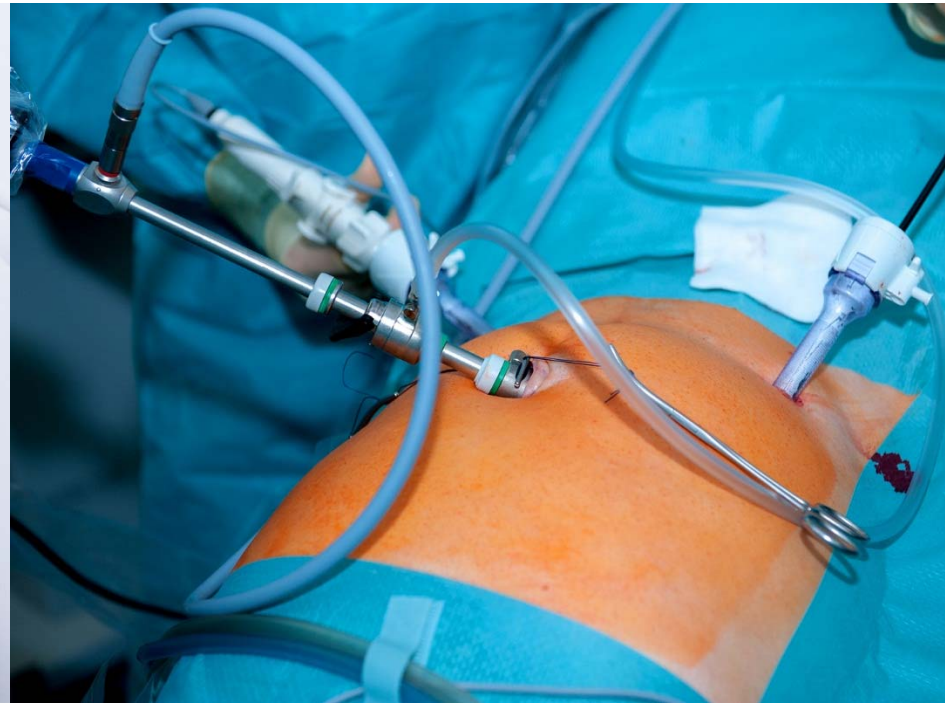
CE REPORT 253S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

RENAL CANCER IN ADULTS: DIAGNOSIS, TREATMENT AND FOLLOW-UP

SUPPLEMENT



KCE REPORT 253S
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

RENAL CANCER IN ADULTS: DIAGNOSIS, TREATMENT AND FOLLOW-UP

SUPPLEMENT

NADIA BENAHMED, JO ROBAYS, SABINE STORDEUR, THIERRY GIL, STEVEN JONIAU, NICOLAAS LUMEN, LAURETTE RENARD, SANDRINE RORIVE, DIRK SCHRIJVERS, BERTRAND TOMBAL, BART VAN DEN EYNDEN, GEERT VILLEIRS, SYLVIE ROTTEY

COLOPHON

Title:	Renal cancer in adults: diagnosis, treatment and follow-up – Supplement
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External validators:	Axel Bex (Netherlands Cancer Institute), Sebastien Hotte (Juravinski Cancer Center, Hamilton), Rob Scholten (Universitair Medisch Centrum)
Acknowledgements:	Nicolas Fairon (KCE): information specialist
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Ward Rommel (Kom op tegen Kanker), Elisabeth Van Eycken (BVRO-VBS), Axel Feyaerts (Société Belge d'Urologie) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Axel Bex (Advisory Board Pfizer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Axel Bex (Pfizer symposium October 2014), Nicolaas Lumen (consultance for Ipsen, Janssen, Lilly and Bayer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals), Sylvie Rottey (GSK, Pfizer, Bayer, Novartis), Dirk Schrijvers (post ESMO) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Elisabeth Van Eycken (Kankerregister), Nicolaas Lumen (Board member BAU working group oncology), Geert Villeirs (president Belgische Vereniging voor Radiologie) Participation in scientific or experimental research as an initiator, principal investigator or researcher: Axel Bex (EORTC 30073 Surtime study, partially sponsored by Pfizer), Sebastien Hotte (grant-in-aid for Novartis in a trial using dovitinib for head and neck cancer), Bertrand Tombal (Amgen, Astellas Pharma, Bayer, Sanofi, Ferring Pharmaceuticals), Dirk Schrijvers (studies about renal cell carcinoma)
Layout:	Ine Verhulst, Joyce Grijseels

Disclaimer:	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise, affiliations
Sylvie Rottey, President of the GDG	Medical Oncology, UZ Gent
Gert De Meerleer	Radiotherapy, UZ Gent
Thierry Gil	Medical Oncology, Institut Jules Bordet
Steven Joniau	Urology, KULeuven
Nicolaas Lumen	Urology, UZ Gent
Laurette Renard	Radiotherapy, Cliniques universitaires Saint-Luc
Sandrine Rorive	Pathology, Erasme
Dirk Schrijvers	Medical Oncology, Middelheim Antwerp
Bertrand Tombal	Urology, Cliniques universitaires Saint-Luc
Bart Van den Eynde	Palliative Medicine - Primary Care, GZA
Geert Villeirs	Medical Imaging, UZ Gent

1.2. Composition of the KCE expert team

KCE member	Specific role
Kristel De Gauquier	Program Director
Sabine Stordeur	Project Coordinator
Jo Robays	Principal Investigator
Nadia Benahmed	Scientific Researcher

2. SEARCH STRATEGIES

2.1. Search strategy for guidelines

Table 1 – Search results - Guidelines on renal cancer

Database	# of hits
CMA Infobase: clinical practice guidelines (Canada)	6
CISMeF-BP	16
Centraal Begeleidings Orgaan	1
Cochrane library	132
EBMPracticeNet	1
G-I-N	22
Haute Autorité de Santé	3
National Guideline Clearinghouse	471
NICE	448
OVID Medline	193
Prodigy	1

After removal of duplicate guidelines, 24 guidelines were selected based on title and abstract and retained for full-text evaluation. Of these, 22 guidelines were excluded for the following reasons (see Table 2):

- 15 guidelines were excluded because of unclear or insufficient methodology
- 4 documents could not be considered as guidelines (rapid reviews)
- 2 documents could not be considered as guidelines (reports related to reimbursement requests)
- 1 guideline could not be considered as appropiate guideline because the authors decided to archive it and not to maintain recommendations.

In addition, one guideline was found in the reference list of a systematic review. Finally, 3 guidelines were retained for an evaluation of the methodological quality.

Table 2 – List of excluded guidelines

Source	Year	Title	Final appraisal
Haute Autorité de Santé (NICE)	2012	Cancer du rein de l'adulte. Guide Affection de longue durée.	Not recommended (unclear methodology) No search method provided
American College of Radiology (AHRQ)	2011	Appropriateness Criteria® renal cell carcinoma staging.	Not recommended (unclear methodology) No search method provided
American College of Radiology (AHRQ)	2010	ACR Appropriateness Criteria® indeterminate renal masses.	Not recommended (unclear methodology) No search method provided
American College of Radiology (AHRQ)	2009	Interferon-alfa in the treatment of patients with inoperable locally advanced metastatic renal cell cancer: guideline recommendations. Program in Evidence-based Care	Not recommended (out-dated) Guideline archived
American College of Radiology (AHRQ)	2010	ACR Appropriateness Criteria® renal cell carcinoma staging. American College of Radiology.	Not recommended (unclear methodology) No search method provided
European Association of Urology (EAU)	2013	Guidelines on renal cell carcinoma	Not recommended (unclear methodology and updated version in 2014 is included by hand searching reference list of SR) No detailed search strategy provided
Alberta Health Services, Cancer Care	2012	Renal Cell Carcinoma	Not recommended (scientific methodology insufficient) No details on evidence supporting recommendation
American Urological Association (AUA)	2013	Follow-up for clinically localized renal neoplasms	Not recommended (unclear methodology) No search method provided
American Urological Association (AUA)	2009	Guideline for management of the clinical stage 1 renal mass	Not recommended (scientific methodology insufficient) Search only in Medline
Department of Health Western Australia	2012	Renal cell carcinoma	Not recommended (unclear methodology) No search method provided

Source	Year	Title	Final appraisal
NICE	2011	NICE issues final guidance on everolimus for the second-line treatment of advanced renal cell carcinoma	Reimbursement request
NICE	2011	NICE issues guidance on pazopanib for the first-line treatment of metastatic renal cell carcinoma	Reimbursement request
NICE	2013	IPG443 Irreversible electroporation (IRE) for treating renal cancer: guidance	Rapid review
Department of Health Western Australia	2012	Renal Mass	Not recommended (scientific methodology insufficient) Search only in Medline
NICE	2011	IPG405 Cryotherapy for renal cancers: guidance	Rapid review
NICE	2011	IPG402 Percutaneous cryotherapy for renal tumours: guidance	Rapid review
NICE	2010	IPG353 Percutaneous radiofrequency ablation of renal cancer: guidance	Rapid review
British Association of Urological Surgeons	2013	Multi-disciplinary team (MDT) guidance for managing renal cancer	Not recommended (unclear methodology) No search method provided
Association Française d'Urologie (Urofrance)	2013	Recommandations en onco-urologie 2013 du CCAFU: Cancer du rein.	Not recommended (scientific methodology insufficient) Search only in Pubmed
Canadian Kidney Cancer Forum	2013	Management of advanced kidney cancer:	Not recommended (unclear methodology) No search method provided
Canada-clinical practice guidelines	2011	Renal cell carcinoma and genetic testing	Not recommended (unclear methodology) No search method provided
European Society for Medical Oncology	2012	Escudier B, et al. 2010 Annals of Oncology 137(21):- Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Not recommended (unclear methodology) No search method provided

2.2. Search strategies for other publications (systematic reviews, meta-analyses, individual RCT)

2.2.1. Diagnosis, prognosis, prediction of treatment effectiveness and follow-up

PICO

Project Number	2013-06
Project Name	GCP Renal Cancer
Search question	Diagnosis
Structured search question (PICO, SPICE, ECLIPSE,...)	
P Patient	Renal cancer
I Intervention	For diagnosis purpose, Ultrasonography, CT-scan, MRI, Scintigraphy, DMSA Scan, Biopsy, Fine Needle Aspiration Cit., Angiography, FDG-PET, Carbonic anhydrase IX, VEGF, VEGF Receptor 2, Hypoxia Inducible Factor, Ki67, P53, PTEN, E-cadherin, CD44, Interleukine 6, Hepatocyte Growth Factor, Diagnosis filter + renal neoplasms,
C Comparison	All
O Outcome	Sensitivity, specificity, positive predictive value, negative predictive value, true positive, false positive, false negative, true negative, likelihood ratio +, likelihood ratio -
S Settings	>=2009

Medline @ Ovid

Date	**2014-05-19**		
Database	**Medline (OVID)**		
Search Strategy	*#*	***Query***	***Results***
	1	exp Kidney Neoplasms/	**57884**
	2	((kidney or renal) adj3 (neoplasm or cancer or tumor or carcinoma or adenocarcinoma or onco or malign)).tw.	**38855**
	3	1 or 2	**67964**
	4	limit 3 to yr=2009 -Current	**15510**
	5	exp animal/ not humans.mp.	**3883828**

	6	4 not 5	**15150**
	7	exp Diagnosis/	**6458743**
	8	di.xs.	**4393506**
	9	diagnosis.tw.	**1042950**
	10	7 or 8 or 9	**8511138**
	11	6 and 10	**10757**
	12	exp Ultrasonography/	**247658**
	13	us.fs.	**196920**
	14	ultraso*.tw.	**248182**
	15	echotomograph*.tw.	**753**
	16	sonograph*.tw.	**43094**
	17	echograph*.tw.	**8629**
	18	12 or 13 or 14 or 15 or 16 or 17	**452952**
	19	6 and 18	**794**
	20	limit 19 to systematic reviews	**19**
	21	tomograph*.tw.	**250550**
	22	"ct scan".tw.	**36962**
	23	"ct scans".tw.	**21946**
	24	"x-ray ct".tw.	**1254**
	25	"x-rays ct".tw.	**133**
	26	"x-ray cat".tw.	**4**
	27	"cine-ct".tw.	**142**
	28	tomodensitometr*.tw.	**790**
	29	(ct adj2 (volume or volumic or cone)).tw.	**2764**
	30	cone-beam.tw.	**4565**
	31	exp Tomography, X-Ray Computed/	**299463**
	32	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	**455806**
	33	6 and 32	**2018**

