NR
Notes	Not reported if systemic therapy was given		
Lee et al (2006)[32] (various [63% lung])			
No metastasectomy + systemic therapy (n=37)	Metastasectomy (45% complete) + systemic therapy (n=20)	Median CSS 13 *vs* 23 months. Median PFS 5 *vs* 13 months	CSS 0·11; PFS 0·0226

(Table 2 continues on next page)

	Comparator	Outcome	p value
(Continued from previous page)			
Incomplete metastasectomy + systemic therapy (n=11)	Complete metastasectomy + systemic therapy (n=9)	Median CSS 20 *vs* 28 months (unadjusted HR 3·47, 95% CI 1·26–9·56)	0·016
Notes	Adjuvant systemic therapy was a combination of interferon alfa, interleukin 2, and flourouracil. HR was only available for incomplete metastasectomy subgroup *vs* complete metastasectomy subgroup		
Zelefsky et al (2012)[33] (bone [various locations])			
Single-dose IGRT ≥24 Gy/dose (n=45)	Hypofractionated IGRT (n=46)	Local PFS at 3 years 88% *vs* 17%	0·001
Single-dose IGRT (n=59)	Hypofractionated IGRT (n=46)	Local PFS adjusted HR 0·28 (95% CI 0·11–0·72)	0·008
Notes	HR for PFS is for all participants in intervention arm. Not reported if systemic therapy was given		
Hunter et al (2012)[34] (bone [spine C1 to sacrum])			
CRT (n=34)	Single-dose SBRT (n=76)	Pain relief ORR 68% *vs* 62%, unadjusted HR 1·28 (95% CI 0·78–2·08)	0·67
CRT (n=34)	Single-dose SBRT (n=76)	Median time to pain relief 0·6 *vs* 1·2 weeks	0·29
CRT (n=25)	Single-dose SBRT (n=54)	Median duration of pain relief 1·7 *vs* 4·8 months (n=54)	0·095
Notes	Not reported if systemic therapy was given. Unclear amount of metastatic burden		
Fuchs et al (2005)[35] (bone [various locations])			
Metastasectomy and local stabilisation (n=33)	Non-surgical treatment (n=27)	5-year CSS 36% *vs* 8%	0·0066
Notes	Type of systemic therapy given only stated as chemotherapy. 82% of all patients also received radiation therapy for metastases		
Fokas et al (2010)[36] (brain)			
SRS (n=51)	WBRT (n=20)	OS at 2 years 40% *vs* 0%	<0·001
SRS + WBRT (n=17)	WBRT (n=20)	OS at 2 years 35% *vs* 0%	<0·001
SRS (n=51)	SRS + WBRT (n=17)	OS at 2 years 40% *vs* 35%	0·703
SRS RPA class I (n=17)	SRS + WBRT RPA class I (n=3)	OS at 2 years 52% *vs* 60%	<0·001
SRS RPA class II–III (n=34)	WBRT RPA class II–III (n=20)	OS at 2 years 24% *vs* 0%	<0·001
SRS RPA class II–III (n=34)	SRS + WBRT RPA class II–III (n=14)	OS at 2 years 24% *vs* 21%	<0·001
SRS + WBRT class II–III (n=14)	WBRT RPA class II–III (n=20)	OS at 2 years 21% *vs* 0%	<0·001
SRS (n=51)	WBRT (n=20)	Intracerebral control at 2 years 38% *vs* 0%	<0·001
SRS + WBRT (n=17)	WBRT (n=20)	Intracerebral control at 2 years 29% *vs* 0%	<0·001
SRS (n=51)	SRS + WBRT (n=17)	Intracerebral control at 2 years 38% *vs* 29%	0·032
SRS RPA class I (n=17)	SRS + WBRT RPA class I (n=3)	Intracerebral control at 2 years 59% *vs* 100%	<0·001
SRS RPA class II–III (n=34)	WBRT RPA class II–III (n=20)	Intracerebral control at 2 years 27% *vs* 0%	<0·001
SRS (n=34) RPA class II–III	SRS + WBRT RPA class II–III (n=14)	Intracerebral control at 2 years 27% *vs* 21%	<0·001
SRS + WBRT class II–III (n=14)	WBRT RPA class II–III (n=20)	Intracerebral control at 2 years 21% *vs* 0%	<0·001
Notes	Three-arm study. OS and intracerebral control outcomes for SRS or SRS + WBRT *vs* WBRT alone for RPA class I not in table because the WBRT subgroup for RPA class I=0 patients. No specific definition of symptom control given. Not reported if systemic therapy was given		
Ikushima et al (2000)[37] (brain)			
FSRT (n=10)	Metastasectomy + CRT (n=11) and CRT alone (n=12)	CSS at 1 year 90% *vs* 64% and 25%. CSS at 2 years 54% *vs* 27% and 17%. CSS at 3 years 41% *vs* 9% and 8%	NR
FSRT (n=10)	Metastasectomy + CRT (n=6)	2-year LC 55·2% *vs* 70·0%	0·61
FSRT (n=10)	CRT alone (n=4)	2-year LC 55·2% *vs* NR	NR
Notes	Three-arm study. Actuarial LC rates only for patients who were followed up by imaging studies. Not reported if systemic therapy was given		

