EVIDENCE TABELLEN N.A.V. UITGANGSVRAGEN REVISIE RICHTLIJN NIERCELCARCINOOM

Revisie Richtlijn Niercelcarcinoom –Evidence tabel uitgangsvraag 1 - Welke behandeling voor patiënten met kleine (<4 cm) niertumoren geeft de grootste kans op een hoge disease free en/of overall survival?

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure(s) Secondary Outcome Measure(s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
(Kunkle, 2008)	SR	Funding reported. No conflicts of interest reported.	Hospital	Not stated	Inclusion: - Series that analyzed clinically localized, sporadic renal tumors that were managed by either open, laparoscopic, and percutaneous cryoablation or RFA. - Data taken from series that reported ablation of both sporadic and hereditary renal lesions were censored to include only those that reported sporadic RCC. - Prospective and retrospective series. - Multi-institutional series as well as single-institution experiences were analyzed, provided that other inclusion criteria were met. - In the case of multiple series from an institution or overlapping patient cohorts with potentially redundant data, only the most recent series or the series with the largest study population was selected.	47 series representing 1375 renal tumors that were treated at 45 institutions.	Not applicable	Not applicable	No statistically significant differencesbetween ablation modalities with regard to patient age (p=0.17), tumor size (p=0.12), or duration of postablation follow-up (p=0.53). Reported approaches to renal cryoablation included laparoscopy (64.8%), percutaneous (23.2%), and open surgery (12%). Percutaneous renal tumor RFA was described for 93.7% of lesions, and laparoscopy was used for 6.3%.	Cryoablation (laparoscopy, percutaneous, open) Radiofrequency ablation (RFA)	-	Local tumor progression Distant metastases	Local tumor progression: 5.2% after renal cryoablation vs. 12.9% after RFA (p<0.0001). Progression to metastatic disease: 1% vs. 2.5% (p=0.06).	-	Low-quality SR. Medline search only, no search terms reported. Search date: Oct 2007. Limited quality appraisal (no information on included study designs, etc.).	C

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					Exclusion: - Series that included only patients with hereditary or metastatic RCC. - Series that were purely technical and did not assess tumor recurrence or other oncologic endpoints. - Single case reports.											
(van Poppel, 2007)	RCT	Funding: National Cancer Institute, Vlaamse Liga tegen Kanker, Belgium, and the Fédération Belge contre le Cancer, Belgium. Conflicts of interest reported.	Hospital	With RN the expected 5-yr survival rate in this group of patients is expected to be approximately 90%. To rule out the possibility that NSS could decrease the 5-yr survival rate by ≥2.8%,	Inclusion: - Patients with a solitary T1–T2 N0 M0 renal tumour, suspicious for renal adenocarcinoma, and a normal contralateral kidney. - The tumour was single on computed tomography (CT) scanning, did not exceed 5 cm in diameter, and did not show invasion of the perirenal fat (T1–T2) on the CT scan or intravenous urography (IVU). - The WHO performance status was ≤2. Exclusion: - Patients with a solitary kidney, von Hippel-Lindau disease,	N=541 Twelve patients were not operated or had no surgical information.	Not stated	Central randomization at EORTC	No apparent differences, but no p-values provided.	Radical nephrectomy (RN)	Nephron-sparing surgery (NSS)	Morbidity (efficacy date were not yet sufficiently mature)	Perioperative blood loss <0.5l: 96% (RN) vs. 87.2% (NSS), p<0.001. Severe hemorrhage >1l: 1.2% vs. 3.1%. Ten patients (4.4%), all of whom were treated with NSS, developed urinary fistulas. Pleural damage: 11.5% (NSS) vs. 9.3% (RN), NS. Spleen damage: 0.4% (NSS) vs. 0.4% (RN), NS. Postoperative CT		No information on blinding of patients or investigators. Not clear if intention-to-treat analysis.	A2

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				a total of 368 deaths are required.	multifocal disease. - T3–T4 tumours. - Clinical presence of distant or lymphatic metastases. - WHO performance status >2. - Patients with another carcinoma, except for adequately treated non-melanoma skin cancer.								abnormalities: 5.8% (NSS) vs. 2.0% (RN), NS. Reoperation for complications: 4.4% (NSS) vs. 2.4% (RN), NS.			
(Manikandan, 2004)	SR	Not reported	Not reported	Not stated	Inclusion: RCC up to 4 cm, treated with either radical nephrectomy (RN) or nephron-sparing surgery (NSS); a normal contra lateral kidney Exclusion: cryosurgery and high- intensity focused ultrasound	26 studies including 2008 patients. 15/26 studies reported on NSS; 3/26 studies reported on RN, 8/26 studies reported on both/not reported	Not applicable	It is likely that all included studies were non-randomised	Not reported	NSS; compliance not reported	RN; compliance not reported	Disease specific survival; incidence of metastasis; incidence of local recurrence	NSS: 26 studies including 1211 patients and a mean follow-up of 47.4 months (range: 33-120 months): mean local recurrence/disease progression of 1.47% (range: 0-7.3%); mean metastasis 0.69% (range: 0-5.2%); mean cancer-specific survival 98.3% (range: 92-100%) RN: 11 studies including 797 patients and a mean follow-up of 61.2 months (range: 38-120 months): mean	The authors made statistical comparisons of disease specific outcomes. See critical appraisal of study quality The authors reported 4 studies on laparoscopic radical nephrectomy and 4 studies on laparoscopic nephron sparing therapy	SR of studies of an unspecified nature, but likely non-randomised studies as the authors concluded that only a large RCT with a long follow-up would provide a definitive answer The authors made statistical comparisons of disease	C

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													local recurrence of 0.4% (range: 0- 2.3%); mean metastasis 4.8% (range: 1.5-8.6%); mean cancer-specific survival 94.8% (range: 89-97%)		specific outcomes. These are invalid as selection bias is likely to be a substantial problem The methods used to calculate means across studies are unclear, are these weighted means? There is one obvious error in the range of the mean follow-up of table 1 Follow-up differed widely between studies No quality appraisal	

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															of included studies. Search strategy cannot be replicated	

Abbreviations
NSS: nephron-sparing surgery; RCC: renal cell cancer; RN: radical nephrectomy; RCT: randomized controlled trial; RFA: radiofrequency ablation; SR: systematic review.

References
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Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 2 - Welke adjuvante behandeling voor patiënten met operabel hoog risico (niet gemetastaseerd) primair niercelcarcinoom geeft de grootste kans op een hoge disease free en/of relapse free en/of overall survival?

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(Atzpodien, 2005)	RCT	J Atzpodien is supported by grants of Deutsche Krebshilfe, Wilhelm-Sander-Stiftung and Deutsche Gesellschaft zur Förderung immunologischer Krebstherapien e.V.	Hospital	The potential 2-year relapse-free survival rates were hypothesised to show a 20% advantage of Arm A over Arm B (90 vs. 70%).	Histologically confirmed renal cell carcinoma (pT3b/c pN0 or pT4pN0; pNþ; R0). Age between 18 and 80 years. White blood cell count ≥3500 ml^{-1}. Platelet count ≥100.000 ml^{-1}. Hematocrit ≥30%. Serum bilirubin ≤1.25. Creatinine ≤1.5 of the upper normal limit. Karnofsky performance status ≥80%. No evidence of congestive heart failure. No severe coronary artery disease. No cardiac arrhythmias. No clinically symptomatic CNS disease or seizure disorders. No human immunodeficiency virus infection. No evidence of chronic active hepatitis. No concomitant corticosteroid therapy. No chemotherapy or immunmodulatory treatment performed during the previous 4 weeks. Pregnant and lactating women were excluded.	N=203 No information on lost to follow up.	Median follow-up = 4.3 years	Not stated	No p-values provided, but differences in systemic pre-treatment is likely.	Arm A: 8-week treatment cycle of sc rIFN-a2a ($5x10^6$ IUm^{-2}, day 1, weeks 1+4; days 1, 3, 5, weeks 2+3; $10x10^{-6}$ IUm^{-2}, days 1, 3, 5, weeks 5–8), sc rIL-2 ($10x10^6$ IUm^{-2}, twice daily days 3–5, weeks 1+4; $5x10^6$ IUm^{-2}, days 1, 3, 5, weeks 2+3) and iv 5-FU (1000 mgm^{-2}, day 1, weeks 5–8). No information on compliance.	Arm B: No adjuvant treatment.	Overall survival Relapse-free survival	2-year survival: 81% vs. 91% 5-year survival: 58% vs. 76% 8-year survival: 58% vs. 66% Significantly decreased survival after immuno-chemotherapy. No significant differences in relapse-free survival (2-year 54 vs. 62%, 5-year 42 vs. 49%, 8-year 39 vs. 49%).	-	No information on randomisation procedure or blinding of patients and investigators.	B
(Wood, 2008)	RCT	Funding: Antigenics Inc. Several authors are linked to Antigenics Inc.	Hospital	Not explicitly stated	Pre-surgery eligibility criteria: The presence of primary-intact resectable renal cell carcinoma with no known distant metastases; tumours of stage cT1b–T4 N0 M0, or cTany N1-2 M0; patients had to be scheduled for nephrectomy with curative intent. Patients with performance status of 1 or less, aged 18 years or older with a life expectancy of 3 months or longer, and who had received no previous treatment for renal cell carcinoma	N=728 3.6% lost to follow up in active treatment group, 5.2% in control group	Median follow-up = 1.9 years	Central randomisation. Computer-generated pseudo-random number generator.	No p-values provided, but probably comparable groups.	Vitespen within 8 weeks of surgery. Patients received 25 µg autologous vitespen intradermally once a week for 4 weeks, then every 2 weeks until vaccine supply depletion or disease progression. Of the 361 patients	Observation alone	Recurrence-free survival (RFS)	Recurrence events: 136 (37.7%) patients in the vitespen group, 146 (39.8%) in the observation group (HR 0.923, 95%CI 0.729-1.169; p=0.506) Deaths: 70 (19.4%) vs. 72	No treatment-related grade 3 or 4 adverse events. The most commonly reported adverse events in the vitespen group were	Blinded clinical events committee. No information on blinding of subjects. Intention-to-treat analysis.	A2