	34	limit 33 to systematic reviews	**34**
	35	exp Magnetic Resonance Imaging/	**310029**
	36	mri.tw.	**140413**
	37	fmri.tw.	**23535**
	38	"magnetic resonance imaging".tw.	**134312**
	39	nmr.tw.	**119240**
	40	35 or 36 or 37 or 38 or 39	**496254**
	41	6 and 40	**790**
	42	limit 41 to systematic reviews	**12**
	43	exp Radionuclide Imaging/	**112243**
	44	ri.fs.	**117867**
	45	scintigraphy.tw.	**33657**
	46	scintiphotography.tw.	**160**
	47	radionuclide imaging.tw.	**1590**
	48	43 or 44 or 45 or 46 or 47	**181731**
	49	6 and 48	**295**
	50	limit 49 to systematic reviews	**5**
	51	"Technetium Tc 99m Dimercaptosuccinic Acid".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	**1169**
	52	exp "Technetium Tc 99m Dimercaptosuccinic Acid"/	**1165**
	53	dmsa.tw.	**2022**
	54	succimer.tw.	**135**
	55	technetium.tw.	**13323**
	56	dimercaptosuccinic.tw.	**1570**
	57	dimercaptosuccinate.tw.	**145**
	58	51 or 52 or 53 or 54 or 55 or 56 or 57	**15794**
	59	6 and 58	**20**

	60	limit 59 to systematic reviews	**0**
	61	exp Biopsy/	**222406**
	62	biopsy.tw.	**215028**
	63	biopsies.tw.	**95862**
	64	61 or 62 or 63	**403475**
	65	6 and 64	**1059**
	66	limit 65 to systematic reviews	**25**
	67	exp Biopsy, Fine-Needle/	**9151**
	68	aspiration.tw.	**58485**
	69	(needle? adj3 cytology).tw.	**6817**
	70	67 or 68 or 69	**61912**
	71	6 and 70	**164**
	72	limit 71 to systematic reviews	**1**
	73	exp Angiography/	**197097**
	74	angiograph*.tw.	**136926**
	75	arteriograph*.tw.	**17903**
	76	73 or 74 or 75	**263951**
	77	6 and 76	**123**
	78	limit 77 to systematic reviews	**1**
	79	exp Fluorodeoxyglucose F18/	**18714**
	80	fluorine-18-fluorodeoxyglucose.tw.	**1055**
	81	fluorodeoxyglucose.tw.	**8971**
	82	f18.tw.	**550**
	83	18f*.tw.	**12090**
	84	exp Positron-Emission Tomography/	**31686**
	85	(pet adj3 scan?).tw.	**6872**
	86	(positron adj3 (tomography or scan*)).tw.	**35592**
	87	84 or 85 or 86	**53779**

	88	79 or 80 or 81 or 82 or 83	**26662**
	89	87 and 88	**21402**
	90	6 and 89	**130**
	91	limit 90 to systematic reviews	**5**
	92	79 or 80 or 81 or 82 or 83 or 84 or 85 or 86	**59039**
	93	6 and 92	**278**
	94	limit 93 to systematic reviews	**8**
	95	exp Carbonic Anhydrases/	**7471**
	96	"carbonic anhydrase".tw.	**9847**
	97	"carbonic dehydratase".tw.	**3**
	98	95 or 96 or 97	**11388**
	99	("9" or IX or nine).tw.	**1019109**
	100	98 and 99	**1581**
	101	CaIX.tw.	**323**
	102	100 or 101	**1694**
	103	6 and 102	**142**
	104	limit 103 to systematic reviews	**4**
	105	exp Vascular Endothelial Growth Factors/	**36544**
	106	vegf*.tw.	**42663**
	107	"vascular endothelial growth factor".tw.	**37756**
	108	"vascular endothelial growth factors".tw.	**619**
	109	105 or 106 or 107 or 108	**57593**
	110	6 and 109	**934**
	111	limit 110 to systematic reviews	**44**
	112	exp Receptors, Vascular Endothelial Growth Factor/	**10116**
	113	"vascular permeability factor".tw.	**592**
	114	receptor?.tw.	**1027194**

115	(receptor? adj3 ("vascular permeability factor" or vegf* or "vascular endothelial growth factor" or "vascular endothelial growth factors")).tw.	**10232**
116	112 or 115	**14409**
117	6 and 116	**367**
118	limit 117 to systematic reviews	**18**
119	exp Hypoxia-Inducible Factor 1/	**10311**
120	"hypoxia inducible factor".tw.	**9296**
121	hif?1.tw.	**403**
122	119 or 120 or 121	**13126**
123	6 and 122	**298**
124	limit 123 to systematic reviews	**13**
125	Ki-67 Antigen/	**11883**
126	(mib-1 adj2 (protein or antigen)).tw.	**191**
127	ki?67.tw.	**6110**
128	125 or 126 or 127	**15584**
129	6 and 128	**72**
130	limit 129 to systematic reviews	**3**
131	Tumor Suppressor Protein p53/	**39538**
132	Genes, p53/	**14421**
133	p53.tw.	**64880**
134	tp53.tw.	**5572**
135	pp53.tw.	**34**
136	trp53.tw.	**549**
137	131 or 132 or 133 or 134 or 135 or 136	**73902**
138	6 and 137	**205**
139	limit 138 to systematic reviews	**6**
140	PTEN Phosphohydrolase/	**5433**
141	(pten adj3 (phosphatase? or protein? or phosphohydrolase?)).tw.	**1785**

	142	mmac?1.tw.	**233**
	143	140 or 141 or 142	**5878**
	144	6 and 143	**40**
	145	limit 144 to systematic reviews	**1**
	146	exp Cadherins/	**15607**
	147	e?cadherin?.tw.	**25**
	148	e-cadherin.tw.	**11592**
	149	e-cadherins.tw.	**103**
	150	146 or 147 or 148 or 149	**19952**
	151	6 and 150	**91**
	152	limit 151 to systematic reviews	**2**
	153	Antigens, CD44/	**6580**
	154	cd44.tw.	**9574**
	155	(hyaluron* adj3 (receptor? or "binding protein")).tw.	**1342**
	156	153 or 154 or 155	**11806**
	157	6 and 156	**17**
	158	limit 157 to systematic reviews	**0**
	159	(b-cell adj2 (differentiation or stimulatory) adj2 factor*).tw.	**505**
	160	((hybridoma? or plasmacytoma?) adj2 "growth factor").tw.	**95**
	161	il6.tw.	**3383**
	162	il-6.tw.	**64712**
	163	interleukin-6.tw.	**32950**
	164	mgi-2.tw.	**66**
	165	"ifn-beta 2".tw.	**104**
	166	"bsf-2".tw.	**101**
	167	"hepatocyte-stimulating factor".tw.	**99**
	168	"myeloid differentiation-inducing protein".tw.	**6**
	169	159 or 160 or 161 or 162 or 163 or 164 or 165 or 166 or 167 or 168	**79988**

	170	6 and 169	**56**
	171	limit 170 to systematic reviews	**1**
	172	Hepatocyte Growth Factor/	**6307**
	173	"hepatocyte growth factor".tw.	**7754**
	174	scatter factor.tw.	**1169**
	175	hepatopoietin.tw.	**58**
	176	172 or 173 or 174 or 175	**9092**
	177	6 and 176	**26**
	178	limit 177 to systematic reviews	**3**
	179	19 or 33 or 41 or 49 or 59 or 65 or 71 or 77 or 90 or 93 or 103 or 110 or 117 or 123 or 129 or 138 or 144 or 151 or 157 or 170 or 177	**5030**
	180	limit 179 to systematic reviews	**129**
	181	limit 11 to systematic reviews	**338**
	182	181 NOT 180	**246**
Notes	**The following lines indicate line number relative to diagnostic test in search strategy combined with Renal neoplasms. Ex: Line 33 CT scan AND renal neoplasms (year>2009, no animal studies). Line n+1 is the same limited to Systematic reviews.** **Line 10 is particular as it includes a search filter for diagnostic studies.** **In right column, number of results (all and systematic reviews)**		
	#	Topic	**#All / #SR**
	6	Kidney Neoplasm s > 2009 NOT animals	
	10	Diagnosis filter	
	11	diagnosis	
	19	Ultrasonography	**794 / 19**
	33	CT-scan	**2018 / 34**
	41	MRI	**790 / 12**
	49	Scintigraphy	**295 / 5**
	59	DMSA Scan	**20 / 0**
	65	Biopsy	**1059 / 25**

71	Fine Needle Aspiration Cit.	**164 / 1**
77	Angiography	**122 / 1**
93	FDG-PET	**278 / 8**
103	Carbonic anhydrase IX	**142 / 4**
110	VEGF	**964 / 44**
117	VEGF Receptor 2	**367 / 18**
123	Hypoxia Inducible Factor	**298 / 13**
129	Ki67	**72 / 3**
138	P53	**205 / 6**
144	PTEN	**40 / 1**
151	E-cadherin	**91 / 2**
157	CD44	**17 / 0**
170	Interleukine 6	**56 / 1**
177	Hepatocyte Growth Factor	**26 / 3**
181	Diagnosis filter + renal neoplasms	**10757 / 338**

Embase @ Embase.com

Date	**2014-06-04**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	*#*	***Query***	***Results***
	#1	((kidneys OR kidney OR renal) NEAR/3 (cancer OR cancer* OR neoplasm OR neoplasm* OR tumor OR tumour OR tumor* OR tumour* OR sarcom* OR oncol* OR carcinom* OR adenocarcinom* OR malign*)):de,ab,ti	**96,726**
	#2	'kidney tumor'/exp	**95,480**
	#3	#1 OR #2	**110,115**
	#4	#3 AND [2009-2014]/py	**39,390**
	#5	#4 AND [animals]/lim	**3,437**

	#6	#4 AND [humans]/lim	**32,898**
	#7	#5 NOT #6	**1,300**
	#8	#4 NOT #7	**38,090**
	#9	'diagnosis'/exp	**4,738,513**
	#10	'diagnosis':lnk	**2,537,324**
	#11	'diagnosis':ab,ti	**1,382,561**
	#12	#9 OR #10 OR #11	**6,087,611**
	#13	#8 AND #12	**18,728**
	#14	'meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review'	**170,185**
	#15	#13 AND #14	**264**
	#16	'echography'/exp	**509,847**
	#17	ultraso*:ab,ti	**329,557**
	#18	echotomograph*:ab,ti	**1,079**
	#19	sonograph*:ab,ti	**55,538**
	#20	echograph*:ab,ti	**13,045**
	#21	#16 OR #17 OR #18 OR #19 OR #20	**671,337**
	#22	#8 AND #21	**2,764**
	#23	#14 AND #22	**27**
	#24	'computer assisted tomography'/exp	**595,330**
	#25	tomograph*:ab,ti	**294,822**
	#26	'ct scan':ab,ti	**56,289**
	#27	'ct scans':ab,ti	**29,665**
	#28	'x-ray ct':ab,ti	**1,635**
	#29	'x-rays ct':ab,ti	**181**
	#30	'x-ray cat':ab,ti	**9**
	#31	'cine-ct':ab,ti	**157**
	#32	tomodensitometr*:ab,ti	**2,303**
	#33	(ct NEAR/2 (volume OR volumic OR cone)):ab,ti	**4,155**