CRT=conventional radiotherapy. CSS=cancer-specific survival. FSRT=fractionated stereotactic radiotherapy. HR=hazard ratio. IGRT=image-guided radiotherapy. LC=local control. NR=not reported. ORR=overall response rate (complete pain relief response and partial pain relief response in total). OS=overall survival. PFS=progression-free survival. RPA=recursive partitioning analysis. SBRT=Single-fraction high-dose stereotactic body radiation therapy. SRS=stereotactic radiosurgery. WBRT=whole-body radiotherapy.

Table 2: **Summary of results regarding comparative effectiveness and harms of all included studies**

pancreas (table 1).[28] Three studies[23,24,26] were abstracts only (table 1). The heterogeneity of data did not allow for a meta-analysis; a narrative synthesis of the evidence is presented instead. There was great variation in the type and distribution of systemic treatments and in their reporting across studies. Generally, systemic treatment consisted of cytokines and VEGF inhibitors. Eight studies[23,26,27,31,33,34,36,37] contained no information on whether systemic treatment was given; three studies[12,24,35] did not specify the type of systemic treatment. Three studies[25,28,32] used treatment after metastasectomy and one study[29] used treatment beforehand. In one study,[30] systemic treatment was not used.

Complete versus no or incomplete metastasectomy

All of the eight studies[12,24,26,27,29–32] that assessed metastases from renal cell carcinoma in various organs reported on complete metastasectomy versus no metastasectomy, incomplete metastasectomy, or both (table 2). However, in one study,[32] complete resection was achieved in only 45% of the metastasectomy group, which was compared with patients with no metastasectomy. No other focal treatment modalities were applied. In six of the eight studies,[12,24,26,27,30,32] a significantly longer median overall survival or cancer-specific survival was reported after complete metastasectomy compared with incomplete or no metastasectomy (median of medians overall survival or cancer-specific survival 40·8 months, IQR 31·6–48·0), or both (14·8 months, 13·3–21·0). Of the two remaining studies, in one[29] there was no significant difference in cancer-specific survival between complete metastasectomy and no metastasectomy (58 *vs* 50 months; p=0·223); however, only 18 and 16 patients were assessed in the respective study groups. In the other study[31] there was a numerically longer median overall survival for the metastasectomy group (30 *vs* 12 months), but the p value was not provided. A forest plot of hazard ratios for overall survival or cancer-specific survival in studies in which incomplete or no metastasectomy was compared with complete metastasectomy for metastatic renal cell carcinoma to various organs shows improved overall survival and cancer-specific survival for complete metastasectomy (figure 2).