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					were eligible. Pre-surgery exclusion criteria: A history of primary or secondary immunodefi ciency, or immunosuppressive drug use; current malignancies at other sites or distant metastases; other cancer within the previous 5 years; renal artery embolisation before nephrectomy; active, uncontrolled infection; and other serious medical illnesses.					allocated to vitespen, 43 patients did not receive the allocated treatment (2 due to non-compliance). 6% discontinued treatment because of an adverse event.			(19.6%) (HR 0.978, 95%CI 0.702-1.364; p=0.896)	injection-site erythema (n=158) and injection-site induration (n=153). One serious adverse event: autoimmune thyroiditis of grade 2 severity		
(Margulis, 2009)	RCT	Not stated	Hospital	Not explicitly stated	Completely resected locally advanced high-risk RCC, as defined by one of the following criteria: pT2 (Fuhrman grade 3 or 4), pT3a-c, T4, or N1-2 disease resected to no evidence of residual disease. Patients had to have recovered from any effects of surgery, which must have been performed within 30 days of enrolment.	N=46 No information on lost to follow up.	Median follow-up of 43.9 months (range 9.7-74.2 months)	Not stated	Similar groups	Thalidomide orally daily. Starting dose 100 mg/d for 2 weeks, then 200 mg/d for 2 weeks, followed by the maximum dose of 300 mg/d. Only 35.7% received the planned course of therapy.	Observation	Recurrence-free survival (RFS) Cancer-specific survival (CSS) Overall tolerability and safety of thalidomide	Median RFS: 18.5 months in the thalidomide arm, not reached in the observation cohort (p=0.022). 2-year RFS: 47.8% vs. 69.3% 3-year RFS: 28.7% vs. 69.3% P=0.022 Median CSS: 71.1 months in the thalidomide arm, not reached in the observation cohort (p=0.392). The 2- and 3-year CSS were similar in both study arms. No treatment-related mortality. 19% experienced 5 grade 3 adverse events.	-	No information on randomisation procedure or blinding of patients and investigators.	B

Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 2 - Welke adjuvante behandeling voor patiënten met operabel hoog risico (niet gemetastaseerd) primair niercelcarcinoom geeft de grootste kans op een hoge disease free en/of relapse free en/of overall survival?

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(Jocham, 2004)	Phase III RCT	Source of funding not stated. Three authors received honoraria for scientific presentations and travel grants from the vaccinemanufacturer.	55 German hospitals	Vaccine group would have a progression-free (PFS) and overall survival benefit	Postoperative <u>inclusion criteria</u>: primary renal-cell carcinoma stage pT2–3b pN0–3 M0 (1993 UICC classification) treated by radical nephrectomy; age 18–70 years; Eastern Cooperative Oncology group (ECOG) performance status 0–2; ability to cooperate; and provision of written informed consent. <u>Exclusion criteria</u>: no histologically proven renal-cell carcinoma; primary renal-cell carcinoma stage pT1 or pT4 or M1 (1993 UICC classification); surgery other than radical nephrectomy; relapse of renal-cell carcinoma; mbolisation or other treatment for renal-cell carcinoma; immunosuppressive treatment; ECOG performance status 3–4; serious chronic or acute illness; severe hypertension; myocardial infarction in the past 3 months; cerebral infarction in the past 6 months; autoimmune disease; previous cancer except basal-cell carcinoma; active or chronic infection; pregnancy or lactation; no contraception in women of child-bearing potential; participation in a clinical trial over the past 30 days; simultaneous participation in another clinical trial; or lack of cooperation	N=379 32 lost to follow-up	Enrolment between January 1997 and September 1998 with a follow-up of at least 4.5 years	Centralised, independent process	Similar groups Overall: Median age 59 years; 84% ECOG status 0; median tumour size 5.5 cm; <1% bilateral tumours; 72% pT2 and 28% pT3 (1993 classification); 15% pT1a, 42% pT1b, 14% T2; 28% T3 (2003 classification); 96% N0; 68% clear cell renal cell carcinoma	Autologous renal tumour cell vaccine (6 i.d. applications at 4-weeks intervals postoperatively)	Observation	**Primary:** PFS (no progression (local recurrence or distant metastasis confirmed by physical examination, imaging, or both) or death) **Secondary**: quality of life, vaccine production process (total number of cells, % of tumour cells) and the number of vaccine doses on patients' outcome and tolerability of the vaccine, and rate of adverse events	**Primary:** <u>5-year PFS rate (all patients)</u> 77.4% vs. 67.8% (p=0.02) <u>5-year PFS rate (T2 patients)</u> 81.3% vs. 74.6% (p=0.22) <u>5-year PFS rate (T3 patients)</u> 67.5% vs. 49.7% (p=0.04) <u>5-year hazard ratio for progression</u> 1.58 (95% CI 1.05-2.37, p=0.02) in favour of vaccine group **Secondary:** Global health status and QoL results were closely similar 12 vaccine-related adverse events of mild to moderate severity occurred		No placebo. Unclear whether outcome assessment was blinded. Vaccine-related adverse events are not described in detail.	B

References

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Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 3 - Welke eisen dienen aan het biopteren c.q de biopten en de kleuringen te worden gesteld, zodat de diagnose met zekerheid geteld kan worden, en de medisch oncoloog de juiste systemische behandeling kan starten bij patiënten met gemetastaseerd of vergevorderd maar nog lokaal niercelcarcinoom of gemetastaseerde niercelkanker in het kader van hereditaire syndromen?

Author, year	Level of evidence	Study type	Population	Inclusion criteria	Index test (diagnostic test)	Control (golden standard, reference test)	Outcome (effect measure)	Result	Comments
(Barocas, 2007)	B	Cohort?	Patients with renal masses whom underwent nephrectomy	Patients undergoing nephrectomy for a renal mass (n = 42) Exclusion: non-RCC (n = 6) 36 patients included	Needle core biopsy with a 14-gauge needle taken of the surgical specimen Needle core biopsy + FISH (chromosomes 3, 7, 10, 13, 17, and 21 and the locus 3p25–26)	Histology of the surgical sample	Sub typing of RCC Sensitivity Specificity PPV NPV For clear cell, papillary, chromophobe and oncocytoma	Core biopsy(clear cell n = 20): Sensitivity: 87% Specificity: 100% PPV: 100% NPV: 89% Core biopsy + FISH (clear cell n = 20): Sensitivity: 94% Specificity: 100% PPV: 100% NPV: 94%	Underpowered study. With 3/36 RCC biopsies insufficient. Data for papillary (n = 7) chromophobe (n = 3) and oncocytoma (n = 5) are not cited here because of low numbers. The improvement of sub typing in clear cell carcinomas was not significant Sampling bias (taking biopsies from surgical specimens) Study examination bias (insufficient biopsies were excluded for further evaluation) Patient selection not described Blinded index testing Possibly procedure-based selection bias (only patients selected for nephrectomy underwent index testing)
(Lebret, 2007)	B	Retrospect ive chart review	119 renal core biopsies (102 patients). Mean tumour size 33 mm (range: 10-100 mm)	Inclusion Solid renal mass Exclusion No formal evidence for carcinoma or benign lesion on CT; haemostasis disorder, positive urinary cytology, perirenal fat infiltration or lack of a safe percutaneous path (anterior or hilary renal masses)	Needle core biopsy with an 18-gauge automatic core biopsy system	Histology of the surgical sample or clinical follow-up	Sensitivity Specificity Impact on clinical management Adverse events Track seeding	Sensitivity: 94.2% Specificity: 100% RCC subtype accuracy: 86% Fuhrman grade accuracy (high vs. low grade) : 76.9% Impact on clinical management: 30.4% of patients did not undergo surgery because of biopsy Adverse events: no bleeding requiring	Analyses are biopsy-based, not patient-based Test-review bias and information bias (retrospective study) Follow-up was not standardised (mean follow-up 36 months; range: 21 to 46 months) Blinding is not

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Author, year	Level of evidence	Study type	Population	Inclusion criteria	Index test (diagnostic test)	Control (golden standard, reference test)	Outcome (effect measure)	Result	Comments
								transfusion, no fistula or urinary tract or cutaneous infections Track seeding: not found	described
(Maturen, 2007)	B	Retrospective chart review	152 renal biopsies taken at a radiology department (125 patients) . Mean tumour size 4.1 cm (range 1-13 cm)	Inclusion All patients who underwent a renal biopsy Exclusion Random biopsies, performed to assess rejection in transplant kidneys or to determine the cause of renal failure	Needle core biopsy with an 18-gauge spring-loaded biopsy gun	Histology of the surgical sample or clinical follow-up	Sensitivity Specificity PPV NPV Impact on clinical management Adverse events Track seeding	Sensitivity: 97.7% Specificity: 100% PPV: 100% NPV: 100% Impact on clinical management: 60.5% of biopsies impacted clinical management (change between no therapy and therapy, including surgery, percutaneous ablation, transcatheter ablation, external beam radiation, or systemic chemotherapy Adverse events: 2/125 (2%) post procedural hematomas (one required blood transfusion); one (0.7%) delayed renal pseudo aneurysm Track seeding: not found	Patient selection is not described in detail, e.g. was malignancy expected or not, where lesions solid or cystic Analyses are biopsy-based, not patient-based Test-review bias and information bias (retrospective study) Follow-up was not standardised and short for some patients (mean 9.7 months, range: 0–60 months) with leads to verification bias Blinding is not described

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(Neuzillet, 2004)	B	Cohort (prospective?)	Patients with a renal mass of less than 4 cm	Inclusion: renal mass less than 4 cm Exclusion: bleeding risk, Bosniak category I or II cystic mass and patients with radiological suspicion of angiomyolipoma or transitional cell tumour	CT-guided tumour mass core biopsy with a 18-gauge needle	Histology of the surgical sample or clinical follow-up	Sensitivity Specificity RCC subtype accuracy Fuhrman grade accuracy Impact on clinical management Adverse events Track seeding	Sensitivity: 91.7% Specificity: 100% RCC subtype accuracy: 92.1% Fuhrman grade accuracy : 69.8% Fuhrman grade accuracy (high or low grade): 86.9% Impact on clinical management: 47.8% of patients avoided radical nephrectomy Adverse events: no clinical hematoma´s, no surgery or hospitalisations needed Track seeding: not found	Possible verification bias because clinical follow-up seems non-standardised and of varying length Blinding is not described Follow-up seemed unstandardised and was of an unspecified duration
(Schmidbauer, 2008)	B	Prospective observational cohort	In 90% of 78 patients renal tumours were detected incidentally; 58% of tumours were small (≤4 cm)	Inclusion Patients with renal masses Exclusion Cystic lesions; suspected transitional cell carcinoma; no surgical removal of tumour	CT-guided tumour mass core biopsy (n=78) with a 18-gauge core biopsy needle, to take 2 or 3 core biopsies Fine needle aspiration cytology (FNAC) (n=44) with a 17-gauge co-axial needle	Histological examination of surgical specimen	Sensitivity Specificity RCC subtype accuracy Fuhrman grade accuracy Adverse events	Core biopsy: Sensitivity: 92.3% Specificity: 100% RCC subtype accuracy: 91% Fuhrman grade accuracy:76% (96.6% if only specimens were a grading was assigned are included) FNAC: Sensitivity:90.6% PPV: 100% NPV:70% RCC subtype accuracy:86% Fuhrman grade accuracy:28% FNAC was Insufficient: 11% (5/44) Adverse events: Four minor hematomas detected	Authors stopped using FNAC after the first 44 patients because of the higher rate of insufficient samples and a lower diagnostic accuracy. In addition, they found that the need for an experienced cytologist made FNAC less attractive Possible verification bias (39 patients were treated by energy ablative techniques and excluded) Study examination bias (insufficient biopsies were excluded for further evaluation of accuracy) Blinding not described