	#34	'cone beam':ab,ti	**5,456**
	#35	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	**699,921**
	#36	#8 AND #35	**5,672**
	#37	#14 AND #36	**55**
	#38	'nuclear magnetic resonance imaging'/exp	**531,116**
	#39	mri:ab,ti	**210,340**
	#40	fmri:ab,ti	**29,751**
	#41	'magnetic resonance imaging':ab,ti	**157,276**
	#42	nmr:ab,ti	**134,995**
	#43	#38 OR #39 OR #40 OR #41 OR #42	**694,660**
	#44	#8 AND #43	**2,719**
	#45	#14 AND #44	**40**
	#46	'scintigraphy'/exp	**28,989**
	#47	scintigraph*:ab,ti	**52,452**
	#48	scintiphotograph*:ab,ti	**305**
	#49	radionuclide AND imaging:ab,ti	**7,972**
	#50	'kidney scintiscanning'/exp	**8,887**
	#51	#46 OR #47 OR #48 OR #49 OR #50	**81,164**
	#52	#8 AND #51	**381**
	#53	#14 AND #52	**11**
	#54	'fluorodeoxyglucose f 18'/exp	**33,019**
	#55	'fluorine 18 fluorodeoxyglucose':ab,ti	**1,200**
	#56	fluorodeoxyglucose:ab,ti	**11,453**
	#57	f18:ab,ti	**877**
	#58	18f*:ab,ti	**9,388**
	#59	#54 OR #55 OR #56 OR #57 OR #58	**40,081**
	#60	'positron emission tomography'/exp	**81,507**
	#61	(pet NEAR/3 scan*):ab,ti	**17,070**

	#62	(positron NEAR/3 (tomograph* OR scan*)):ab,ti	**44,410**
	#63	#60 OR #61 OR #62	**94,574**
	#64	#59 AND #63	**31,216**
	#65	#8 AND #64	**346**
	#66	#14 AND #65	**11**
	#67	'angiography'/exp	**302,390**
	#68	angiograph*:ab,ti	**180,072**
	#69	arteriograph*:ab,ti	**22,165**
	#70	#67 OR #68 OR #69	**353,181**
	#71	#8 AND #70	**454**
	#72	#14 AND #71	**4**
	#73	'succimer tc 99m'/exp	**2,076**
	#74	'technetium tc 99m dimercaptosuccinic acid':ab,ti	**10**
	#75	dmsa:ab,ti	**2,776**
	#76	succimer:ab,ti	**173**
	#77	technetium:ab,ti	**16,744**
	#78	dimercaptosuccinic:ab,ti	**1,811**
	#79	dimercaptosuccinate:ab,ti	**156**
	#80	#73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79	**20,431**
	#81	#8 AND 80	**3,175**
	#82	#14 AND #81	**75**
	#83	'biopsy'/exp	**477,221**
	#84	biopsy:ab,ti	**293,242**
	#85	biopsies:ab,ti	**131,604**
	#86	#83 OR #84 OR #85	**593,382**
	#87	#8 AND #86	**3,665**
	#88	#14 AND #87	**39**
	#89	'fine needle aspiration biopsy'/exp	**30,702**

	#90	(needle* NEAR/3 (aspiration OR biopsy OR cytology)):ab,ti	**44,187**
	#91	#89 OR #90	**57,640**
	#92	#8 AND #91	**653**
	#93	#14 AND #92	**6**
	#94	'carbonate dehydratase ix'/exp	**1,493**
	#95	'carbonic anhydrase':ab,ti	**10,981**
	#96	'carbonic dehydratase':ab,ti	**4**
	#97	#95 OR #96	**10,985**
	#98	'9':ab,ti OR ix:ab,ti OR nine:ab,ti	**2,387,755**
	#99	#97 AND #98	**2,337**
	#100	caix:ab,ti	**616**
	#101	#94 OR #99 OR #100	**2,999**
	#102	#8 AND #101	**405**
	#103	#14 AND #102	**7**
	#104	'vasculotropin'/exp	**65,213**
	#105	vegf*:ab,ti	**60,351**
	#106	'vascular endothelial growth factor':ab,ti	**45,262**
	#107	'vascular endothelial growth factors':ab,ti	**760**
	#108	#104 OR #105 OR #106 OR #107	**88,071**
	#109	#8 AND #108	**2,879**
	#110	#14 AND #109	**86**
	#111	'vasculotropin receptor 2'/exp	**10,234**
	#112	(receptor* NEAR/3 ('vascular permeability factor' OR vegf* OR 'vascular endothelial growth factor' OR 'vascular endothelial growth factors')):ab,ti	**12,918**
	#113	#111 OR #112	**18,293**
	#114	#8 AND #113	**934**
	#115	#14 AND #114	**27**
	#116	'hypoxia inducible factor'/exp	**18,880**

	#117	'hypoxia inducible factor':ab,ti	**11,333**
	#118	hif1:ab,ti OR 'hif 1':ab,ti	**12,703**
	#119	#116 OR #117 OR #118	**21,833**
	#120	#8 AND #119	**919**
	#121	#14 AND #120	**20**
	#122	'ki 67 antigen'/exp	**20,690**
	#123	('mib 1' NEAR/2 (protein OR antigen)):ab,ti	**212**
	#124	ki67:ab,ti OR 'ki 67':ab,ti	**27,366**
	#125	#122 OR #123 OR #124	**34,070**
	#126	#8 AND #125	**358**
	#127	#14 AND #126	**5**
	#128	'protein p53'/exp	**80,807**
	#129	p53:ab,ti	**76,686**
	#130	tp53:ab,ti	**7,881**
	#131	pp53:ab,ti	**53**
	#132	trp53:ab,ti	**616**
	#133	#128 OR #129 OR #130 OR #131 OR #132	**98,152**
	#134	#8 AND #133	**666**
	#135	#14 AND #134	**8**
	#136	'phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase'/exp	**10,435**
	#137	(pten NEAR/3 (phosphatas* OR protein OR proteins OR phosphohydrolas*)):ab,ti	**2,374**
	#138	mmac1:ab,ti OR 'mmac 1':ab,ti	**246**
	#139	#136 OR #137 OR #138	**11,088**
	#140	#8 AND #139	**228**
	#141	#14 AND #140	**4**
	#142	'uvomorulin'/exp	**17,703**
	#143	'e cadherins':ab,ti OR 'e cadherin':ab,ti	**15,338**
	#144	'e cadherin':ab,ti	**15,305**

	#145	'e cadherins':ab,ti	**108**
	#146	#142 OR #143 OR #144 OR #145	**20,061**
	#147	#8 AND #146	**245**
	#148	#14 AND #147	**1**
	#149	'cd44v antigen'/exp	**1,010**
	#150	cd44:ab,ti	**13,264**
	#151	(hyaluron* NEAR/3 (receptor OR receptors OR 'binding protein')):ab,ti	**1,528**
	#152	#149 OR #150 OR #151	**14,414**
	#153	#8 AND #152	**62**
	#154	#14 AND #153	**0**
	#155	'interleukin 6'/exp	**125,204**
	#156	('b cell' NEAR/2 ('differentiation factor' OR 'stimulatory factor' OR 'differentiation factors' OR 'stimulatory factors')):ab,ti	**489**
	#157	((hybridoma* OR plasmacytoma*) NEAR/2 'growth factor'):ab,ti	**96**
	#158	il6:ab,ti	**6,276**
	#159	'il 6':ab,ti	**86,453**
	#160	'interleukin 6':ab,ti	**38,044**
	#161	'mgi 2':ab,ti	**89**
	#162	'ifn-beta 2':ab,ti	**11**
	#163	'bsf-2':ab,ti	**108**
	#164	'hepatocyte-stimulating factor':ab,ti	**101**
	#165	'myeloid differentiation-inducing protein':ab,ti	**6**
	#166	#155 OR #156 OR #157 OR #158 OR #159 OR #160 OR #161 OR #162 OR #163 OR #164 OR #165	**139,771**
	#167	#8 AND #166	**345**
	#168	#14 AND #167	**10**
	#169	'scatter factor'/exp	**11,250**
	#170	'hepatocyte growth factor':ab,ti	**9,039**
	#171	'scatter factor':ab,ti	**1,237**

	#172	hepatopoietin:ab,ti	**60**
	#173	#169 OR #170 OR #171 OR #172	**13,103**
	#174	#8 AND #173	**137**
	#175	#14 AND #174	**6**
Note			

Cochrane Database of Systematic Reviews

Database searched in general search for renal cancer systematic reviews, see specific file.

Date	**2014-05-21**		
Database	**Cochrane Database of Systematic Reviews (CEBAM access)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	***Results***
	#1	MeSH descriptor: [Kidney Neoplasms] explode all trees	**689**
	#2	((kidneys or kidney or renal) near/3 (cancer or cancer* or neoplasm or neoplasm* or tumor or tumour or tumor* or tumour* or sarcom* or oncol* or carcinom* or adenocarcinom* or malign*)):ti,ab,kw	**1312**
	#3	#1 or #2 Publication Date from 2009 to 2014	**461**
Note	**461 results out of which 8 Cochrane reviews and 344 trials**		

2.2.2. Treatment of localized, metastatic or advanced renal cancer and palliative treatment

Project Number	2013-06
Project Name	GCP Renal Cancer
Search question	Treatment
Structured search question (PICO, SPICE, ECLIPSE,...)	
P Patient	Renal cancer (localized, metastatic, advanced or incurable disease)
I Intervention	All surgical, systemic or palliative treatment, ablative techniques, adjuvants treatment, active surveillance, metastasectomy
C Comparison	All
O Outcome	Overall survival, progression free survival, cancer specific survival
S Settings	>=2009

2.2.2.1. Search strategies for systematic reviews and meta-analyses

Medline @ Ovid

Date	**2014-04-25**		
Database	**Medline (OVID)**		
Search Strategy	#	***Query***	***Results***
	1	exp kidney neoplasms/	**57708**
	2	((kidney? or renal) adj3 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or onco* or malign*)).tw.	**48879**
	3	1 or 2	**72137**
	4	limit 3 to systematic reviews	**835**
	5	limit 4 to yr="2009 -Current"	**540**
Note	**The NLM filter for systematic reviews implemented in Ovid has been used.**		

Embase @ Embase.com

Date	**2014-04-25**		
Database	**Embase (Embase.com)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	***Results***
	#1	((kidneys OR kidney OR renal) NEAR/3 (cancer OR cancer* OR neoplasm OR neoplasm* OR tumor OR tumour OR tumor* OR tumour* OR sarcom* OR oncol* OR carcinom* OR adenocarcinom* OR malign*)):de,ab,ti	**93,933**
	#2	'kidney tumor'/exp	**94,758**
	#3	#1 OR #2	**107,327**
	#4	'meta analysis'/exp	**78,484**
	#5	(meta NEAR/2 analy*):de,ab,ti OR metaanalys*:de,ab,ti	**118,280**
	#6	(systematic NEAR/2 (review OR reviews OR overview OR overviews)):de,ab,ti	**104,544**
	#7	#4 OR #5 OR #6	**177,818**
	#8	cancerlit:ab	**632**
	#9	cochrane:ab	**35,287**
	#10	embase:ab	**33,456**
	#11	psychlit:ab OR psyclit:ab	**940**

	#12	psychinfo:ab OR psycinfo:ab	**8,377**
	#13	cinahl:ab OR cinhal:ab	**10,874**
	#14	'science citation index':ab	**2,079**
	#15	bids:ab	**439**
	#16	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	**100,229**
	#17	'reference lists':ab	**9,502**
	#18	bibliograph*:ab	**14,575**
	#19	(hand NEAR/1 search*):ab	**4,501**
	#20	(manual NEAR/1 search*):ab	**2,671**
	#21	'relevant journals':ab	**803**
	#22	#17 OR #18 OR #19 OR #20 OR #21	**28,890**
	#23	'data extraction':ab	**11,628**
	#24	'selection criteria':ab	**19,170**
	#25	#23 OR #24	**29,653**
	#26	review:it	**1,928,870**
	#27	#25 AND #26	**15,777**
	#28	letter:it	**837,305**
	#29	editorial:it	**442,205**
	#30	animal:de	**4,482,596**
	#31	human:de	**14,876,326**
	#32	#30 NOT #31	**3,743,491**
	#33	#28 OR #29 OR #32	**4,999,621**
	#34	#7 OR #16 OR #22 OR #27	**209,078**
	#35	#34 NOT #33	**199,393**
	#36	#3 AND #35	**1,236**
	#37	#36 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)	**822**
Note	**SR filter from SIGN (http://www.sign.ac.uk/methodology/filters.html)**		