Regarding metastasectomy in specific organs, three studies assessed metastases to lung,[23] liver,[25] and pancreas (table 2).[28] In the lung study,[23] there was significantly higher median overall survival after metastasectomy compared with both targeted treatment and immunotherapy (36·3 *vs* 30·4 and 18·0 months, respectively, p<0·05). In the liver study,[25] median overall survival was significantly higher for metastasectomy compared with no metastasectomy (142 months [95% CI 115–169] *vs* 27 months [16–38]; p=0·003). In the pancreas study,[28] 5-year overall survival was numerically higher for metastasectomy compared with no metastasectomy (88% *vs* 47%). Median overall survival was significantly longer for metastasectomy (p=0·0263; table 2).

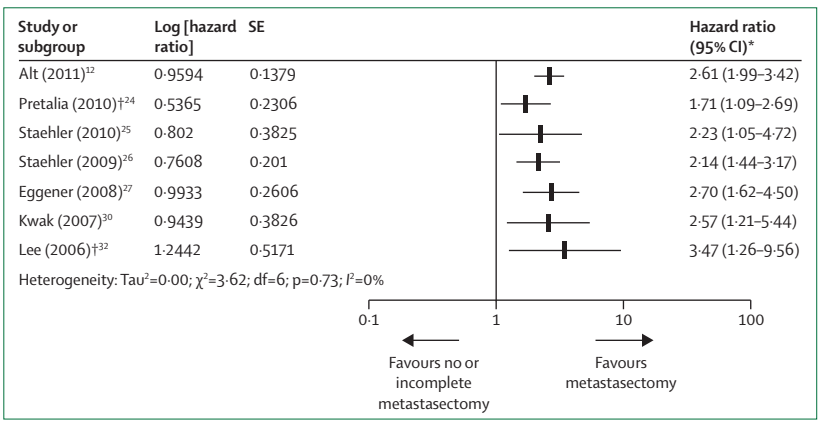

Figure 2: **Forest plot of hazard ratios for overall survival or cancer-specific survival in studies comparing incomplete or no metastasectomy versus complete metastasectomy**
*Variance method, fixed-effects model. †Cancer-specific survival.

Three studies on local treatments for bone metastases were identified (table 2). In one study,[33] single-dose image-guided radiotherapy (IGRT) was compared with hypofractionated IGRT in patients with bone metastases in various locations. Patients treated with single-dose IGRT (≥24 Gy) had a significantly better 3-year actuarial local progression-free survival than those treated with hypofractionated IGRT (88% *vs* 17%; p=0·001), which was also shown with a Cox regression analysis (p=0·008). In another study,[35] metastasectomy with curettage and local stabilisation was compared with no surgical treatment of solitary bone metastases in various locations. A significantly higher proportion of patients who underwent surgical intervention achieved 5-year cancer-specific survival compared with those with no intervention (36% *vs* 8%; p=0·0066). Findings from a multivariate analysis of cancer-specific survival, adjusting for previous nephrectomy, sex, and age, still favoured metastasectomy with curettage and intramedullary stabilisation compared with no surgical treatment (p=0·018). A third study[34] compared the efficacy and durability of pain relief between single-dose SBRT and CRT in patients with bone metastases to the spinal column (C1 sacrum); no significant difference between pain objective responses (p=0·67), time to pain relief (p=0·29), or duration of pain relief (p=0·095) was found (table 2).