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Author, year	Level of evidence	Study type	Population	Inclusion criteria	Index test (diagnostic test)	Control (golden standard, reference test)	Outcome (effect measure)	Result	Comments
								on follow-up ultrasonography. None required treatment. One small pneumothorax without consequences	
(Shah, 2005)	B	Retrospective cohort	66 biopsies performed in patients who underwent biopsies for indeterminate renal mass by imaging or clinical modality	Inclusion: Biopsies that impacted clinical management by having conservative therapy (less than total nephrectomy) Exclusion: biopsies performed for unresectable tumours to rule out metastasis or to document recurrence before non-surgical treatment	core biopsy with a 18-gauge core biopsy needle	Histological examination of surgical specimen	RCC subtype accuracy	RCC subtype accuracy: 93.8%	Narrow selection of cases Retrospective study Blinded index test assessment Analyses are biopsy-based, not patient-based
(Shannon, 2008)	B	(Retrospective?) cohort	221 Patients with Incidentally detected small (<5 cm) renal mass	Incidentally detected, solid, small renal masses, suspicious for malignancy on imaging	CT-guided tumour mass core biopsy with a 18-gauge core biopsy needle, to take 1 to 4 core biopsies per lesion	Histological examination of surgical specimen or follow-up (with no standard work-up)	Sensitivity Specificity RCC subtype accuracy Adverse events	Sensitivity: 90.2% Specificity: 100% RCC subtype accuracy: 98% 1/221 (0.5%) patients needed a blood transfusion because of a post-biopsy bleeding	Most likely a retrospective study, thus possible test-review bias and information bias (follow-up data were taken from medical records and sometimes short. Median follow-up 30 months, range. 3-101 months) Blinding not described Analyses are biopsy-based, not patient-based

Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 3 - Welke eisen dienen aan het biopteren c.q de biopten en de kleuringen te worden gesteld, zodat de diagnose met zekerheid geteld kan worden, en de medisch oncoloog de juiste systemische behandeling kan starten bij patiënten met gemetastaseerd of vergevorderd maar nog lokaal niercelcarcinoom of gemetastaseerde niercelkanker in het kader van hereditaire syndromen?

Author, year	Level of evidence	Study type	Population	Inclusion criteria	Index test (diagnostic test)	Control (golden standard, reference test)	Outcome (effect measure)	Result	Comments
(Somani, 2007)	B	(Retrospective?) cohort	70 biopsies in patients requiring renal core biopsies (tumour size not specified)	Inclusion Indeterminate renal mass on CT	Two to four core biopsies using a 16–18 gauge biopsy gun	Histological examination of surgical specimen or clinical follow-up	Sensitivity Specificity RCC subtype accuracy Adverse events	Sensitivity: 93.8% Specificity: 100% RCC subtype accuracy: 100% Adverse events: bleeding in one patient, conservatively managed	Most likely a retrospective study, thus possible test-review bias and information bias Analyses are biopsy-based, not patient-based Follow-up was not standardised (mean follow-up 32 months; range: 12 to 52 months) Blinding is not described
(Volpe, 2008)	B	Retrospective cohort	100 biopsies (91 patients) for incidentally detected small tumours (4 cm or less)	Incidentally detected small renal tumour	Core biopsy with an 18 gauge automated biopsy gun; FNA	Histological examination of surgical specimen or clinical follow-up	Sensitivity Specificity RCC subtype accuracy Fuhrman grade accuracy Adverse events Track seeding	Sensitivity: 100% Specificity: 100% RCC subtype accuracy: 100% Fuhrman grade accuracy:75.0%(low vs. high grade) Adverse events: no bleeding requiring blood transfusion or embolisation. One patient had a small pneumothorax, managed conservatively Track seeding: not found	Retrospective study, thus possible test-review bias and information bias Analyses are biopsy-based, not patient-based Follow-up was not standardised Blinding is not described

Abbreviations
CT: computer tomography; FNAC: fine needle aspiration cytology; NPV: negative predictive value; PPV: positive predictive value; RCC: renal cell carcinoma

References

Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 3 - Welke eisen dienen aan het biopteren c.q de biopten en de kleuringen te worden gesteld, zodat de diagnose met zekerheid geteld kan worden, en de medisch oncoloog de juiste systemische behandeling kan starten bij patiënten met gemetastaseerd of vergevorderd maar nog lokaal niercelcarcinoom of gemetastaseerde niercelkanker in het kader van hereditaire syndromen?

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Short summary Q7, biopsies

From selected articles the sensitivity and specificity for detecting malignancy of any type, and the accuracy of subtyping of renal cancer, were extracted or recalculated as follows:

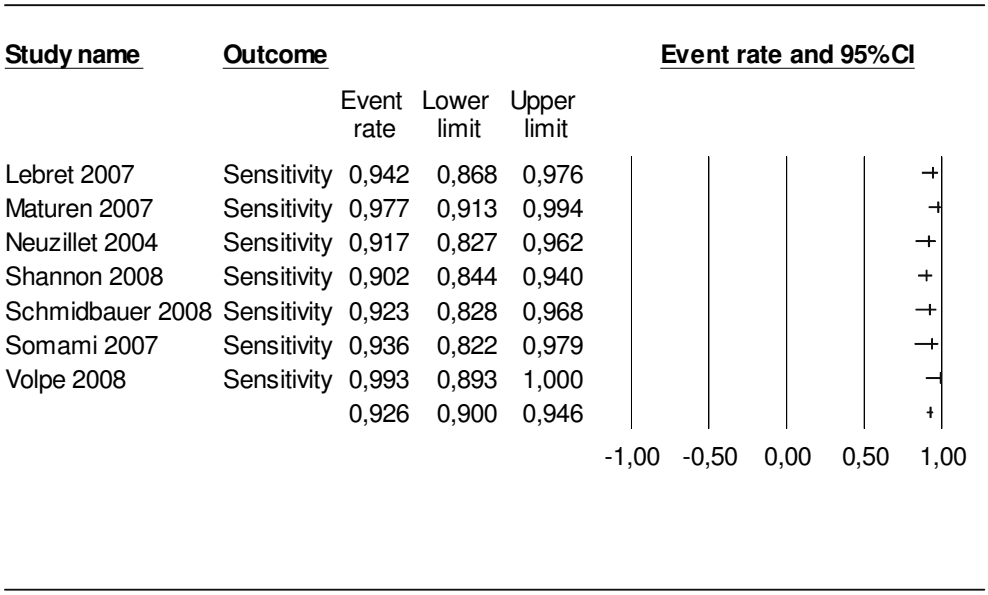
- Patient-based analyses were chosen or recalculated. If not available, biopsy-based analyses were taken
- If not all patients underwent the same reference test (histopathological examination of the surgical specimen) the combined results of two reference tests were taken (histopathological examination of the surgical specimen or clinical follow-up)
- Non-diagnostic biopsies (failed or inconclusive biopsies) were included in the true-positive or false-positive results, according to the results of the (combined) reference tests. If a patient was lost to follow-up this was interpreted as a false-negative index test result
- Second biopsies, if diagnostic for malignancy after a first non-diagnostic biopsy, were included in the true-positives
- The accuracy of a biopsy for subtyping was calculated as the proportion of biopsies in which subtyping/Fuhrman grading (high vs. low) corresponded with subtyping/Furman grading (high vs. low) of the surgical specimen, for patients in whom both tests were performed successfully.
- Meta-analyses calculated with Comprehensive Meta-Analysis version 2.

This led to the following results:

1. The meta-analysed sensitivity to detect any malignancy with a renal biopsy was 92.6% (95% CI: 90.0-94.6%) across seven low quality studies (Figure 1).
2. The meta-analysed accuracy for subtyping of a renal malignancy with a renal biopsy was 91.8% (95%CI: 88.0-94.5%) across seven low quality studies (Figure 2).
3. The meta-analysed accuracy for Fuhrman grading (low vs. high grade) of a renal malignancy with a renal biopsy was 85.5% (95%CI: 72.6-92.9%) across four low quality studies (

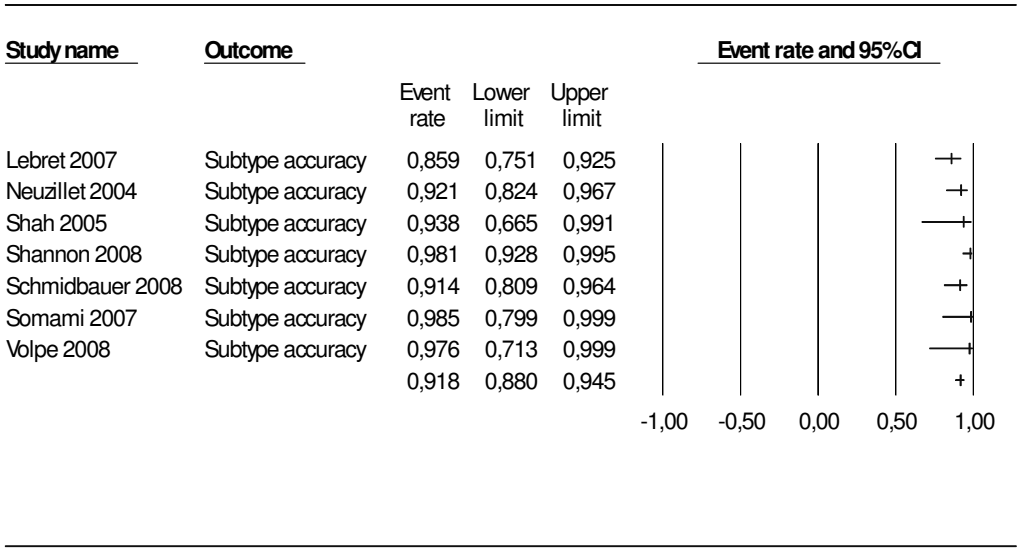
Figure 3).