Cochrane Database of Systematic Reviews

1	**2014-05-21**		
Database	**Cochrane Database of Systematic Reviews (CEBAM access)**		
Search Strategy (attention, for PubMed, check « Details »)	#	***Query***	***Results***
	#1	MeSH descriptor: [Kidney Neoplasms] explode all trees	**689**
	#2	((kidneys or kidney or renal) near/3 (cancer or cancer* or neoplasm or neoplasm* or tumor or tumour or tumor* or tumour* or sarcom* or oncol* or carcinom* or adenocarcinom* or malign*)):ti,ab,kw	**1312**
	#3	#1 or #2 Publication Date from 2009 to 2014	**461**
Note	**461 results out of which 8 Cochrane reviews and 344 trials**		

2.2.2.2. Search for RCT

Medline @ Ovid

Date	**2014-04-25**		
Database	**Medline (OVID)**		
Search Strategy	#	Query	**Results**
	1	exp kidney neoplasms	**57708**
	2	((kidney or renal) adj3 (neoplasm or cancer or tumor or carcinoma or adenocarcinoma or onco or malign)).tw.	**48879**
	3	1 or 2	**72137**
	4	randomized controlled trial.pt.	**371092**
	5	controlled clinical trial.pt.	**88180**
	6	randomized.ti,ab.	**311561**
	7	placebo.ti,ab.	**157238**
	8	clinical trials as topic	**169424**
	9	randomly.ti,ab.	**211550**
	10	trials.ti.	**46754**
	11	4 or 5 or 6 or 7 or 8 or 9 or 10	**885230**

	12	exp animal not humans	**3925205**
	13	11 not 12	**816177**
	14	3 and 13	**2364**
	15	limit 14 to yr=2009 -Current	**852**
Note	**Which filter for RCT?**		

Embase @ Embase.com

Date	**2014-04-25**		
Database	**Embase (Embase.com)**		
Search Strategy	**#**	**Query**	**Results**
	#1	((kidneys OR kidney OR renal) NEAR/3 (cancer OR cancer* OR neoplasm OR neoplasm* OR tumor OR tumour OR tumor* OR tumour* OR sarcom* OR oncol* OR carcinom* OR adenocarcinom* OR malign*)):de,ab,ti	**93,933**
	#2	'kidney tumor'/exp	**94,758**
	#3	#1 OR #2	**107,327**
	#4	random*:ab,ti OR placebo*:de,ab,ti OR (double NEXT/1 blind*):ab,ti	**1,084,081**
	#5	#3 AND #4	**4,517**
	#6	#5 AND (2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)	**2,772**
Note	**RCT filter used: Wong**		

Cochrane Database of Systematic Reviews

Date	**2014-05-21**		
Database	**Cochrane**		
Search Strategy	**#**	**Query**	**Results**
	#1	MeSH descriptor: [Kidney Neoplasms] explode all trees	**689**
	#2	((kidneys or kidney or renal) near/3 (cancer or cancer* or neoplasm or neoplasm* or tumor or tumour or tumor* or tumour* or sarcom* or oncol* or carcinom* or adenocarcinom* or malign*)):ti,ab,kw	**1312**
	#3	#1 or #2 Publication Date from 2009 to 2014	**461**
Note	**Out of which 344 results in CENTRAL.**		

2.2.3. Long-term outcomes of partial nephrectomy in comparison with radical nephrectomy

PICO

Project Number	2013-06	
Project Name	GCP Renal Cancer	
Search question	Outcomes	
Structured search question (PICO, SPICE, ECLIPSE,...)		And related keywords
P Patient	localized Renal cancer	Renal neoplasms/ AND local*
I Intervention	partial nephrectomy	nephron sparing, partial adj3 nephrectomy
C Comparison	total nephrectomy	(total or complete) adj3 nephrectomy
O Outcome	All	
S Settings	>=2005	limit to yr="2005 - Current"

Medline OvidSP

Date	2015-04-27	
Database	Medline OvidSP	
Search strategy		
1	local*.mp.	1075459
2	noninvasive.mp.	68332
3	"non-invasive".mp.	51654
4	"stage 0".mp.	2065
5	"stage 1".mp.	8060
6	"stage I".mp.	29634
7	"stage 2".mp.	7753
8	"stage II".mp.	19745
9	"stage 3".mp.	6680
10	"stage III".mp.	24560
11	"T1".mp.	71594
12	"T1a".mp.	1164

13	"T2".mp.	55727
14	"T3".mp.	35087
15	"T2a".mp.	800
16	"T2b".mp.	720
17	"T3a".mp.	539
18	"T3b".mp.	417
19	"T3c".mp.	81
20	or/1-19	1345846
21	"nephron sparing".mp.	1583
22	(partial adj3 nephrectom*).mp.	4541
23	((partial or hemi or sparing) adj3 (kidney? or renal or nephron?) adj3 (resection or ablation or excision or surgery or removal)).mp.	1498
24	heminephrectom*.mp.	374
25	21 or 22 or 23 or 24	5977
26	((total or complete or radical or full) adj3 nephrectom*).mp.	5078
27	((total or complete or radical or full) adj3 (kidney? or renal or nephron?) adj3 (resection or ablation or excision or surgery or removal)).mp.	234
28	uninephrectom*.mp.	1635
29	nephroureterectom*.mp.	2082
30	26 or 27 or 28 or 29	8761
31	25 and 30	1811
32	20 and 31	679
33	exp kidney neoplasms/	60194
34	((kidney or renal) adj3 (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or onco* or malign*)).tw.	51760
35	33 or 34	75843
36	32 and 35	644
37	exp animals/ not humans/	4025936
38	36 not 37	643
39	38 not editorial.pt.	642

40	limit 39 to yr="2005 -Current"	446
Notes		

Embase

Date	2015-04-27	
Database	Embase	
Search strategy		
1	local*:ab,ti	1164822
2	noninvasive:ab,ti	83439
3	'non-invasive':ab,ti	79871
4	'stage 0':ab,ti	3787
5	'stage 1':ab,ti	13025
6	'stage i':ab,ti	43212
7	'stage 2':ab,ti	12491
8	'stage ii':ab,ti	29035
9	'stage 3':ab,ti	11201
10	'stage iii':ab,ti	37083
11	't1':ab,ti	72977
12	't1a':ab,ti	1993
13	't2':ab,ti	68714
14	't2a':ab,ti	1509
15	't2b':ab,ti	1222
16	't3':ab,ti	34523
17	't3a':ab,ti	902
18	't3b':ab,ti	688
19	't3c':ab,ti	114
20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	1508860

21	'nephron sparing':ab,ti	2590
22	(partial NEAR/3 nephrectom*):ab,ti	7773
23	((partial OR hemi OR sparing) NEAR/3 (kidney* OR renal OR nephron*) NEAR/3 (resection OR ablation OR excision OR surgery OR removal)):ab,ti	2357
24	heminephrectom*:ab,ti	494
25	#21 OR #22 OR #23 OR #24	9838
26	((total OR complete OR radical OR full) NEAR/3 nephrectom*):ab,ti	7852
27	((total OR complete OR radical OR full) NEAR/3 (kidney* OR renal OR nephron*) NEAR/3 (resection OR ablation OR excision OR surgery OR removal)):ab,ti	357
28	uninephrectom*:ab,ti	1882
29	nephroureterectom*:ab,ti	3109
30	#26 OR #27 OR #28 OR #29	12743
31	#25 AND #30	3209
32	#20 AND #31	1113
33	'kidney tumor'/exp	101821
34	((kidney OR renal) NEAR/3 (neoplasm* OR cancer* OR tumor* OR tumour* OR carcinoma* OR adenocarcinoma* OR onco* OR malign*)):ab,ti	70062
35	#33 OR #34	115261
36	#32 AND #35	1035
37	#36 NOT [medline]/lim	519
Notes		

Cochrane Database of Systematic Reviews

Date	27/04/15 12:51:57.512	
Database	Cochrane Database of Systematic Reviews	
Search strategy		
#1	MeSH descriptor: [Kidney Neoplasms] explode all trees	712
#2	((kidneys or kidney or renal) near/3 (cancer or cancer* or neoplasm or neoplasm* or tumor or tumour or tumor* or tumour* or sarcom* or oncol* or carcinom* or adenocarcinom* or malign*)):ti,ab,kw	1533
#3	#1 or #2	1547
#4	local*:ab,ti	31056
#5	noninvasive:ab,ti	3198
#6	'non-invasive':ab,ti	2941
#7	'stage 0':ab,ti	15440
#8	'stage 1':ab,ti	15980
#9	'stage i':ab,ti	5521
#10	'stage 2':ab,ti	16033
#11	'stage ii':ab,ti	5658
#12	'stage 3':ab,ti	14203
#13	'stage iii':ab,ti	5519
#14	't1':ab,ti	4989
#15	't1a':ab,ti	23
#16	't2':ab,ti	3188
#17	't2a':ab,ti	48
#18	't2b':ab,ti	62
#19	't3':ab,ti	2508
#20	't3a':ab,ti	32
#21	't3b':ab,ti	32
#22	't3c':ab,ti	1
#23	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22	65438

#24	'nephron sparing':ab,ti	19
#25	(partial near/3 nephrectom*):ab,ti	51
#26	((partial or hemi or sparing) near/3 (kidney* or renal or nephron*) near/3 (resection or ablation or excision or surgery or removal)):ab,ti	13
#27	heminephrectom*:ab,ti	0
#28	#24 or #25 or #26 or #27	67
#29	((total or complete or radical or full) near/3 nephrectom*):ab,ti	97
#30	((total or complete or radical or full) near/3 (kidney* or renal or nephron*) near/3 (resection or ablation or excision or surgery or removal)):ab,ti	12
#31	uninephrectom*:ab,ti	4
#32	nephroureterectom*:ab,ti	18
#33	#29 or #30 or #31 or #32	121
#34	#3 and #23	254
#35	#28 and #33	20
#36	#35 and #34	8
#37	#28 or #33	168
#38	#34 and #37	53
Notes		

3. QUALITY APPRAISAL

3.1. Quality appraisal tool for guidelines

Table 3 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

3.2. Guidelines selection and quality appraisal

The screening of the **guidelines** was performed on title and abstract by one researcher (NB). Six potentially relevant guidelines were selected (Table 4). From those, 4 included guidelines were retained and their quality were appraised with the AGREE II instrument by two researchers (NB and JR) (Table 5).