Local therapies for brain metastases

Two studies on brain metastases from renal cell carcinoma were included (table 2). One study[36] compared SRS, WBRT, and the combination of both SRS and WBRT. All patients in the WBRT and combination groups had at least two brain metastases, whereas such patients accounted for 17·6% of the SRS group. Each group was further subdivided into recursive partitioning analysis (RPA), a statistical method for undertaking multivariate analysis, based on a decision tree with dichotomous variables classes I–III (I=favourable, II=moderate, and III=poor patient status). A significant

Figure 3: **Risk of bias and confounding assessment summary**
Green circle=low risk of bias and confounding. Red circle=high risk of bias and confounding. Yellow circle=unclear risk of bias and confounding.

improvement in 2-year intracerebral control was found when adding WBRT to SRS compared with SRS alone (p=0·032), but no such difference was noted for 2-year overall survival (p=0·703); both were superior to WBRT alone in the general study population (all p<0·001) and in the RPA subgroup analyses (all p<0·001). In a subgroup analysis of RPA class I, the comparison of SRS with SRS plus WBRT revealed significantly better 2-year overall survival and intracerebral control for the combination group (p<0·001 for both). The other study[37] compared fractionated stereotactic radiotherapy (FSRT) with metastasectomy plus CRT, or CRT alone. Only six (55%) patients after metastasectomy plus CRT and four patients (33%) after CRT were followed up with imaging. Several of the patients in all groups underwent alternative surgical and non-surgical treatments after initial treatment. Survival at 1, 2, and 3 years were 90%, 54%, and 41% for FSRT, 64%, 27%, and 9% for metastasectomy plus CRT, and 25%, 17% and 8% for CRT, respectively. No p value was reported for survival. FSRT did not have a significantly better 2-year local control compared with metastasectomy plus CRT (p=0·61); whether FSRT gave significantly better 2-year local control than CRT alone was not reported.

Risk of bias and confounding

Figure 3 summarises the risk of bias and confounding for all included studies. All studies were retrospective and non-randomised, leading to the high risk of bias associated with non-randomisation, patient attrition, and selective reporting. With the exception of one study,[12] all studies were substantially underpowered. Regarding confounding, about half of studies reported adequate data on age and sex. Systemic treatment type and the frequency of their use were heterogeneous. Although performance status was included in the baseline characteristics in most studies, there was heterogeneity in performance status classification. There was a moderate-to-high risk of confounding regarding previous treatment, tumour histology, grade, and size or volume of metastases, especially in studies on local treatments of bone and brain metastases.[33–37] Regarding different sites treated in the same study, there was generally a moderate-to-high risk of confounding, especially for studies pertaining to treatment of metastases at various sites,[12,27,30–32] because it was often unclear if these confounders were adjusted. Evidence quality was not assessed by GRADE because of the nature of the included studies (ie, retrospective comparative studies), and the high risk of bias across the studies.

Discussion

The results of this systematic review suggest a survival benefit with complete metastasectomy versus either incomplete or no metastasectomy for renal cell carcinoma metastases to parenchymal organs. There was also some evidence in favour of local treatment in terms of symptom control, such as pain relief in patients with bone metastases. The great variation in type and distribution of systemic treatment, and its response being reported in only a subset of studies, prevents any conclusion on the role and effect of targeted treatment in the setting of complete metastasectomy. However, in a non-comparative report,[38] most patients who had a complete response after a combination of targeted treatment and local treatment stopped systemic treatment. After a median follow-up of 10·7 months (range 0·3–54·0), 48% of patients had still not experienced disease progression; these data suggest that local treatment might have a role in delaying return to systemic treatment and associated toxicity.

The main strength of this Review is its robust methodology, which adheres to strict criteria that are rigorous, transparent, and reproducible. We have described the best available contemporary evidence base, from which

some conclusions can be made, and identified knowledge gaps that can only be addressed through well-designed, prospective comparative studies.