Figure 1 Meta-analysed sensitivity to detect malignancy with renal biopsy (fixed effects model)



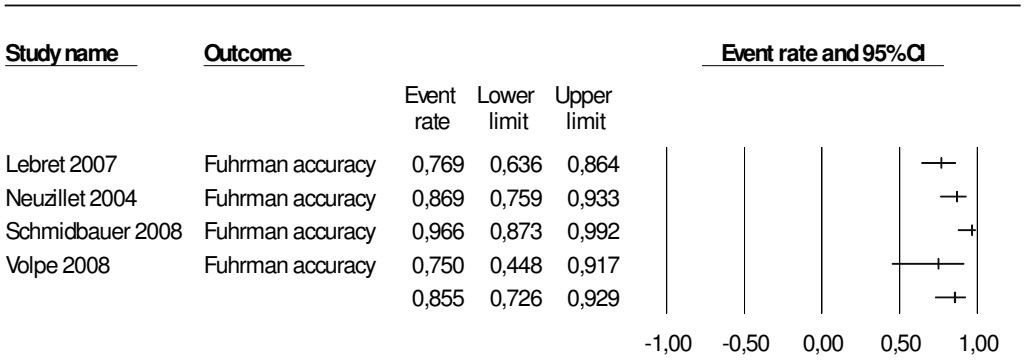
Heterogeneity: Q-value: 7.49; p=0.28; I-squared=19.8.

Figure 2 Meta-analysed accuracy of biopsy for subtyping of renal cell carcinoma, in patients with adequate specimens (fixed effects model)



Heterogeneity: Q-value: 10.0; p=0.12; I-squared=40.1

Figure 3 Meta-analysed accuracy of biopsy for Fuhrman grading (low vs. high grade) of renal cell carcinoma, in patients for whom both tests were performed successfully (random effects model)



Heterogeneity: Q-value: 8.4; p=0.04; I-squared=64.3

Of note:

- Most series are too small to detect adverse events adequately and a retrospective design (chart review) is likely to underestimate adverse events. Needle track seeding was not found. Bleeding requiring blood transfusion was described in 0.5% in two series. In one series a patient developed a renal pseudo aneurysm attributed to the biopsy.
- Mainly small (less than 4 cm) tumours
- Substantial impact on clinical management, though this assessment was often made in retrospect which undermines its reliability
- In patients with non-diagnostic biopsies malignancy is common

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
Targeted therapy																
(Sternberg, 2010)	RCT	GlaxoSmith Kline Pharmaceuticals/many conflicts of interest reported	Hospital, international multicentre	Not explicitly stated	Inclusion: clear-cell or predominantly clear-cell histology, measurable disease, age>18 years; ECOG performance status of 0 or 1, adequate renal, hepatic, and hematologic functions Exclusion: central nervous system metastasis, leptomeningeal lesions, poorly controlled hypertension, QTc interval≥470 milliseconds, or a recent history of	435/22 (including those that withdrew consent)	Accrual: April 2006 – April 2007	Centrally assigned randomisation in a 2:1 ratio	Both treatment-naive (54%) and cytokine-pretreated (46%) patients with advanced and/or metastatic RCC Comparable groups	Pazopanib 800 mg once daily, orally	Placebo	Primary: progression-free survival Secondary: overall survival, tumor response rate, health-related quality of life, safety	Median progression-free survival: 9.2 vs. 4.2 months; hazard ratio: 0.46 (95%CI: 0.34-0.62; p<0.0001) Overall survival: pre-set cut-off not reached Objective response rate: 30% vs. 3% (p<0.001) Health-related quality of life: no differences between groups Safety: arterial thrombotic events: 3% vs. 0%, hemorrhagic events (all	Results were similar in treatment-naïve and cytokine pre-treated populations	Double-blind study Concealment is not described in detail Intention-to-treat analysis Study presents results at the time the pre-set cut-off for progression-free survival was reached	A2

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					cardiac or vascular conditions								grades): 13% vs. 5%			
(Coppin, 2008)	SR	Not stated	Not stated	Not stated	RCTs (except phase I trials)	19 studies	NA	NA	Adult patients with metastatic or locally inoperable renal cell carcinoma, histologically verified at presentation or relapse. Some patients with 'operable' tumors but who have serious comorbidities may be enrolled. Studies of mixed tumor types are eligible only if patients with renal cell carcinoma are stratified and reported separately from other groups.	Targeted therapy (including bevacizumab, sorafenib, sunitinib, thalidomide, AE-941, carboxyamidoimidazole CAI, ABT-510, epidermal growth factor receptor inhibitors, lapatinib and temsirolimus)	Various comparators across studies: 1. dose-finding studies 2. second-line targeted agent after cytokine vs. control 3. first-line targeted agent vs. INF-a 4. miscellaneous	Various outcomes across studies, including major remissions (14 studies), overall survival (13 studies), progression-free survival (11 studies), quality-of-life (4 studies). Not all primary outcomes in all studies.	No meta-analysis done because of different agents used First-line targeted agent vs. INF-a: **1. *Thalidomide + INF-a*** (2 studies): not better than INF-a alone **2. *Temsirolimus*** (1 study): improvement in overall survival (median survival 10.9 vs. 7.3 months for temsirolimus or IFN-a respectively, HR 0.73, p=0.008). Chance of major remission was low	See primary outcomes	High-quality SR Search date: December 2007	A1

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
									Patients may or may not have received prior immunotherapy				and not improved with temsirolimus. Temsirolimus + INF-a not better than INF-a alone. **3. *Bevacizumab + INF-a*** (1 study): major remission rate 31% vs. 13% for INF-a alone (OR 3.1, 95%CI 2.0-4.7). Median progression-free survival 10.2 vs. 5.4 months for INF-a alone (HR 0.61, 95%CI 0.51-0.73, p<0.0001 log rank). **4. *Sunitinib*** (1 study): In patients with mostly good or intermediate prognostic			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													risk with clear cell renal cancer, oral sunitinib improves the chance of major remission (OR 6.34, 95%CI 4.4-9.2, p<0.000001 log rank), the probability of symptomatic improvement, and freedom from disease progression **5. Sorafenib** (1 study): no significant difference in progression-free survival. <u>Second-line targeted agent after cytokine vs. control</u>: In patients			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													with clear cell renal cancers who had failed prior cytokine therapy, oral sorafenib gives a better quality of life than placebo as well as improved chance of being free of disease progression ; overall survival may have improved but is hard to evaluate because of crossover of placebo-assigned patients after the study closed to accrual			
(Escudier, 2009a)	RCT	Supported by Bayer Pharmaceuticals and Onyx Pharmaceuticals.	Hospital	Original sample size was calculated to detect a 0.77 HR in OS	Inclusion: - Histologically confirmed metastatic clear cell renal-cell carcinoma,	N=903 No lost to follow up	Unclear	Unclear	No statistically significant differences	Sorafenib 400 mg oral bid administered in 6-week cycles for the first 24 weeks and	Placebo	Primary: Overall survival (OS) Secondary: Progression -free	Final OS: 17.8 months (sorafenib) vs. 15.2 months (placebo) (HR 0.88;	-	TARGET trial: update of (Escudier, 2007a) (included in (Coppin, 2008)), 16	A2

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
		Conflicts of interest are reported			which had progressed after one systemic treatment within the previous 8 months - Performance status of 0 or 1 on the basis of Eastern Cooperative Oncology Group criteria - Intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score - Life expectancy of at least 12 weeks - Adequate bone marrow, liver, pancreatic, and renal					in 8-week cycles thereafter		survival, response rate, patient-reported outcomes	p=0.146). When post–cross-over placebo survival data were censored, the difference became significant (17.8 vs. 14.3 months; HR 0.78; p=0.029) Similar adverse events as previously reported		months after cross-over from placebo to sorafenib Double-blind study Unclear if adequate concealment method	

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					function - Prothrombin time or partial-thromboplastin time of less than 1.5 times the upper limit of the normal range Exclusion: Patients with brain metastases or previous exposure to VEGF pathway inhibitors											
(Escudier, 2009b)	RCT	Partially funded by Bayer. Conflicts of interest reported	Hospital	66% increase in PFS	Inclusion: - Patients with unresectable and/or metastatic, measurable and confirmed, predominantly clear cell RCC with no prior systemic therapy; - Eastern Cooperative Oncology Group performanc	N=189 No lost-to-follow-up reported	Unclear	Not stated	Similar, but no p-values provided	First-line sorafenib 400 mg twice daily (period 1), with dose-escalation to 600 mg bid if progression (period 2)	INFa 9 million U three times weekly (period 1), with switch to sorafenib 400 mg bid if progression (period 2)	Primary: Progression-free survival Secondary: Overall best response (OR) according to RECIST Disease control rate (DCR) Response duration Patient-reported outcomes	Median PFS: 5.7 vs. 5.6 months in period 1; HR 0.88; p=0.50 DCR: 79.4% vs. 64.1%, p=0.006 Median time-to-progression: 5.7 vs. 5.6 months (HR 0.89, p=0.537)	Treatment-emergent adverse events ≥ grade 3: 70.1% vs. 54.4%	Phase II open-label study Blinded radiologic review in period 1 Intention-to-treat analysis	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					e score (ECOG PS) ≤1; - Age ≥18 years; - Life expectancy ≥12 weeks; - Complete surgical excision of primary RCC at initial diagnosis; - Adequate bone marrow, liver, and renal function assessed 7 days before screening. <u>Exclusion</u>: Previous malignancy, distinct in primary site/histology from that evaluated in this study; complete renal failure that required dialysis; history of severe cardiac									<u>Patient-related outcomes</u>: Fewer RCC-related symptoms in sorafenib group (total FKSI-15 score 40.5 vs. 34.6, p=0.015). Overall QOL better in sorafenib group (total FACT-BRM scores 104 vs. 93, p=0.073). Greater treatment satisfaction			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					disease (however, myocardial infarction ≥ 6 months before study entry was allowed, and beta blockers or digoxin were permitted); active, clinically serious bacterial or fungal infections; history of HIV, hepatitis B virus, or hepatitis C virus; symptomatic metastatic brain or meningeal tumors; seizure disorders that required medication history of organ allograft; pregnancy/ breastfeeding; substance											