Table 4 – Critical appraisal of clinical practice guidelines

Source	Year	Title	Final appraisal
European Association of Urology (EAU)[1]	2014	Guidelines on Renal Cell carcinoma	Recommended
NICE[2]	2013	IPG443 Irreversible electroporation (IRE) for treating renal cancer: guidance	Rapid review excluded
American Urological Association (AUA)[3]	2013	Follow-up for clinically localized renal neoplasms: AUA Guideline	Recommended
Integraal Kankercentrum Nederland (IKNL)[4]	2010	Renal cell carcinoma	Recommended
American College of Radiology (AHRQ)[5]	2009	Interferon-alfa in the treatment of patients with inoperable locally advanced metastatic renal cell cancer: guideline recommendations. Program in Evidence-based Care	Excluded duplicate with Cancer Care Ontario
Cancer Care Ontario[6]	2009	The use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic renal cell cancer: guideline recommendations.	Recommended

Table 5 – AGREE scores of included guidelines

Source	Title	Standardised Score (%)					
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence
IKNL 2010[4]	Renal cell carcinoma	94.4	80.6	94.8	100	58.3	75.0
EAU 2014[1]	Guidelines on Renal Cell carcinoma	88.9	61.1	6.3	88.5	62.5	100
AUA 2013[3]	Follow up for clinically localized renal neoplasms	94.4	50.0	87.5	66.7	0.0	33.3
Cancer Care Ontario 2009[6]	The use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic renal cell cancer: guideline recommendations.	57.4	66.7	90.6	97.2	8.3	100

3.3. Quality appraisal tool for systematic reviews

Table 6 – AMSTAR checklist

1. Was an 'a priori' design provided?	Yes / No / Unclear / Not applicable
2. Was there duplicate study selection and data extraction?	Yes / No / Unclear / Not applicable
3. Was a comprehensive literature search performed?	Yes / No / Unclear / Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes / No / Unclear / Not applicable
5. Was a list of studies (included and excluded) provided?	Yes / No / Unclear / Not applicable
6. Were the characteristics of the included studies provided?	Yes / No / Unclear / Not applicable
7. Was the scientific quality of the included studies assessed and documented?	Yes / No / Unclear / Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes / No / Unclear / Not applicable
9. Were the methods used to combine the findings of studies appropriate?	Yes / No / Unclear / Not applicable
10. Was the likelihood of publication bias assessed?	Yes / No / Unclear / Not applicable
11. Was the conflict of interest included?	Yes / No / Unclear / Not applicable

3.5. Quality appraisal for diagnostic studies (QUADAS 2 tool)

Table 7 – QUADAS 2 tool

DOMAIN	PATIENT SELECTION	INDEX TEST
Description	Patients with suspicion of recurrence tested	All enrolled patients received test
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?
	Did the study avoid inappropriate exclusions?	
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN	REFERENCE STANDARD	FLOW AND TIMING
Description	Histology of secondary lesions (available in 10 patients) or the sum of clinical and all radiological data available (CECT, MRI, US).	timing variable
Signalling questions (yes/no/unclear)	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
		Did all patients receive the same reference standard?
		Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

3.6. Study selection and quality appraisal

3.6.1. Diagnosis and follow-up

3.6.1.1. Selection of systematic reviews and primary studies

Figure 1 – PRISMA flowchart: Diagnosis and follow up – systematic reviews and meta-analysis

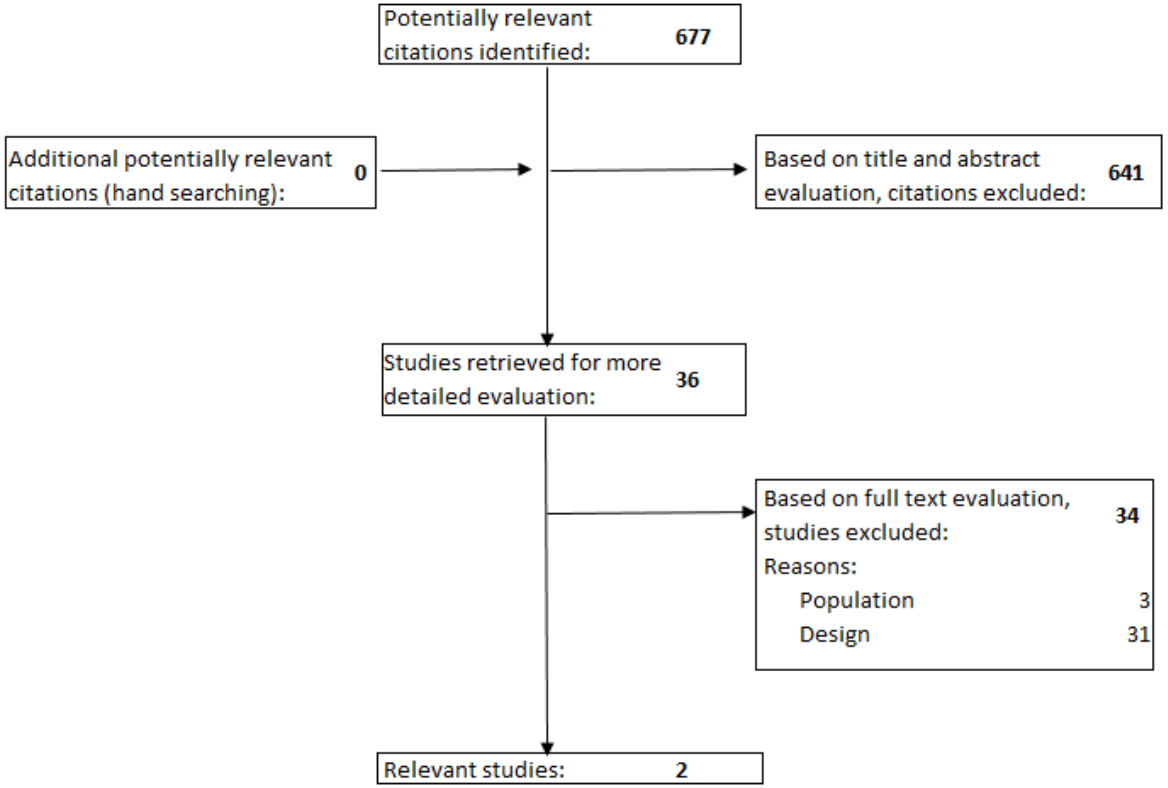


Figure 2 – PRISMA flowchart: Diagnosis and follow up (FDG PET update) – primary studies

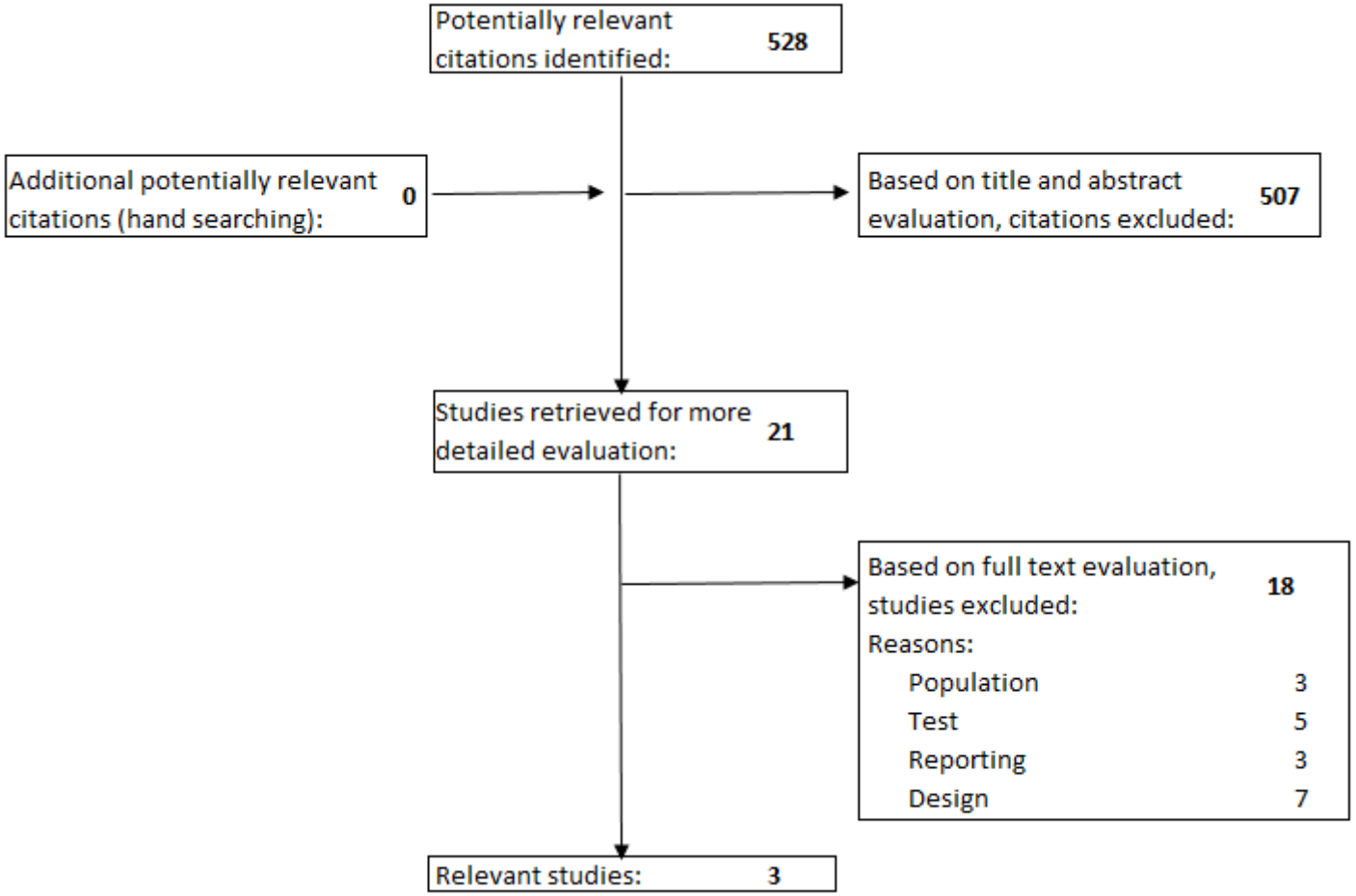
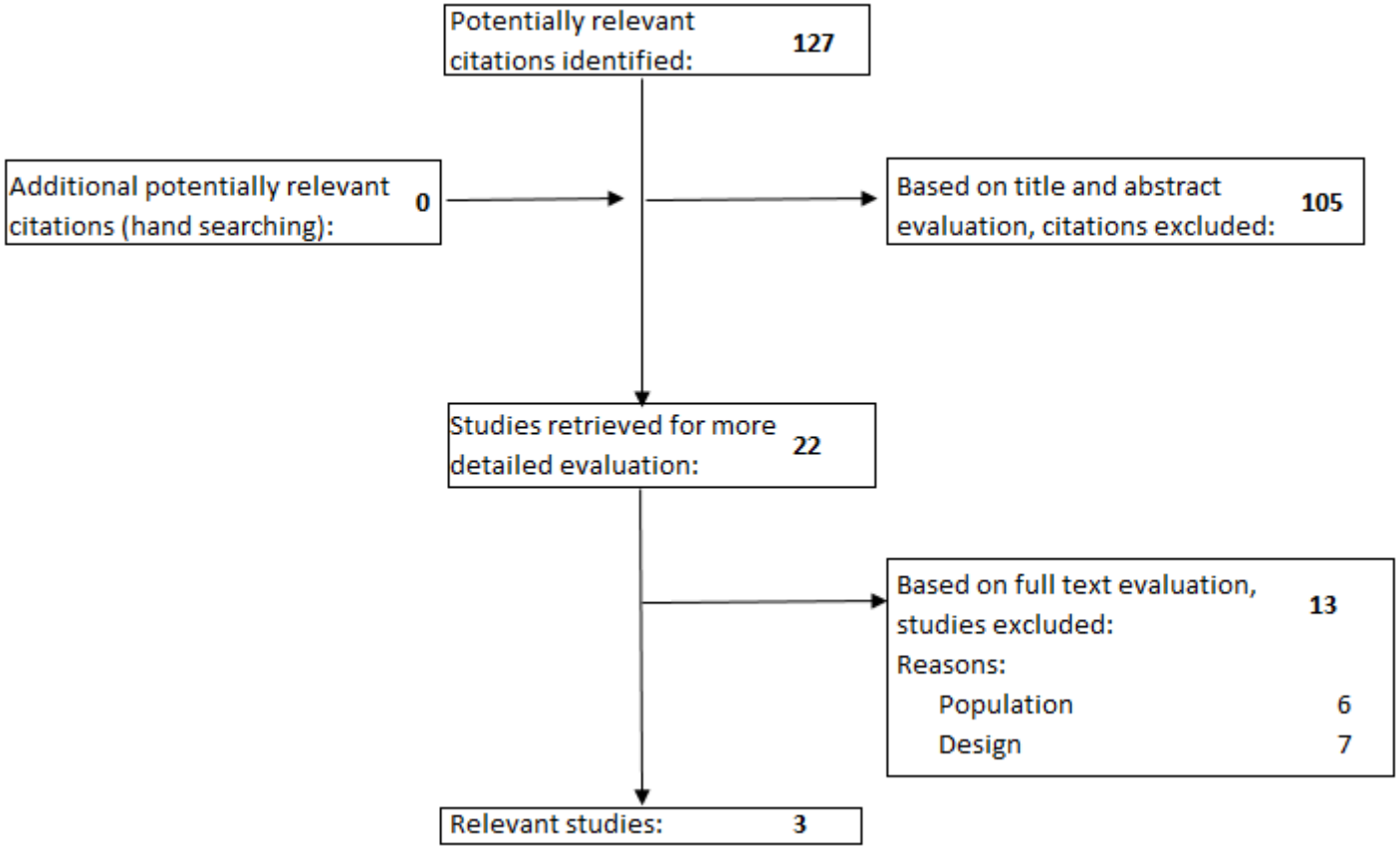