However, there are several limitations. All included studies were retrospective comparative studies, involving small numbers of patients; there were no randomised controlled trials or prospective non-randomised comparative studies. There were generally high risks of bias across all included studies and across most domains, including a substantial risk of confounding. As a result, only a narrative synthesis of the evidence was presented; a meta-analysis was not possible because of the aforementioned limitations. Additionally, the search was limited to studies published from 2000 onwards; earlier publications might have been missed, although a scoping exercise of the available published work before 2000 did not reveal any randomised controlled trials. The generally poor quality of the evidence base imply that there is significant uncertainty regarding our findings, and, therefore, caution is needed in their interpretation. For instance, we cannot rule out that the reported benefit is largely due to an indication bias on the basis of differences in tumour aggressiveness. Potentially, patients with oligometastasis and long metachronous intervals are more likely to be candidates for metastasectomy, whereas those with a high-volume metastasis, rapid progression, and reduced performance status often do not undergo resection. Several non-comparative studies suggest that the disease dynamic might be more important than any intervention. Low tumour grade[39] and long metachronous intervals with repeat resection[40] are associated with long survival. No reliable data exist on the proportion of patients with metastatic renal cell carcinoma who would be eligible for local treatment of their metastases. At diagnosis, 57–65% of patients with metastatic renal cell carcinoma have single sites; the percentage of patients with single sites increases with age.[10] Estimates suggest that 25% of patients with metachronous metastasis might be candidates for local treatment.[12] For synchronous metastatic disease, this proportion may be less than 10%.[41] The investigators of most studies identified in this systematic review acknowledge that patient selection for local treatment of metastases is complex because of the heterogeneous course of metastatic renal cell carcinoma, surgical resectability, and anatomical access.

There is general consensus that several clinical and pathological factors, such as performance status, disease-free interval, burden and site of metastases, histological subtype, and Fuhrman grade affect the prognosis and management of metastatic renal cell carcinoma to a large extent.[42] Most of the data on metastasectomy exist for patients with clear-cell renal cell carcinoma; little is known for other subtypes such as papillary renal cell carcinoma.[43] Accurate information on prognosis is of utmost importance for treatment decisions. The Memorial Sloan Kettering Cancer Centre (MSKCC) risk score is one of the most commonly used prognostic models and establishes which patients have favourable, intermediate, and poor risks using Karnofsky performance status, the time from diagnosis to treatment, and serum haemoglobin, calcium, and lactate dehydrogenase concentrations.[44] Surprisingly, we identified only two studies that reported the MSKCC score.[25,27] For patients receiving targeted treatment, the MSKCC score and the validated Database Consortium model share concordance indices of 0·66–0·65 to assess prognosis.[8,45,46] In one of the studies included in the systematic review, a more favourable risk category and metastasectomy were each independently associated with better survival.[27] However, this may be because, with a median survival of 6 months for poor-risk patients, these patients do not live long enough to derive benefit from metastasectomy. Other more site-specific clinical factors that might have prognostic value for local treatment of metastases are recognised, and were partly discussed in the studies included in the systematic review.

Most data exist for lung metastases, which are the most common metastases from renal cell carcinoma. Large, non-comparative case series not included in the systematic review reported 5-year survival of 37–54% for completely resected solitary or oligometastatic pulmonary metastases.[47–53] Multivariate analyses consistently identified a pattern of prognostic factors (panel). Having a higher number of removed pulmonary metastases,[12,51,54] concomitant mediastinal nodal metastasis,[47,51–53] or incomplete resection[12,48,51–54] was associated with poorer 5-year survival of 0–24·4%. Additionally, a short disease-free interval after nephrectomy or synchronous metastasis was associated with a poor outcome, [48,51,52,54] as was size of lung metastases.[47,52,55] A lung-specific prognostic score including these factors has been developed from 200 consecutive patients with pulmonary metastases; this score needs external validation.[56]

Interpretation of the identified studies for bone and brain metastases that assessed radiotherapy or compared radiotherapy to surgery is problematic. During the long study periods of 6–15 years represented by the included studies, substantial advances were made in radiotherapy, including changes in dosage and modalities. Additionally, location, size, and soft-tissue involvement of metastases varied substantially between studies, and were inconsistently reported, which prevented a direct comparison of results. Although findings from this systematic review suggest prolonged disease-free survival after SBRT or metastasectomy of single and multiple bone metastases, no recommendations can be made as to the best treatment modality. However, findings from a randomised controlled trial in patients with bone metastasis from various cancers, including renal cell carcinoma, showed that immediate decompressive surgery and postoperative radiotherapy is superior to radiotherapy alone for patients with spinal cord compression.[57] Findings from a further small non-comparative study suggested