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					abuse; and conditions that could jeopardize patients' safety and/or participation											
(Rini, 2008)	RCT	Supported by grants of the National Cancer Institute Conflicts of interest reported	Hospital	30% improvement in median survival in patients randomly assigned to bevacizumab plus IFN-a	Inclusion: - Patients 18 years of age and older with metastatic RCC, a clear-cell histologic component confirmed by local pathology review, and no prior systemic therapy for RCC. - Karnofsky performance status of ≥ 70%. - Adequate bone marrow, hepatic, and renal function Exclusion: - Patients with CNS metastases, New York	N=732 Lost-to-follow-up: 4/363 in INF-a group, 2/369 in INF-a + bevacizumab group	Not stated	Stratified random block design	No p-values, slight differences in sex distribution	Bevacizumab (10 mg/kg given IV every 2 weeks) plus IFN-a (9 million U s.c. three times weekly)	IFN-a (9 million U s.c. three times weekly)	Primary: overall survival (OS) Secondary: progression-free survival (PFS), overall response rate (ORR), safety	Pre-specified stopping rule for OS not reached. Median PFS: 8.5 months in patients receiving bevacizumab plus IFNa (95%CI 7.5-9.7) vs. 5.2 months (95%CI 3.1-5.6) for IFN monotherapy (p<0.0001). ORR: 25.5% (20.9-30.6%) vs. 13.1% (9.5-17.3%), p<0.0001	Adverse events: At least grade 3 toxicity: 79% vs. 61%, p<0.0001. Bevacizumab plus IFN-a resulted in significantly more grade 3 toxicities, including hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%)	Included in (Thompson Coon, 2009) No blinding	B

Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 4 - Welke systemische behandeling voor patiënten met gemetastaseerd niercelcarcinoom geeft de grootste kans op een hoge disease free en/of relapse free en/of overall survival?

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					Heart Association class II to IV heart failure, bleeding (e.g., hemoptysis, gastrointestinal bleeding) within 6 months, blood pressure that could not be controlled to less than 160/90 mmHg with medication, history of venous thrombosis within 1 year, or arterial thrombosis (including cerebrovascular accident, unstable angina, myocardial infarction, or claudication with < one block of exertion)											

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					within 6 months or who required ongoing therapeutic anticoagulation. - Patients with uncontrolled thyroid function, pregnancy, requirement for systemic corticosteroids greater than physiologic replacement doses, or delayed healing of wounds, ulcers, or bone fractures											
(Motzer, 2009)	RCT	Pfizer/ conflicts of interest reported	Hospital	35.7% improvement in overall survival	Inclusion: - Patients who were at least 18 years of age and had metastatic renal-cell carcinoma with a clear-cell histologic component; - Patients	N=750 No lost-to-follow-up	Not stated	Random permuted blocks of four	No p-values, but comparable characteristics	Sunitinib 50 mg once daily orally, 4 weeks on, 2 weeks off	INF-a s.c. thrice weekly, 3 MU per dose the first week, 6 MU the second week, and 9MU thereafter	Primary: Progression-free survival (PFS) Secondary: objective response rate (ORR), overall survival (OS), patient-reported	Median PFS: 11 months vs. 5 months (p<0.001) Median OS: (26.4 vs. 21.8 months, HR 0.821; 95%CI 0.673-1.001; p=0.051)	-	Update of (Motzer, 2007), which is included in (Coppin, 2008) Blinded radiologists Intention-to-treat analysis	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					who had not received previous treatment with systemic therapy for renal-cell carcinoma. - Presence of measurable disease. - An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. - Adequate hematologic, coagulation, hepatic, renal, and cardiac function							outcomes, and safety	<u>ORR</u>: 47% vs. 12%, p<0.001 Significantly more grade 3+4 adverse events with sunitinib			
(Dutcher, 2009)	RCT	Funded by Wyeth Research. Conflicts of interest not reported.	Hospital	Not stated	Patients with previously untreated advanced RCC (stage IV or locally recurrent, unresectable disease) who had at least three	N=416 for this sub-analysis	Unclear	Permuted blocks of 3	No p-values	INF-a 3 MU thrice weekly for the first week, 9 MU for the second week and 18 MU for week 3	Temsirolimus 25 mg IV weekly Combination: Temsirolimus 15 mg IV weekly + INF-a 3 MU thrice weekly for	<u>Primary</u>: overall survival (OS) <u>Secondary</u>: progression-free survival (PFS), objective response	<u>Temsirolimus</u>: - Comparable OS between clear cell and other histologies (10.7 vs. 11.6 months)	-	Sub-analysis of (Hudes, 2007) (included in (Coppin, 2008)). Only analysis of single agent arms	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					of six protocol specified risk factors for short survival						week 1 and 6 MU thereafter	rate (ORR), clinical benefit rate	- Comparable PFS: 5.5 vs. 7.0 months INF-a: - OS: 8.2 vs. 4.3 months - PFS: 3.7 vs. 1.8 months			
(Motzer, 2008)	RCT	Conflicts of interest are reported. Source of funding = Novartis Oncology	Hospital	Not stated	Inclusion: - Adults (aged 18 years and above) with metastatic renal cell carcinoma that showed a clear-cell component, which had progressed on or within 6 months of stopping treatment with sunitinib or sorafenib, or both drugs. Previous therapy with bevacizumab, IL-2, or IFN-a was also	N=410 0.7% lost-to-follow-up in everolimus group, 0% in placebo group	Not stated	Randomisation was done centrally via an interactive voice response system using a validated computer system	No p-values, but comparable characteristics	Everolimus	Placebo	Primary: progression-free survival Secondary: safety, objective tumor response rate, overall survival, disease-related symptoms, and quality-of-life	Progression-free survival: Median progression-free survival 4.0 (95%CI 3.7-5.5) vs. 1.9 (1.8-1.9) months. Progression events: HR 0.30, 95%CI 0.22-0.40, p<0.0001 in favour of everolimus Safety: Stomatitis: 40% vs. 8% Rash 25% vs. 4% Fatigue 20% vs. 16% Pneumonitis (any	-	Double-blind study Intention-to-treat analysis Second interim analysis	A2

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					permitted - The presence of measurable disease (as per the Response Evaluation Criteria in Solid Tumours [RECIST]) - Karnofsky performance status score of 70% or more (on a scale of 0 to 100, with higher scores indicating better performance) - Adequate bone marrow, hepatic, and renal function. <u>Exclusion</u>: - Patients previously receiving m-TOR inhibitor therapy (temsirolimus) - Untreated								grade) was detected in 22 (8%) patients in the everolimus group, of whom eight had pneumonitis of grade 3 severity 1% objective <u>tumour response</u> in everolimus group, 0% in placebo group No significant difference between groups in terms of <u>overall survival</u> (HR 0.83, 95%CI 0.50-1.37; p=0·23), probably due to confounding by crossover No significant differences			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					CNS metastases - Uncontrolled medical conditions (e.g., unstable angina pectoris, symptomatic congestive heart failure, recent myocardial infarction, or diabetes)								in quality-of-life			
(Ravaud, 2008) Included as an abstract in (Coppin, 2008).	RCT	Conflicts of interest reported. Source of funding = GlaxoSmith Kline	Hospital	Not stated	Inclusion: - Histologically or cytologically confirmed, locally advanced or metastatic RCC of any histologic subtype that was not amenable to curative surgery or radiotherapy. - Disease progression after or	N=416 5 patients lost-to-follow-up	Not stated	Centrally via an interactive voice response system	No p-values provided	Lapatinib 20/209 discontinued because of adverse event	Hormone therapy (HT) 11/207 discontinued because of adverse events	Primary: time-to-progression (TTP) Secondary: tumor response rate, time to response, clinical benefit, overall survival (OS)	Median TTP: 15.3 weeks in the lapatinib arm vs. 15.4 weeks in the HT arm (HR 0.94; 95%CI 0.75-1.18, p=0.595). Median OS: 46.9 vs. 43.1 weeks (HR 0.88; 95%CI 0.69-1.12, p=0.290). Tumor response	Overall incidence of grade 3 and 4 adverse events: 7.3 vs. 2.0%. No grade 4 events in lapatinib group. Two adverse events-related deaths in lapatinib group.	Phase III trial Included as an abstract in (Coppin, 2008) Open-label study. Blinded radiologic review board Intention-to-treat analysis.	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					intolerance to first-line cytokine-based therapy. - Expression of EGFR and/or HER-2 in tumor tissue with immunohistochemistry (IHC) 1+, 2+, or 3+ - Measurable disease according to the Response Evaluation Criteria in Solid Tumors - Cardiac ejection fraction within institutional normal limits as measured by multigated acquisition scan or echocardiography - Age at least 18 years								rate: 1.4% vs. 0.5% Clinical benefit rates: 8.1% vs. 9.7%			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					- Karnofsky performance status (KPS) at least 70% - Life expectancy at least 12 weeks. - Prior systemic neoadjuvant or adjuvant therapy was allowed. - Patients had to have adequate hematologic, renal, and hepatic function <u>Exclusion</u>: - Prior or concurrent treatment with an EGFR or HER-2 inhibitor -Concurrent systemic corticosteroid therapy - Recently completed or concurrent treatment with											