Figure 3 – PRISMA flowchart: Diagnosis and follow up (Nomograms/prognostic systems update) – primary studies



3.6.1.2. Quality appraisal of selected systematic reviews

Table 8 – AMSTAR - Prognostic factors and predictive models in renal cell carcinoma: a contemporary review[7]

1. Was an 'a priori' design provided?	No
2. Was there duplicate study selection and data extraction?	No
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes
5. Was a list of studies (included and excluded) provided?	No
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Unclear
9. Were the methods used to combine the findings of studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	Non applicable
11. Was the conflict of interest included?	No

Table 9 – AMSTAR - Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma[8]

1. Was an 'a priori' design provided?	Yes
2. Was there duplicate study selection and data extraction?	No
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Yes
5. Was a list of studies (included and excluded) provided?	No
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes
10. Was the likelihood of publication bias assessed?	Non applicable
11. Was the conflict of interest included?	No

Table 10 – AMSTAR - A systematic review of predictive and prognostic biomarkers for VEGF-targeted therapy in renal cell carcinoma[9]

1. Was an 'a priori' design provided?	Yes
2. Was there duplicate study selection and data extraction?	No
3. Was a comprehensive literature search performed?	Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Unclear
5. Was a list of studies (included and excluded) provided?	No
6. Were the characteristics of the included studies provided?	Yes
7. Was the scientific quality of the included studies assessed and documented?	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
9. Were the methods used to combine the findings of studies appropriate?	Non applicable
10. Was the likelihood of publication bias assessed?	Non applicable
11. Was the conflict of interest included?	No

3.6.1.3. Quality appraisal of studies on PET CT (update) - QUADAS

Table 11 – QUADRAS – PET CT (update)

Bretagna et al.[10]

DOMAIN	PATIENT SELECTION		INDEX TEST	
Description	Patients with suspicion of recurrence tested		All enrolled patients received test	
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Unclear	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Was a case-control design avoided?	Yes	If a threshold was used, was it pre-specified?	NA
	Did the study avoid inappropriate exclusions?	Unclear		
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Unclear	Could the conduct or interpretation of the index test have introduced bias?	Low
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	No	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	No

DOMAIN	REFERENCE STANDARD		FLOW AND TIMING	
Description	Histology of secondary lesions (available in 10 patients) or the sum of clinical and all radiological data available (CECT, MRI, US).		timing variable	
Signalling questions(yes/no/unclear)	Is the reference standard likely to correctly classify the target condition?	No	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	Did all patients receive a reference standard?	No
			Did all patients receive the same reference standard?	No
			Were all patients included in the analysis?	Yes
Risk of bias: High/low/unclear	Could the reference standard, its conduct, or its interpretation have introduced bias?	High	Could the patient flow have introduced bias?	Unclear
Concerns regarding applicability: High/low/unclear	Are there concerns that the target condition as defined by the reference standard does not match the review question?	No		

Fuccio et al. [11]

DOMAIN	PATIENT SELECTION		INDEX TEST	
Description	whole-body F-FDG PET/CT to restage the disease after nephrectomy for clinical or radiological suspicion of metastases.		All enrolled patients received test	
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Unclear	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
	Was a case-control design avoided?	Yes	If a threshold was used, was it pre-specified?	NA
	Did the study avoid inappropriate exclusions?	Unclear		
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Unclear	Could the conduct or interpretation of the index test have introduced bias?	Low
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	No	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	No

DOMAIN	REFERENCE STANDARD		FLOW AND TIMING	
Description	Clinical/imaging follow up (minimum-6 months) with histopathology (when available) were taken as reference standard		timing variable because of follow up	
Signalling questions(yes/no/unclear)	Is the reference standard likely to correctly classify the target condition?	Unclear	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	Did all patients receive a reference standard?	No
			Did all patients receive the same reference standard?	No
			Were all patients included in the analysis?	Yes
Risk of bias: High/low/unclear	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear	Could the patient flow have introduced bias?	High
Concerns regarding applicability: High/low/unclear	Are there concerns that the target condition as defined by the reference standard does not match the review question?	No		

Mishra et al.[12]

DOMAIN	PATIENT SELECTION		INDEX TEST	
Description	patients with renal cell carcinoma (RCC) for detection of recurrence, either when suspected clinically/ on imaging and during routine follows up		All enrolled patients received test	
Signalling questions(yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Unclear	Were the index test results interpreted without knowledge of the results of the reference standard?	No
	Was a case-control design avoided?	Yes	If a threshold was used, was it pre-specified?	NA
	Did the study avoid inappropriate exclusions?	Unclear		

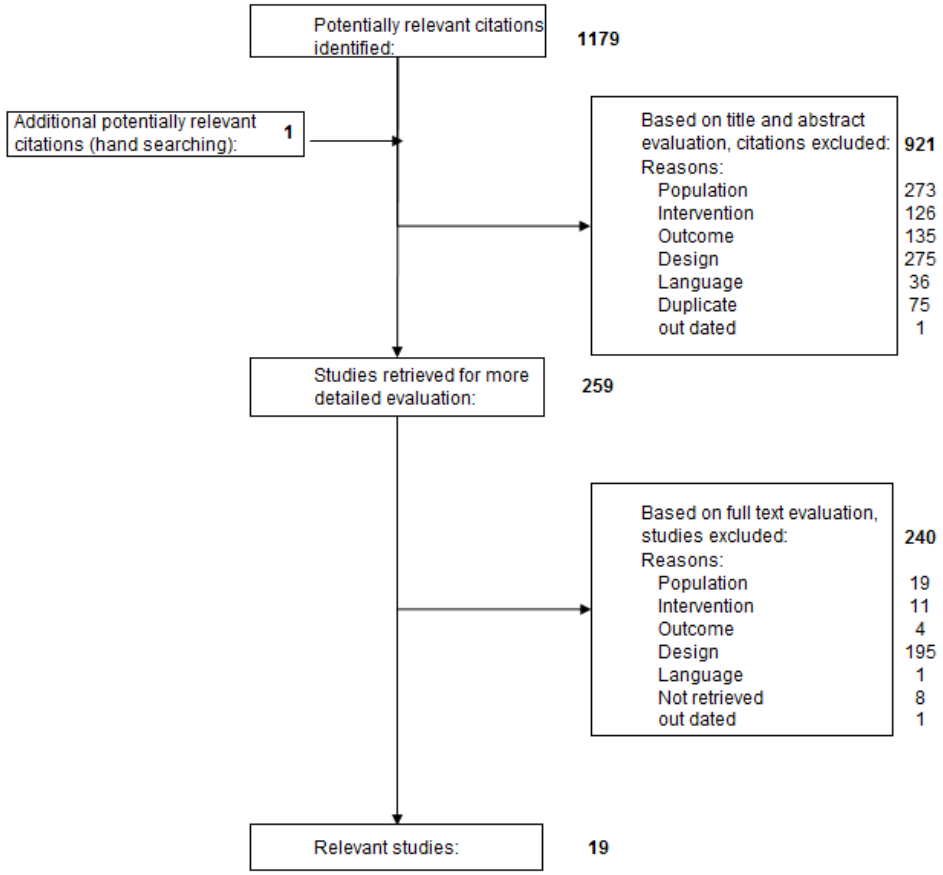
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Unclear	Could the conduct or interpretation of the index test have introduced bias?	Low
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	No	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	No

DOMAIN	REFERENCE STANDARD		FLOW AND TIMING	
Description	Histology of secondary lesions (available in 10 patients) or the sum of clinical and all radiological data available (CECT, MRI, US).		timing variable	
Signalling questions(yes/no/unclear)	Is the reference standard likely to correctly classify the target condition?	No	Was there an appropriate interval between index test(s) and reference standard?	Unclear
	Were the reference standard results interpreted without knowledge of the results of the index test?	No	Did all patients receive a reference standard?	No
			Did all patients receive the same reference standard?	No
			Were all patients included in the analysis?	Yes
Risk of bias: High/low/unclear	Could the reference standard, its conduct, or its interpretation have introduced bias?	High	Could the patient flow have introduced bias?	Unclear
Concerns regarding applicability: High/low/unclear	Are there concerns that the target condition as defined by the reference standard does not match the review question?	No		

3.6.2. Treatments

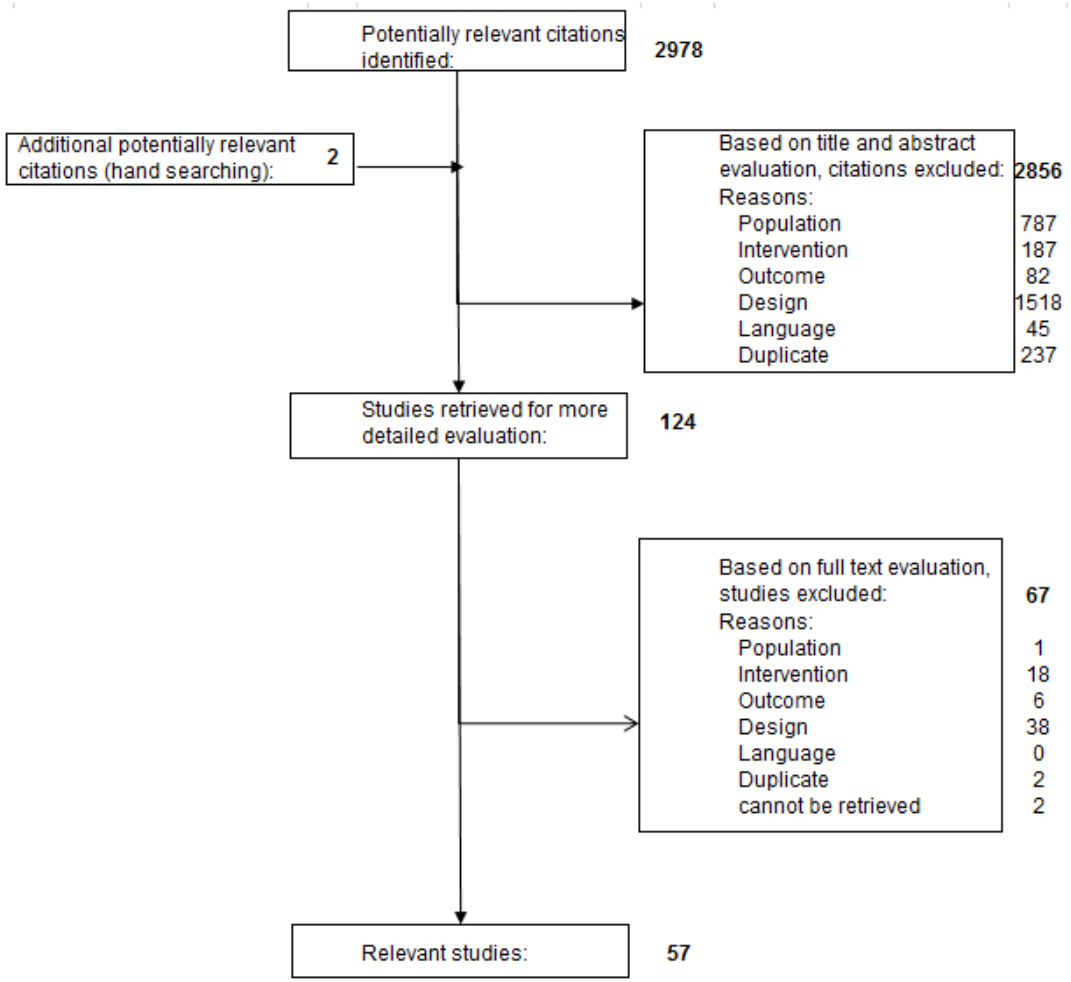
3.6.2.1. Selection of systematic reviews and meta-analyses

Figure 4 – PRISMA flowchart: Treatment – systematic review and meta-analysis



3.6.2.2. Selection of RCTs

Figure 5 – PRISMA flowchart: Treatment – RCTs



From the 57 papers retrieved, 26 articles were original manuscripts and 31 publications described outcomes from 9 original RCTs. Finally, the quality appraisal of the evidence was done for the 35 primary RCTs.