Panel: **General and site-specific factors for lung, bone, and brain associated with a favourable outcome after local treatment of metastases from renal cell carcinoma**

General*

Patient factors

- Good performance status (Karnofsky performance status, Eastern Cooperative Oncology Group performance status, WHO)
- Memorial Sloan Kettering Cancer Center or Heng favourable and intermediate risk

Extent of disease

- Solitary or oligometastatic lesions
- Single organ site
- Absence of nodal metastases

Course of disease

- Metachronous metastasis
- Disease-free interval of over 2 years
- Absence of progression to treatment

Tumour biology

- Absence of sarcomatoid component
- Clear-cell subtype
- Low-to-moderate Fuhrman grade

Surgical factor

- Complete resection

Lung

- Fewer than seven metastases
- Absence of mediastinal lymph node metastases
- Metastases less than 4 cm in diameter
- Unilateral lung involvement

Bone

- Peripheral location of metastases

Brain

- Radiation Therapy Oncology Group recursive partitioning analysis class I:
  - Karnofsky performance status greater than 70
  - Age younger than 65 years
  - Absence of extracranial metastatic sites
  - Control of the primary tumour
- Karnofsky performance status 90–100 and single lesion

*Other sites follow the general factors.

SRS reduced progression and pain in patients with renal cell carcinoma spinal lesions.[58] In addition to general prognostic factors, peripheral location of bone metastases is a favourable factor.[12,59–62]

Only two studies were identified that compared different radiotherapy modalities, including in combination with surgery, for brain metastases from renal cell carcinoma. Thus, recommendation of a specific treatment modality is not possible. However, findings from additional studies on non-renal cell carcinoma brain metastases suggest a prognostic score-related approach. With SRS, craniotomy is now not frequently used except for brain metastases larger than 3 cm in size, and rapidly symptomatic lesions with midline shift.[63,64] Brain metastases from renal cell carcinoma were mostly assessed collectively with cerebral lesions from other malignancies. Recommendations for radiotherapy follow the Radiation Therapy Oncology Group RPA developed from brain metastases irrespective of the primary tumour site (RPA class I: Karnofsky performance status ≥70, age <65 years, primary tumour controlled, no extracranial sites; class II: Karnofsky performance status ≥70 with absence of at least one of the other factors; class III: Karnofsky performance status <70).[65] About three-quarters of patients belong to RPA class II.[63,66] In a retrospective non-comparative study, 85 patients with renal cell carcinoma with brain metastases who underwent SRS were assessed.[63] Median metastatic volume was 1·2 cm (range 0·1–14·2) and 65% of patients had multiple cerebral metastases. After SRS, median overall survival was 11 months with 94% of patients achieving local control. Most patients (78%) died of extracranial progression. Median overall survival was 24·2 months for RPA class I, 9·2 months for class II, and 7·5 months for class III. In a study of 4295 patients with brain metastases from renal cell carcinoma, Karnofsky performance status and number of brain metastases were identified as significant prognostic factors.[67] Patients with a Karnofsky performance status of 90–100 and one brain lesion had a median overall survival of 14·8 months (95% CI 12·9–17·1) versus 3·3 months (3·0–3·8) for those with a Karnofsky performance status less than 70 and more than three metastases. Present data suggest that WBRT is adequate for patients with poor performance who need palliative treatment for multiple lesions. SRS can provide effective local control comparable to surgery, even for multiple and recurrent metastases, and is recommended for patients with RPA classes I and II.[68]