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					another investigational therapy - Active CNS metastases - Malabsorption syndrome or other GI disease or resection that could affect absorption. - Severe cardiovascular disease or cardiac disease requiring a device											
(Hudes, 2007) included in (Coppin, 2008)	RCT	Wyeth/Wyeth Research designed the trial in collaboration with the principal academic investigators, whom were responsible for the decision to publish the data. All authors had access to the primary	Hospital (multicenter)	Temsirolimus improves survival in patients with advanced RCC	Inclusion: histologically confirmed advanced RCC (stage IV or recurrent disease); Karnofsky performance score of 60 or more; with no previous systemic therapy; tumor measurable according to the	626/19	Accrual: July 2003 – April 2005	Stratified permuted block randomisation (method not stated)	Advanced RCC (80% clear cell) patients with poor prognosis (67% with previous nephrectomy, 80% has more than 2 sites of organ metastasis) with no previous systemic treatment Groups	Temsirolimus: i.v. 25 mg weekly as a 30- to 60-min infusion, plus diphenhydramine i.v. 25–50 mg or similar H1 blocker 30 min preinfusion	INF-a: 3 MU s.c. thrice weekly for week 1; dose was escalated as tolerated to 9 MU thrice weekly for week 2, then 18 MU thrice weekly for study duration. Combination arm: INF-	Primary: overall survival Secondary: progression -free survival assessed by site investigator, progression -free survival assessed by blinded assessment of imaging studies,	Temsirolimus: median overall survival – months (95%CI): 10.9 (8.6–12.7); median progression -free survival (investigators´ assessment): 3.8 (3.6–5.2); progression -free survival	Adverse events (see also (Bellmunt, 2008)): rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, whereas asthenia	Intention-to-treat analyses Unclear if an adequate concealment method was used Non-blinded RCT, except for radiological response rate outcome. 3% of the	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
		data and vouch for the integrity and completeness of the data reported in the article. All authors report conflicts of interest			Response Evaluation Criteria in Solid Tumors (RECIST); adequate bone marrow, renal, and hepatic functions; patients with a history of brain metastases: neurologically stable and no requirement for corticosteroids; at least three of six predictors of short survival				were comparable		a 3 MU thrice weekly during week 1; beginning on week 2, INF-a 6 MU was administered thrice weekly, with temsirolimus 15 mg weekly	objective response rate, clinical benefit rate	(independent assessment): 5.5 (3.9–7.0); median time to treatment failure: 3.8 (3.5–3.9); objective response rate (%): 8.6 (4.8–12.4); clinical benefit (objective response or stable disease ≥24 weeks) (%): 32.1 (25.7–38.4) IFN-a: median overall survival – months (95%CI): 7.3 (6.1–8.8); median progression-free survival (investigators´ assessment): 1.9 (1.9–2.2); progression	was more common in the IFN group. There were fewer patients with serious adverse events in the temsirolimus group than in the IFN group	IFN group did not receive any treatment vs. 0.5% of the temsirolimus group, withdrawal of consent before or during treatment is not reported; drop-outs are not reported Relation between adverse event and active treatment is measured in a subjective and non-blinded way ´Clinical benefit´ is an artificial outcome: is it of use to patients?	

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													-free survival (independent assessment): 3.1 (2.2–3.8); median time to treatment failure: 1.9 (1.7–1.9); objective response rate (%): 4.8 (1.9–7.8); clinical benefit (objective response or stable disease ≥24 weeks) (%): 15.5 (10.5–20.4) Combination: median overall survival – months (95%CI): 8.4 (6.6–10.3); median progression -free survival (investigators´ assessment): 3.7 (2.9–4.4);			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													progression-free survival (independent assessment): 4.7 (3.9–5.8); median time to treatment failure: 2.5 (1.9–3.6); objective response rate (%): 8.1 (4.4–11.8); clinical benefit (objective response or stable disease ≥24 weeks) (%):28.1 (22.0–34.2)			
(Motzer, 2007) included in (Coppin, 2008) and updated by (Motzer, 2009)	RCT	Pfizer/many conflicts of interest reported	Hospital, international and multicenter	Not stated	Inclusion: metastatic RCC with a clear-cell histologic Component, >18 years of age, no previous treatment with systemic therapy for RCC, presence of measurable	750/	Accrual: August 2004 – October 2005	Stratified permuted block randomisation	Metastatic clear cell RCC (no brain metastasis) with no previous systemic treatment and an ECOG performance status of 0 or 1/groups were	Sunitinib orally 50 mg daily in 6-weeks cycles (4 weeks of treatment, 2 weeks without treatment)	IFN-a-2a s.c. three times per week on non-consecutive days at 3 MU per dose in the first week, 6 MU per dose in the 2nd week and 9 MU thereafter	Primary: progression-free survival Secondary: objective response rate, overall, survival, patient-reported outcomes, safety	Median progression-free survival: 11 months (95%CI: 10-12) vs. 5 (4-6): hazard ratio 0.42 (0.32-0.54, p<0.001) Median overall survival was not	Subgroup analyses: median progression-free survival was longer in sunitinib treated patients in all three prognostic risk categories	See also update (Motzer, 2009) Intention-to-treat analyses Unclear if an adequate concealment method was used	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					disease, an ECOG performance status of 0 or 1, adequate hematologic, coagulation, hepatic, renal, and cardiac function Exclusion: brain metastases, uncontrolled hypertension, clinically significant cardiovascular events or disease during the preceding 12 months				comparable				reached for either group at the time of analysis: hazard ratio for death 0.65 (0.45-0.94; p=0.02) Objective response rate: 31% (26-36%) vs. 6% (4-9) (p<0.001) Safety: more patients with grade 3 or 4 treatment-related fatigue in the IFN-a group; more grade 3 or 4 diarrhea in the sunitinib group. More grade 3/4 hypertension and more all grade decline I ejection fraction in sunitinib		Non-blinded RCT, except for radiological response rate outcome. 8% of patients in the IFN-group withdrew consent vs. 1% in the sunitinib group; this questions the validity of the outcome health-related quality of life Relation between adverse event and active treatment is measured in a subjective and non-blinded way	

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													group Health-related quality of life: significantly better in the sunitinib group			
(Escudier, 2007a) included in (Coppin, 2008) and updated by (Escudier, 2009a)	RCT	Bayer Pharmaceuticals and Onyx Pharmaceuticals/many conflicts of interest reported	Hospital, multicentre international	Not explicitly stated	Inclusion: histologically confirmed metastatic clear cell RCC, which had progressed after one systemic treatment within the previous 8 months; performance status of 0 or 1 (ECOG criteria); intermediate-risk or low-risk status, according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score; life	903/0	Accrual November 2003 March 2005	Block randomisation by ?	Patients with metastatic clear cell RCC (no brain metatstasis), which had progressed after one systemic treatment No statistically significant differences between groups	Sorafenib 400 mg orally, twice daily administered in 6-week cycles for the first 24 weeks and in 8-week cycles thereafter	Placebo	Primary: overall survival Secondary: progression-free survival, response rate, patient-reported outcomes, safety	Overall survival before cross-over: HR 0.72 (95%CI: 0.54-0.94); p=0.02) Median progression-free survival before cross-over: 5.5 vs. 2.8 months, hazard ratio for disease progression 0.44 (0.35-0.55) Response rate: partial responses were reported as the best response in 10% of sorafenib patients vs.	Median overall survival (after cross-over from placebo to sorafenib was allowed): 19.3 vs. 15.9 months, hazard ratio 0.77 (0.63-0.95; p=0.02)	Updated by (Escudier, 2009a) Double-blind study with an independent safety committee. Unclear if an adequate concealment method was used At interim analysis it was decided that patients were allowed to cross-over to sorafenib because of the hazard ratio of 0.72, though the pre-	A2

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					expectancy of at least 12 weeks; adequate bone marrow, liver, pancreatic, and renal function; prothrombin time or partial-thromboplastin time of less than 1.5 times the upper limit of the normal range Exclusion: brain metastases, previous exposure to VEGF pathway inhibitors								2% of placebo patients (p<0.001) Safety: hypertension and cardiac ischemia were more frequently in the sorafenib group. Cardiac ischemia or infarction occurred in 3% of sorafenib patients vs. <1% of placebo patients (p=0.01)		specified statistical significance was not reached. The outcomes after cross-over are difficult to interpret	
(Escudier, 2007b) included in (Coppin, 2008)	RCT	Hoffmann-La Roche/conflicts of interest reported	Hospital, multicentre international	Not explicitly stated	Inclusion: 18 years or older, predominantly (>50%) clear-cell metastatic RCC, had undergone nephrectomy or partial	649	Accrual June 2004 – October 2005	Block design randomisation with a randomisation list kept in a secure central location	Metastatic RCC (no brain metastasis) with no previous systemic treatment	Bevacizumab (10 mg/kg every 2 weeks) + IFN-a-2a (9MIU subcutaneous three times weekly)	Placebo + IFN-a-2a (9MIU subcutaneous three times weekly)	Primary: overall survival Secondary: progression-free survival, response rate, safety	Overall survival: not mature at this point Median progression-free survival at time of unblinding: 10.2 vs. 5.4 months,	-	Double-blind study: unblinding occurred at the time of final progression-free analysis, which results are presented here	A2

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					nephrectomy, a Karnofsky performance status of 70% or more, a normal hepatic, hematopoietic, and renal function Exclusion: prior systemic treatment for metastatic renal cell carcinoma, recent major surgical procedures, evidence of brain metastases, ongoing full-dose oral or parenteral anticoagulant or anti-platelet aggregation treatment, uncontrolled hypertension on								hazard ratio 0.63 (95% CI: 0.52-0.75; p=0.0001) with a consistent effect across risk-groups Response rate: 70% reported tumor shrinkage in the bevacizumab group, compared with 39% in the control group (p=0.0001) Safety: serious adverse events were reported in 29% of patients who received bevacizumab and in 16% of those who did not		Intention-to-treat analysis	

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					medication, clinically significant cardiovascular disease, or chronic corticosteroid treatment											
Targeted therapy: side effects only																
(Zhu, 2009)	SR	Conflicts of interest are reported. No information on source of funding	Not stated	Not stated	Phase II and III clinical trials using sunitinib as a single agent either at a continuous daily dosing (37.5 mg daily) or intermittent dosing (50 mg daily for 4 weeks, followed by 2 weeks off, for a 6-week cycle)	4 original studies + 9 abstracts	NA	NA	Patients with renal cell cancer, GIST or other cancer	Sunitinib	NA	Hypertension	Incidence of all-grade and high-grade hypertensions: 21.6% (95%CI 18.7-24.8%) and 6.8% (95%CI 5.3-8.8%) respectively. Sunitinib was associated with a significantly increased risk of high-grade hypertension (RR 22.72, 95%CI 4.48-115.29, p<0.001) and renal dysfunction (RR 1.36,	-	Low-quality SR Search date: July 2007. Search of Medline, ASCO abstracts, Web of Science. English studies only. No information on quality appraisal Meta-analysis performed Not exclusively renal cell cancer	C

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													95%CI 1.20-1.54, p<0.001) in comparison with controls			
(Bellmunt, 2008) Original study = (Hudes, 2007)	RCT	Source of funding = Wyeth Pharmaceuticals. No information on conflicts of interest	Not stated	Not stated	Patients had advanced RCC with three or more of six poor prognostic features, including more than one organ site of metastasis, lactate dehydrogenase >1.5x upper limit of normal, hemoglobin below lower limit of normal, corrected serum calcium >10 mg/dl, <1 year from diagnosis to randomization, and Karnofsky performance status of 60 or 70	N=616 (safety population that received treatment) Lost-to-follow-up: 4.8% in INF-a group, 1.9% in temsirolimus group, 2.4% in combination group (See Hudes 2007)	Not stated	Permuted blocks of three	No p-values, but no apparent differences (See Hudes 2007)	INF-a: 3 MU s.c. thrice weekly for week 1; dose was escalated as tolerated to 9 MU thrice weekly for week 2, then 18 MU thrice weekly for study duration	Temsirolimus: i.v. 25 mg weekly as a 30- to 60-min infusion, plus diphenhydramine i.v. 25–50 mg or similar H1 blocker 30 min preinfusion. Combination arm: INF-a 3 MU thrice weekly during week 1; beginning on week 2, INF-a 6 MU was administered thrice weekly, with temsirolimus 15 mg weekly	Drug-related adverse events	In patients receiving temsirolimus, anemia (13%) and hyperglycemia (9%) were the most common drug-related grades 3–4 adverse events; with IFN, asthenia (20%) was the most common. In all three groups, the greatest difference between reports of all-causality and drug-related AEs was observed for anemia, dyspnea, and pain	-	Original study = (Hudes, 2007) Relation between adverse event and active treatment is measured in a subjective and non-blinded way	B
Immunotherapy																

Revisie Richtlijn Niercelcarcinoom – Evidence tabel uitgangsvraag 4 - Welke systemische behandeling voor patiënten met gemetastaseerd niercelcarcinoom geeft de grootste kans op een hoge disease free en/of relapse free en/of overall survival?