3.6.2.3. Quality appraisal of systematic reviews and RCTs

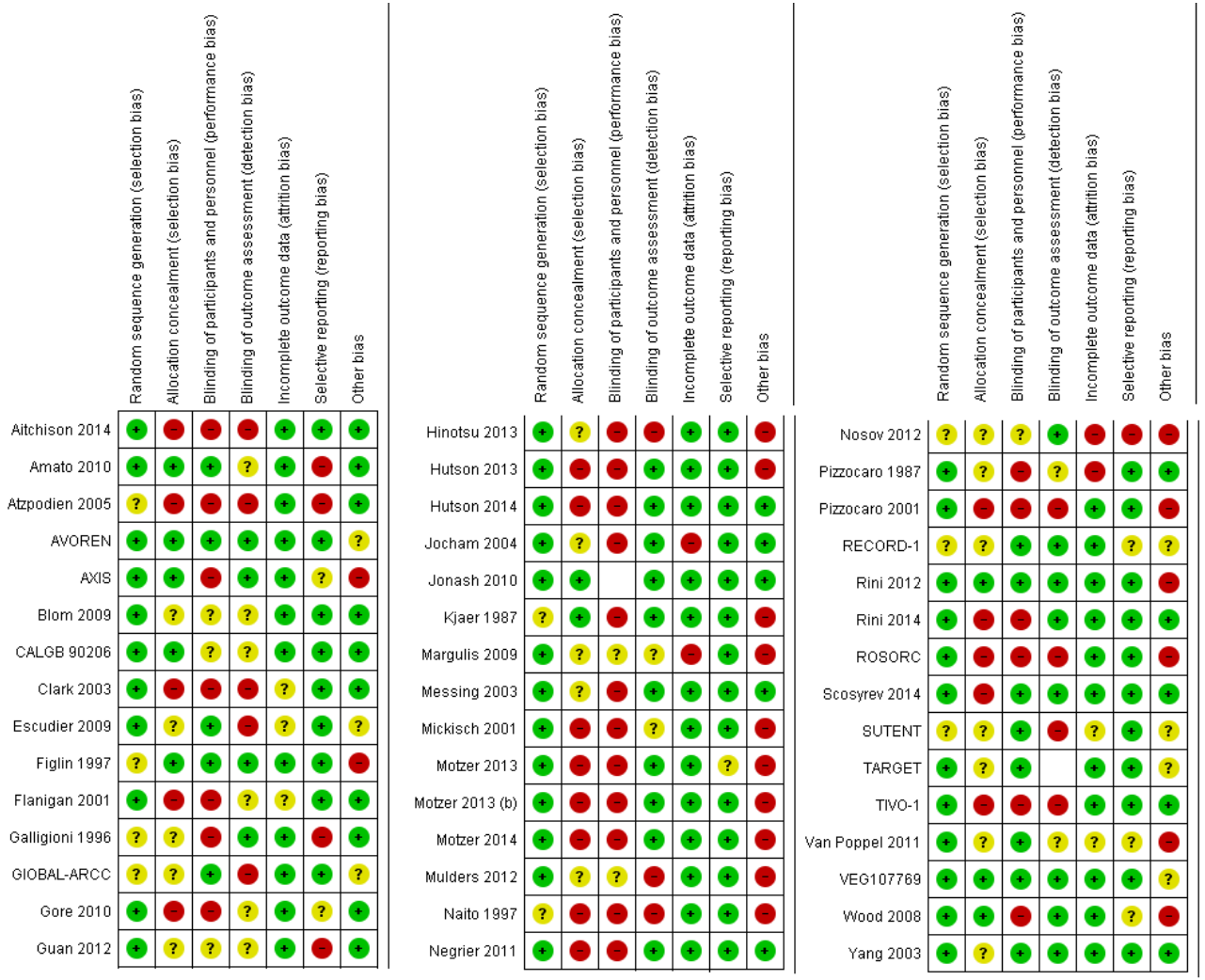
Table 12 shows the results of the risk of bias assessment for the included systematic reviews, using AMSTAR criteria.

Table 12 – AMSTAR - Quality appraisal of the included systematic reviews

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and exclude d studies	Charac-teristics of included studies provided	Study quality assessed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihoo d of publica-tion bias assessed	Conflict of interest stated	Global evalua-tion
Coppin 2006 [13]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included
Coppin 2010[14]	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Included
Froghi 2013[15]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Included
Katsanos 2014 [16]	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Included as a source of RCT
Kim 2012[17]	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Included
Klatte 2014 [18]	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Included
McLennan 2012[19]	Y	Can't answer	Y	Y	N	Y	Y	Y	Y	Y	N	Included
McLennan 2012[20]	Y	Can't answer	Y	Y	N	Y	Y	Y	Y	Y	N	Included
Ren 2014[21]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Included
Su 2012[22]	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	Included
Tang 2013[23]	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Included
Zheng 2013[24]	Y	Y	Y	Y	N	Y	Y	Y	Y	Can't answer	N	Included

Rem: No quality appraisal was performed for 7 SR[14, 25-30] because they did not retrieve additional RCTs in comparison with Coppin 2010[14]. Bekema 2013[31] included only 1 RCT, the quality appraisal was done for this RCT (Blom 2009).[32]

Figure 6 – Risk of bias summary of RCTs - treatment

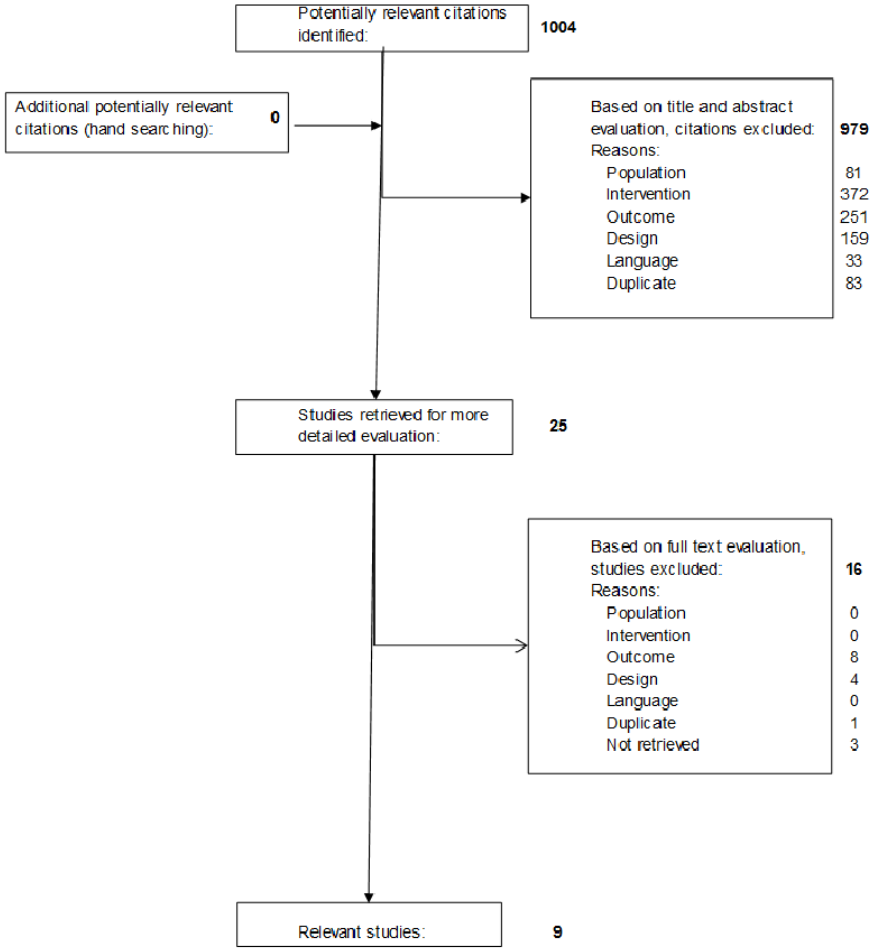


Note: A quality appraisal was performed for 35 retrieved RCTs and for 12 additional studies retrieved from guidelines.

3.6.3. Evaluation of long term outcomes of partial nephrectomy in comparison with radical nephrectomy

3.6.3.1. Selection of primary studies

Figure 7 – PRISMA flowchart: Long-term outcomes of partial nephrectomy in comparison with radical nephrectomy



3.6.3.2. Quality appraisal of primary studies

Cohort studies

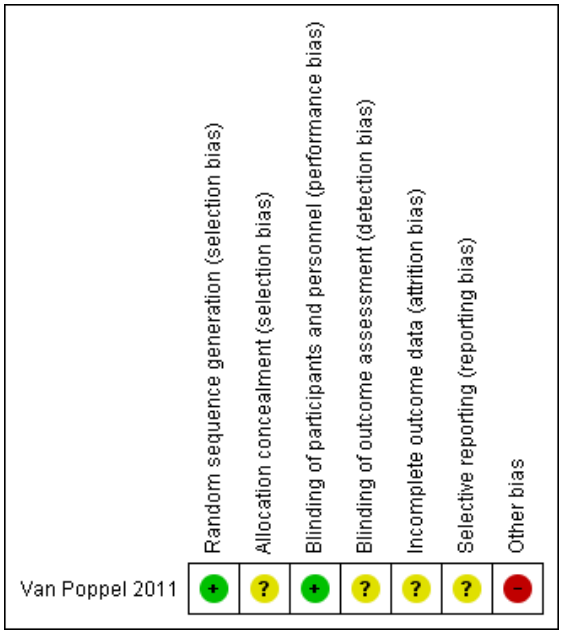
Table 13 – Quality appraisal of cohort studies - Long-term outcomes of partial nephrectomy in comparison with radical nephrectomy

Question	Antonelli 2011	Becker 2006	Capitanio 2015	Daugherty 2014	Roos 2014	Stewart 2014	Tan 2012	Zini 2009
SELECTION BIAS								
1. Can selection bias sufficiently be excluded?	No	No	No	II	No	No	No	Yes
2. Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis?	Yes	No	No	No	No	Yes	No	Yes
DETECTION BIAS								
3. Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups?	II	II	Yes	Yes	Yes	Yes	Yes	No
4. Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
5. Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	NA	Yes	NA	NA	Yes	NA	NA
6a. Is the assessment of outcome made blind to exposure status?	No	No	No	No	No	No	No	No
6b. If no, does this has an influence on the assessment of outcome?	No	No	No	No	No	No	No	No
7. Is the follow-up sufficiently long to measure all relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ATTRITION BIAS								
8. Can selective loss-to-follow-up be sufficiently excluded?	Yes	II	Yes	II	II	II	II	II

NA: non aprropriate, II: Insuffisant Information

RCT

Figure 8 – Risk of bias summary of RCTs - Long-term outcomes of partial nephrectomy in comparison with radical nephrectomy



4. EVIDENCE TABLES

4.1. Guidelines

Note: Evidence tables accurately reflect the guidelines. Therefore, the sentences used in evidence tables were copy-pasted from the original texts.

Information for the reader:

- **Methodological information regarding AUA guideline**

  The level of evidence was assigned a rating of A (high), B (moderate) or C (low). When grade A or B evidence is available, a standard statement is formulated while a recommendation is formulated when grade C evidence is available on a specific topic. An option is formulated when evidence leaves the decision to the individual clinician. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinion (for more information see table below).