For liver and pancreatic metastases, a potential benefit needs to be balanced against morbidity and mortality of local treatment. In the study included in this systematic review, liver metastasectomy was associated with significant morbidity in 20·1% of patients,[25] with no benefit for those with high-grade renal cell carcinoma and synchronous metastases. By contrast, a non-comparative retrospective analysis of 43 patients reported low morbidity and mortality, resulting in a 3-year overall survival of 62·1% and a median recurrence-free survival of 15·5 months.[69] Additionally, ablative techniques and SRS have resulted in effective local control of small liver metastases.[70–72]

Cumulative data suggest that pancreatic metastasectomy might be beneficial in patients with good performance status and one metastatic site.[73] However, 2·8% in-hospital mortality after extensive surgery, done as pancreaticoduodenectomy in 35·8% of patients and total pancreatectomy in 19·9% of patients, suggests that morbidity and mortality might outweigh the potential benefit. In view of the overall low quality of the data, and the substantial surgical morbidity, patients with a short interval to pancreatic metastasis after nephrectomy may be best treated with systemic therapy.

Despite lymph nodes being the third metastatic site in 21·8% of patients,[10] we identified few studies reporting

on only subgroups of patients who underwent nodal metastasectomy, compared with either no or incomplete resection. Isolated metachronous nodal metastases are rare and most patients harbour additional extensive metastatic disease at multiple sites,[74] precluding complete metastasectomy, which might explain the low number of comparative retrospective studies retrieved.

In conclusion, to the best of our knowledge, this is the first systematic review to identify the evidence base regarding the role of local treatment of metastases from renal cell carcinoma. The results consistently point towards a benefit of complete metastasectomy in terms of overall survival and cancer-specific survival. With the exception of brain and possibly bone metastases, metastasectomy remains by default the most appropriate local treatment for most sites. There is also some evidence for local control benefits such as pain relief for bone metastases. Because of the poor quality of included studies, whether the reported survival benefit is a consequence of local treatment, or a selection bias of those patients whose tumour biology allowed them to proceed to metastasectomy, or both, remains unresolved. Future prospective studies, preferably with randomised design and larger populations, are needed to increase the quality of evidence regarding local treatment of metastases from renal cell carcinoma. Finally, from a clinical perspective, the possible survival and symptom control benefits in patients with metastatic renal cell carcinoma who are eligible for local treatment should be discussed in multidisciplinary boards to tailor treatments individually. Despite prognostic factors consistently being associated with a favourable outcome after metastasectomy, no general treatment guideline can be given, because of the large uncertainties that exist in the evidence base. Careful patient selection is of paramount importance, and the decision to resect metastases has to be taken for each site, and on a case-by-case basis. Performance status, risk profiles, patient preference, and alternative techniques to achieve local control, such as SRS or ablation, must be considered. There might also be a role for local treatment of metastases in terms of delaying systemic treatment and associated toxicity.

Contributors

SD, LM, FH, FS, TBLL, and AB contributed to study design, literature search, figures, data collection, data analysis, data interpretation, presentation of results, and writing of the manuscript. TBBL and AB provided additional comments and supervision. MS provided additional study data, contributed to data interpretation, and provided expert comments. TP, SEC, and BL contributed to data analysis and interpretation, and provided expert and critical comments. All authors approved the final version of the report.

Declaration of interests

SEC has received honoraria as a speaker for Amgen, Bayer, and Genomic Health. MS has received honoraria and research grants from Pfizer, GlaxoSmithKline, Novartis, Astellas, Roche, Bayer, and Imatics. TP has received research grants and honoraria for advisory board participation and as a speaker for Pfizer, GlaxoSmithKline, Novartis, and Astellas. BL has received honoraria for advisory board participation from Bayer, Novartis, GlaxoSmithKline, Roche, and Pfizer. AB has received honoraria for advisory board participation and as a speaker for Pfizer, GlaxoSmithKline, Novartis, and Astellas, and is the primary investigator of the EORTC 30073 SURTIME trial, which is supported by a research grant from Pfizer to the EORTC. All other authors declare no competing interests.

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