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
(Coppin, 2005)	SR	Not stated	Not stated	1. High dose IL-2 yields better survival than other options 2. IFN-a yields better survival than other options	RCTs (except phase I trials)	6880 patients (58 studies)	NA	NA	Patients with metastatic or locally inoperable renal cell carcinoma, histologically verified at presentation or relapse. Studies of mixed tumor types were eligible only if patients with renal cell carcinoma were stratified and reported separately from other groups	Immunotherapy, including natural and recombinant IFN-a, beta, and gamma, IL-2 at high dose and at modified dose, combinations of these agents with each other or with various enhancing agents, and other immunotherapy approaches (plasma, vaccine with BCG, IL-12, or autolymphocyte therapy)	Chemotherapy (three trials); hormone therapy (eight trials); lectin, cimetidine, or nephrectomy (one each); placebo (one trial).	Overall survival	No published RCTs of high-dose IL-2 vs. a non-immunotherapy control, or of high-dose IL-2 vs. IFN-a reporting survival. Results from four studies (644 patients) suggest that IFN-a is superior to controls (OR for death at 1 year = 0.56, 95%CI 0.40-0.77). Up-front nephrectomy improved median survival over IFN-a alone in highly selected fit patients with metastases at diagnosis and minimal symptoms	Not reported	High-quality SR Search date: June 2005	A1

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
													(lower risk of death in the first year (OR 0.53, 95%CI 0.33-0.83, p=0.006)			
(Coppin, 2005) continued												Remission	Combined data for a variety of immunotherapies gave an overall chance of partial or complete remission of only 12.4%, compared to 2.4% in non-immunotherapy control arms			
(Negrier, 2008)	RCT	Conflicts of interest reported. Source of funding = Roche	Hospital	15% improvement in overall survival at 4 years	Inclusion: - Patients older than 18 years; - Histologically confirmed, clearly progressive metastatic renal carcinoma, no more than one metastatic organ site;	N=153 No lost-to-follow-up	Median follow-up = 42.5 months	Central randomization through a specific website	No significant differences	INF-a s.c. $6x10^6$ IU thrice a week + IL-2 continuous IV infusion, $18x10^6$ IU/m² Induction treatment consisted of two 5-day courses of IL-2 separated by a 1-week	INF-a s.c. $6x10^6$ IU thrice a week throughout the two 4-week cycles + IL-2 s.c. $9x10^6$ IU twice daily for 5 days during the 1st week, then twice daily for 2 days and once	Primary: overall survival Secondary: progression-free survival, objective tumor response, toxicity, quality of life	Overall survival difference was not significant: median 33 months (95%CI 27.0-40.2; p=0.202). The median survival time was 37.7 months (95%CI 28.2-55.6)	-	No information on blinding of patients and investigation Intention-to-treat analysis	B

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					- Good performance status (Karnofsky score ≥90%) - Normal blood and liver functions with creatinine level <150 µmol/L; - All histologic subtypes of renal cell cancer were eligible <u>Exclusion</u>: - Patients with previous systemic treatment or radiotherapy within 6 weeks of randomization; - Evidence of active brain metastases, severe cardiac dysfunction, active infections,					break. This treatment cycle was repeated after 3 weeks of rest. INF-a was given throughout each of the two treatment cycles. In patients who did not progress, maintenance consisted of four 5-day courses of the combination of IL-2 and INF-a, separated by 3 weeks of rest	daily for 3 days during the following 3 weeks. After a week of rest, an identical 4-week cycle was administered		and 30.1 months (95%CI 25.1-34.5) in arms A and B, respectively Progression-free survival rates were not significantly different: 7.2 months (95%CI 6.0-9.6) in arm A, 6.2 months (95%CI 5.1-8.5) in arm B Response rates at 3 months were 17.9% vs. 21.3% in arms A and B (p=0.60) Grade 3/4 adverse events: 85.9% vs. 74.7% patients (p=0.08) No significant			

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure (s) Secondary Outcome Measure (s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
					or current corticosteroid treatment; - Patients with a history of organ transplantation, or with other cancer or seizure, as well as pregnant or lactating women								differences in quality of life			
(Atzpodien, 2006)	RCT	Conflicts of interest reported. No information on source of funding	Hospital	The 3-year survival rates were hypothesized to show a 20% advantage of arm B over arm A (40 vs. 20%), and a 15% advantage of arm D over arm C (30 vs. 15%).	Inclusion: - Histologically confirmed progressive and irresectable metastatic renal cell carcinoma; - An expected survival duration of more than 3 months; - Karnofsky performance status 480%; age between 18 and 80 years; - White blood cell count	N=379	Not stated	Per centre block randomization. No information on allocation concealment	No p-values provided	Group I: patients with pulmonary metastases: Arm A: sc-IFN-a2a ($5x10^6$ IU m^{-2}, day 1, weeks 1+4; days 1, 3, 5, weeks 2–3; $10x10^6$ IUm^{-2}, days 1, 3, 5, weeks 5–8), sc-IL-2 ($10x10^6$ IUm^{-2}, twice daily, days 3–5, weeks 1+4; $5x10^6$ IUm^{-2}, days 1, 3, 5, weeks	Group II: all others Arm C: arm A plus iv-5-FU (1000 mg m^{-2}, day 1, weeks 5–8) Arm D: treatment arm A combined with oral Capecitabine (1000 mg m^{-2} twice daily, days 1–5, weeks 5–8)	Overall survival Progression-free survival Objective response	Median overall survival was 22 months (arm A) and 18 months (arm B) in group I, and 18 months (arm C) and 16 months (arm D) in group II. No statistically significant differences in overall survival, progression-free survival, and objective response between	No toxic deaths. All treatment were moderately well tolerated	No information on allocation concealment or blinding of patients and investigation Intention-to-treat analysis	B

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					43500/ml; platelet count 4100000 /ml; haematocrit >30%; serum bilirubin, and creatinine <1.25 of the upper normal limit; - No evidence of congestive heart failure, no severe coronary artery disease, no cardiac arrhythmias, no clinically symptomatic CNS disease or seizure disorders, no human immunodeficiency virus infection, no evidence of chronic active hepatitis, no					2+3), and po-13cRA (20 mg 3x daily) over 8 weeks Arm B: treatment arm A combined with inhaled-IL-2 ($9x10^6$ IU/2.5 ml basic solution, four times a day, days 1–5, weeks 2+3 and weeks 5–8)			arms A and B, and between arms C and D, respectively			

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					concomitant corticosteroid therapy. <u>Exclusion</u>: - Chemotherapy or immunomodulatory treatment during the previous 4 weeks. - Pregnant and lactating women were excluded											
(Kinouchi, 2006) Included in (Coppin, 2005) as an abstract	RCT	Not stated	Hospital	Not stated	<u>Inclusion</u>: - Histological or cytological confirmation of renal cell carcinoma, and measurable metastatic lesions either in the lung alone, or in the lung and other organs. - An ECOG performance status of	N=71	Not stated	Central randomization using minimization technique	Similar groups	IFN-a alone	IFN-a + cimetidine 2x400 mg orally	<u>Primary</u>: response rate <u>Secondary</u>: time to progression	Response rate: 13.9% vs. 28.6% (p=0.13) Median time to progression: 112 vs. 125 days (p=0.87)	6 patients stopped treatment because of adverse events	No blinding Intention-to-treat analysis Included in (Coppin, 2005)as an abstract	B

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					0 or 1; - An age of 20-75 years - Life expectancy greater than 3 months - No complications with severe diabetes mellitus, cardiovascular or pulmonary diseases; - No previous INF-a therapy, more than a 6-month period after stopping adjuvant IFN-a therapy; - Adequate liver function, renal function; - A white blood cell count of at least 4,000/ mm^3; a platelet count of at least 100,000/m											

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					m3 and written informed consent. The exclusion criteria included: cases with an active peptic ulcer; cases who used histamine type-2 antagonists for more than 2 weeks immediately before this study; cases with other types of cancer that were not cured or had been cured within 1 year; cases with autoimmune diseases; cases with allergies to IFN drugs and cases with psychogenic diseases, including depression											

Abbreviations

95%CI: 95% confidence intervals; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; GI: gastrointestinal; HR: hazard ratio; IFN-a : interferon-alpha; IL-2: interleukin-2; IU: international units; MIU; million international units; MU: million units; NA: not applicable; ORR: overall response rate; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCC: renal cell cancer; RCT: randomized controlled trial; RR: relative risk; S.C.: subcutaneous; SR: systematic review; TTP: time-to-progression.

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Immunotherapy																
(Adiga, 2004)	Single arm cohort study	Supported by the Kidney Cancer Fund of the Cancer Research Foundation/ Not reported	Hospital	None	Not stated	19 (pain data are available for 16 patients only)	Not stated	None	Patients with bone metastasis from renal cell carcinoma..	High or moderate dose Il-2	None	Need for pain medication for bone pain Changes in pain medication Serum calcium and alkaline phosphatase levels Need for additional therapy, including RT and surgical interventions	No significant effect on the requirement for pain medication for bone pain. None of the patients had hypercalcaemia; there was no significant association between bone metastases and elevated alkaline phosphatase levels. Il-2 may have prevented skeletal complications requiring surgery or radiotherapy. IL- associated toxicities were hypotension requiring pressors, oliguria, weight gain, neurotoxicity, dyspnoea	Disease progression	Observational cohort study with no control group Blinded/independent outcome assessment is not reported This might be a retrospective study 3/16 patients for whom data on pain were available did not have drugs for bone pain at the start of therapy No formal statistical calculations provided	C

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													at rest, nausea/vomiting, arrhythmia and granulocytopenia. Toxicity was dose dependent and reversible on discontinuing Il-therapy.			
Immunochemotherapy and radiotherapy																
(Brinkmann, 2005)	Single arm cohort study	Not stated	Hospital	None	Not stated	20/0	Sep 1997 – Sep 1999	None	20 patients with symptomatic bone metastases (15 patients) or local recurrence (5 patients)	A combination of RT and ICT (IL-2, IFN-a and 5-fluorouracil)	Not applicable	Pain medication	19/20 patients required less pain medication 10/20 patients did not need further pain treatment 19/20 patients showed pain relief after the first 2 weeks of RT 2/20 patients needed morphine medication	Disease progression and survival	Observational cohort study with no control group Blinded/independent outcome assessment is not reported Pain is only reported in relation to drugs. 5/20 patients did not have bone metastasis	C
Radiotherapy																

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(Gerszten, 2005)	Single arm cohort study	Volker Sontag Award (research grant of the American Association of Neurological Surgeons)/None reported	Outpatient department	Spinal radiosurgery is safe, feasible and clinically effective for the treatment of spinal metastases of renal cell carcinoma	Not stated Exclusion criteria: evidence of overt spinal instability; neurological deficit because of osseaous compression of neurological structures	48patients with 60 metastatic spine lesions (for 38 patients the primary indication for radiosurgery was pain)/not stated	Follow-up 14 to 48 months (median 37 months)	None	Consecutive patients with spinal metastases from renal cell carcinoma 42/60 lesions had been treated with external-beam radiation therapy	Single-fraction radiosurgery (CyberKnife)	None	Pain	37/38 patients with pain as a primary indication for radiosurgery pain was reported as improved 34/38 patients reported long-term pain improvement	Disease progression	Observational cohort study with no control group Blinded/independent outcome assessment is not reported The assessment of pain improvement is limited. The nature, magnitude and duration of pain improvement is not described	C
(Lee, 2005)	Single arm cohort study	Not reported/not reported	Two hospitals	None stated	Pathologically confirmed diagnosis of RCC and at least one symptomatic site of metastasis <u>Inclusion:</u> ECOG performance status ≤ 3 and a life expectancy of ≥ 3 months	31 (only 23 evaluable)/	1996 – 2002 (median follow-up 4.3 months)	None	Symptomatic metastatic renal cell carcinoma 24/31 patients had bone pain	Radiotherapy/100%	None	Pain Analgesic use QoL	83% experienced site-specific pain relief. 48% did not have an associated increase in analgesic medication use. The median duration of site specific pain response was 3 months (range: 1–15). The global	None	Observational cohort study with no control group Independent outcome assessment Small number of participants	C

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					Exclusion: RT, chemotherapy, or immunotherapy within 4 weeks before enrollment; an isolated metastasis deemed appropriate for surgical excision; prior RT to the symptomatic site.								pain response rate was only 15% because many patients developed other painful metastases. Global QOL was found to improve in 33% (n =8) of the evaluable patients			
(Reichel, 2007)	Single arm cohort study	Not reported/none stated	Hospital	Irradiation provides adequate palliative effect (prevention of fracture, pain relief, restoration of functional level until death)	Bone metastasis from renal cancer	28/0	1990-2002	None	Multifocal osseous metastatic renal cancer patients	Radiotherapy (22% of sites underwent repeat RT)	None	Pathological fracture Pain Functional level	At 1/36 metastatic sites a pathological fracture occurred 2/36 sites needed surgical fixation of the spine Median time to return to pretreatment pain and functional levels was 2 and 1 months	None	Observational cohort study with no control group Blinded/independent outcome assessment is not reported	C

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RF ablation therapy combined with Cement/osteoplasty																
(Hoffmann, 2008)	Single arm cohort study	Not reported/not reported	Hospital	The combination of RF ablation and osteoplasty has a synergistic effect on pain	Not stated. Patients had to be recommender the treatment by the local tumor board	22(5 with primary renal cell carcinoma)/0	Mean follow-up 7.7 months	Not applicable	22 patients with painful bone metastasis (5 from renal cell carcinoma)	RF ablation and osteoplasty of bone lesions	No control	Pain relief Analgesics reduction Clinical success (either of the above) Technical success	Pain relief achieved in all patients Mean VAS pain score went down from 8.5 to 5.5 after 24 hours and 3.5 after 3 months In 15 patients the amount or strength of analgesics was reduced; in 5 unchanged; in 2 increased because of tumor progression elsewhere Technical success achieved in all patients	No major complications	Retrospective analysis of prospectively collected data Observational cohort study with no control group Blinded/independent outcome assessment is not reported Only 5 patients with renal cell carcinoma	C

Study (trial) ID	Study type	Source of funding/ conflicts of interest	Setting	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up	Duration of the Study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/ Comparator (including duration, dose)	Primary Outcome Measure(s) Secondary Outcome Measure(s)	Effect size - Primary outcome(s) Effect size – Secondary outcome (s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
(Toyota, 2005)	Single arm cohort study	Not reported	Hospital	The combination of RF ablation and cementoplasty has a synergistic effect on pain	Not stated	17 (5 with primary renal cell carcinoma)/1	Oct 2001 – Jan 2004	Not applicable	17 patients with painful bone metastasis (5 from renal cell carcinoma)	RF ablation and cementoplasty of bone lesions	No control	Pain score VAS score Analgesic reduction Days to achievement of pain relief ADL post therapy Duration of pain relief Recurrence of pain	Initial pain relief was achieved in 100% of patients). The mean VAS scores dropped from 63 to 24 ($p < 0.001$) ($n = 8$). Analgesic reduction was achieved in 41% (7 out of 17 patients). The mean duration of pain relief was 7.3 months (median: 6 months). Pain recurred in three patients (17.6%) from 2 weeks to 3 months.	Survival	Observational cohort study with no control group Blinded/independent outcome assessment is not reported Only 5 patients with renal cell carcinoma	C
Surgery																
(Ibrahim, 2008)	Observational cohort study	Funded with an educational grant from Johnson & Johnson/Not reported	Six international spinal surgery centers		Patients ≥ 18 years old with an extradural spinal metastasis, of epithelial	223 (40 renal carcinoma)/not stated	Jan 2002 – Dec 2003 (follow-up 13 to 37	None	Consecutive patients with extradural spinal metastasis treated surgically	Spinal surgery (en bloc resection, debulking or palliative) with spinal instrumented	None	Perioperative death (within 30 days) Pain control	5.8% died peri-operatively 71% had better pain control; 11%	Median survival was 352 days Patients with	Observational cohort study with no control group Blinded/independent outcome	C

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					cancer origin, treated surgically Exclusion criteria: primary spinal tumours; non-epithelial secondary tumours; previous spinal tumour surgery		months)		92% of patients presented with pain and 24% with paraparesis	fixation in 92% 26% of patients received RT; 31% chemotherapy and 12% both		(not further defined) Mobility Neurological function Urinary sphincter function	had no change; 18% had worsening of pain The % of patients with back or radiculair pain decreased from 92% preoperatively to 32% postoperatively 51% of immobile patients regained mobility. 73% of patients were mobile pre surgery vs. 87% post surgery 39% of those with impaired sphincter function regained normal urinary control	excision survived significantly longer than those with palliative surgery (p=0.003)	assessment is not reported 40/223 patients had renal cell carcinoma The assessment of pain control is limited. The nature, magnitude and duration of pain control is not described	
Zoledronic acid																

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(Lipton, 2003)	Retrospective analysis of a subset from a randomised, controlled trial	Sponsor is not stated, likely to be stated in original study/2 out of 3 authors are employed by Novartis	Multicenter, international, hospital	Not stated	Inclusion: ECOG performance status ≤ 2 Exclusion: liver metastases, high total bilirubin or serum creatinine, symptomatic brain metastases; another bisphosphonate within 30 days of receiving zoledronic acid; severe cardiovascular disease, hypertension refractory to treatment, or symptomatic coronary artery disease within 6 months of randomisation	46/not stated No efficacy conclusions were drawn from the 8/4-mg group, which leaves 46 patients in the analyses	Not stated	Not stated	Patients with bone metastases secondary to renal cell carcinoma Groups seem comparable (no p-values provided)	Zoledronic acid (4 mg as a 15-minute infusion) with concomitant antineoplastic therapy every 3weeks for 9 months Compliance: not stated	Placebo with concomitant antineoplastic therapy every 3 weeks for 9 months	Primary: proportion of patients with one or more skeletal-related events at 9 months Secondary: time to first skeletal related event, morbidity rate (events per year), disease progression, and multiple event analysis	Skeletal related events: 37% vs. 74% (p= 0.015) Mean skeletal morbidity rate: 2.68 vs. 3.38 (p=0.014) Time to the first event: median not reached vs. 72 days (p= 0.006) Multiple event analysis: risk of developing a skeletal related event was reduced by 61% compared with placebo (hazard ratio of 0.394; p= 0.008). The median time to progression of bone lesions was significantly longer for patients who	1 patient in the 4 mg zoledronic group experience renal failure vs. none in the placebo group Serious adverse events were reported by 48% of patients in the 4-mg zoledronic acid group compared with 68% of patients in the placebo group. The most frequently reported, serious adverse events, regardless of relation to study drug, were malignant	Small population (n=46) in this subanalysis; analysis at 9 months Population to small to detect difference in adverse events At onset an 8 mg zoledronic acid arm was included which was later reduced to 4 mg, the reason for this change is not explicitly stated (renal complications?) Not all trial characteristics are stated in this publication but the original publication stated it was a double-blind study	B

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													were treated with zoledronic acid (p=0.014)	neoplasm bone pain, dehydration, dyspnea, and pneumonia		

Abbreviations:
ADL: activities of daily living; ECOG: Eastern Cooperative Oncology Group; ICT: immunochemotherapy; IFN: interferon; IL: interleukin; QoL: quality of life; RF: radiofrequent; RT: radiotherapy; VAS: visual analogue scale.

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