Table 14 – AUA nomenclature linking statement type of evidence strength

Statement type of evidence strength
Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence.
Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence.
Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence.
Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature.
Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

- **Methodological information regarding EAU guideline**
  Level of evidence is graded from 1 to 4 as shown in the following table:

Table 15 – EAU nomenclature for level of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials.
1b	Evidence obtained from at least one randomised trial.
2a	Evidence obtained from one well-designed controlled study without randomisation.
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study.
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports.
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities.

The grading of recommendation was done according the following rules:

Table 16 – EAU nomenclature for the grading of recommendations

Grade	Nature of recommendation
A	Based on clinical studies of good quality and consistency that addressed the specific recommendations, including at least one randomised trial.
B	Based on well-conducted clinical studies, but without randomised clinical trials.
C	Made despite the absence of directly applicable clinical studies of good quality.

- **Methodological information regarding IKNL guideline**

Level of evidence is structured differently according the nature of evidence (see table below)

Table 17 – IKNL nomenclature for level of evidence

Level of evidence for conclusions based on the evidence underlying the conclusions	
Level of evidence	**Conclusion based on**
1	1 systematic review (A1) or at least 2 independently conducted A1- or A2-level studies
2	At least 2 independently conducted B-level studies
3	At least 1 A2-, B-, or C-level study
4	Expert opinion from, for example, working group members
Intervention studies (prevention or therapy)	
Level of evidence	**Conclusion based on**
A1	Systematic reviews covering at least some A2-level studies in which the results of the individual studies are consistent
A2	Randomized comparative clinical studies of good quality (randomized, double blind) and sufficient size and consistency
B	Randomized clinical trials of moderate quality or insufficient size, or other comparative studies (non-randomized, comparative cohort studies, patient-control studies)
C	Non-comparative studies
D	Expert opinion from, for example, working group members
For articles regarding diagnosis	
Level of evidence	**Conclusion based on**
A1	Studies on the effects of diagnosis on clinical outcomes in a prospectively followed, well defined patient population with a predefined protocol based on the results of the study test, or decision theory studies on the effects of diagnosis on clinical outcomes based on the results of A2-level studies with sufficient consideration given the interaction between diagnostic tests.
A2	Studies that include a reference test with predefined criteria for the study test and the reference test and a good description of the test and the clinical population studied; a sufficiently large series of consecutive patients must be included, predefined cut-off values must be used and the results of the test and the gold standard must be evaluated independently. For situations in which multiple diagnostic tests are involved, there is in principle interaction and the analysis should take this into account by using, for example, logistical regression.
B	Comparison with a reference test and description of the study test and population, but lacking the other characteristics of A-level studies
C	Non-comparative studies
D	Expert opinion from, for example, working group members

The grading of recommendation was done according the following rules:

Table 18 – IKNL nomenclature for the grading of recommendations

Conclusion on level of evidence	Remaining considerations	Type of recommendation
1 or 2 **High level of evidence**	Strengthened conclusion or is neutral	Strong recommendation
1 or 2 **High level of evidence**	Weakened conclusion	Recommendation
3 or 4 **Low level of evidence**	Strengthened conclusion or is neutral	Recommendation
3 or 4 **Low level of evidence**	Weakened conclusion	No recommendation

4.1.1. Diagnosis and follow up

Table 19 – Evidence table: Guidelines – General consideration

Reference	Search date	Recommendations/conclusions	Level of evidence
AUA 2013[3]		1. Patients undergoing follow-up for treated or observed renal masses should undergo a history and physical examination directed at detecting signs and symptoms of metastatic spread or local recurrence. (*Clinical Principle*)	
		2. Patients undergoing follow-up for treated or observed renal masses should undergo basic laboratory testing to include blood urea nitrogen (BUN)/creatinine, urine analysis (UA) and estimated glomerular filtration rate (eGFR). Other laboratory evaluations, including complete blood count (CBC), lactate dehydrogenase (LDH), liver function tests (LFTs), alkaline phosphatase (ALP) and calcium level, may be used at the discretion of the clinician. (*Expert Opinion*)	
		3. Patients with progressive renal insufficiency on follow-up laboratory evaluation should be referred to nephrology. (*Expert Opinion*)	
		4. The Panel recommends a bone scan in patients with an elevated alkaline phosphatase (ALP), clinical symptoms such as bone pain, and/or if radiographic findings are suggestive of a bony neoplasm. (*Recommendation*)	Grade C

	5. The Panel recommends against the performance of a bone scan in the absence of an elevated alkaline phosphatase (ALP) or clinical symptoms, such as bone pain, or radiographic findings suggestive of a bony neoplasm. (*Recommendation*)	Grade C
	6. Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo prompt neurologic cross-sectional CT or MRI scanning of the head or spine based on localization of symptomatology. (*Standard*)	Grade A
	7. The Panel recommends against the routine use of molecular markers, such Ki-67, p-53 and VEGF, as benefits remain unproven at this time. (*Recommendation*)	Grade C
	Surgery: Low risk patients (pT1, N0, Nx):	
	8. Patients should undergo a baseline abdominal scan (CT or MRI) for nephron sparing surgery and abdominal imaging (US, CT or MRI) for radical nephrectomy within three to twelve months following renal surgery. (*Expert Opinion*)	
	9. Additional abdominal imaging (US, CT or MRI) may be performed in patients with low risk (pT1, N0, Nx) disease following a radical nephrectomy if the initial postoperative baseline image is negative. (*Option*)	Grade C
	10. Abdominal imaging (US, CT, or MRI) may be performed yearly for three years in patients with low risk (pT1, N0, Nx) disease following a partial nephrectomy based on individual risk factors if the initial postoperative scan is negative. (Option)	Grade C
	11. The Panel recommends that patients with a history of low risk (pT1, N0, Nx) renal cell carcinoma undergo yearly chest x-ray (CXR) to assess for pulmonary metastases for three years and only as clinically indicated beyond that time period. (*Recommendation*)	Grade C
	Surgery: Moderate to High Risk Patients (pT2-4N0 Nx or any stage N+):	
	12. The Panel recommends that moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (US, CXR, CT or MRI) every six months for at least three years and annually thereafter to year five. (*Recommendation*)	Grade C
	13. The Panel recommends site-specific imaging as warranted by clinical symptoms suggestive of recurrence or metastatic spread. (Recommendation)	Grade C
	14. Imaging (US, CXR, CT or MRI) beyond five years may be performed at the discretion of the clinician for moderate to high risk patients. (*Option*)	Grade C
	15. Routine FDG-PET scan is not indicated in the follow-up for renal cancer. (*Expert Opinion*)	
	Active Surveillance	

16. Percutaneous biopsy may be considered in patients planning to undergo active surveillance. (*Option*)	Grade C
17. The Panel recommends that patients undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. The Panel further recommends continued imaging (US, CT or MRI) at least annually thereafter. (*Recommendation*)	Grade C
18. The Panel recommends that patients on active surveillance with biopsy proven renal cell carcinoma or a tumor with oncocytic features undergo an annual chest x-ray (CXR) to assess for pulmonary metastases. (*Recommendation*)	Grade C
Ablation	
19. An urologist should be involved in the clinical management of all patients undergoing renal ablative procedures including percutaneous ablation. (*Expert Opinion*)	
20. The Panel recommends that all patients undergoing ablation procedures for a renal mass undergo a pretreatment diagnostic biopsy. (*Recommendation*)	Grade C
21. The standardized definition of “treatment failure or local recurrence” suggested in the Clinical T1 Guideline document should be adopted by clinicians. This should be further clarified to include a visually enlarging neoplasm or new nodularity in the same area of treatment whether determined by enhancement of the neoplasm on post-treatment contrast imaging, or failure of regression in size of the treated lesion over time, new satellite or port site soft tissue nodules, or biopsy proven recurrence. (*Clinical Principle*)	
22. The Panel recommends that patients undergo cross-sectional scanning (CT or MRI) with and without intravenous (IV) contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years. (*Recommendation*)	Grade C
23. Patients may undergo further scanning (CT or MRI) beyond five years based on individual patient risk factors. (*Option*)	Grade C
24. Patients undergoing ablative procedures who have either biopsy proven low risk renal cell carcinoma, oncocytoma, a tumor with oncocytic features, nondiagnostic biopsies or no prior biopsy, should undergo annual chest x-ray (CXR) to assess for pulmonary metastases for five years. Imaging beyond five years is optional based on individual patient risk factors and the determination of treatment success. (*Expert Opinion*)	

		25. The Panel recommends against further radiologic scanning in patients who underwent an ablative procedure with pathological confirmation of benign histology at or before treatment and who have radiographic confirmation of treatment success and no evidence of treatment related complications requiring further imaging. (*Recommendation*)	
		26. The alternatives of observation, repeat treatment and surgical intervention should be discussed, and repeat biopsy should be performed if there is radiographic evidence of treatment failure within six months if the patient is a treatment candidate. (*Expert Opinion*)	Grade C
		27. A progressive increase in size of an ablated neoplasm, with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress in size over time, satellite or port side lesions, should prompt lesion biopsy. (*Expert Opinion*)	
EAU 2014[1]	2013	Contrast-enhanced multi-phasic abdominal CT and MRI are recommended for the work-up of patients with RCC and are considered equal both for staging and diagnosis.	B
		Contrast-enhanced multi-phasic abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterization and staging prior to surgery.	C
		A chest CT is recommended for staging assessment of the lungs and mediastinum.	C
		Bone scan is not routinely recommended.	C
		Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.	C
		Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	C
		Percutaneous renal tumour biopsy should be obtained with a coaxial technique.	C
		The use of the current TNM classification system is recommended.	B
		We recommend that grading systems and classification of RCC subtype should be used.	B
		We recommend that prognostic systems are used in the metastatic setting.	B
		In localised disease, the use of integrated prognostic systems or nomograms is not routinely recommended, even though these systems can provide a rationale for enrolling patients into clinical trials.	C
		No molecular prognostic marker is currently recommended for routine clinical use.	C
IKNL 2010[4]	2009	Routine work-up for staging of renal cell carcinoma includes a multiphase contrast CT (unenhanced, arterial phase, venous phase) and a chest x-ray. Ultrasound is also	

	possible, but the results are dependent on the device and the weight and girth of the patient. Chest x-rays should be used to screen for metastases. Patients who are suspected of having metastases and/or have some evidence of metastases should undergo a CT scan. Patients with neurological symptoms suspected of having brain metastases should undergo a CT scan with contrast or, preferably, a MRI of the brain. MRI of the brain is also preferable for patients who are allergic to contrast media.	
	Skeletal scintigraphy for the detection of bone metastases is not a routine part of the initial staging of patients with renal cell carcinoma. 18F-FDG PET is not a standard part of the primary staging of renal cell carcinoma.	

4.1.2. Treatment

4.1.2.1. Treatment of localized renal cancer

4.1.2.1.1. Surgery

General consideration

Table 20 – Evidence table: Guidelines Surgery – General consideration

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Recommendation:** Surgery is recommended to achieve cure in localized RCC		B

Radical nephrectomy

Table 21 – Evidence table: Guidelines Surgery – Radical nephrectomy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
Radical nephrectomy				
IKNL 2010[4]	2009	**Conclusions:** The radical (transperitoneal) nephrectomy as described by Robson, including lymphadenectomy and adrenalectomy, appears to no longer be the gold standard for the treatment of small tumours (< 7 cm).	1 guideline	Level 3
		There is evidence that the laparoscopic approach is preferred over open radical nephrectomy for localised tumours.	2 Comparative studies	Level 3
		Consideration: A standard approach to radical tumour nephrectomy has not been established. Laparotomy is preferred for large tumours, while lumbotomy is a good alternative for small tumours (< 7 cm). The laparoscopic approach is increasingly replacing open surgery. Regarding the method of approach or incision for open surgery, no specific preference or definitive choice can be ascertained from the scant literature available. For very large renal cell carcinomas, the transperitoneal approach is usually the most obvious choice. The urologist may choose between midline laparotomy, subcostal access (Chevron's incision), or lumbolaparotomy. However, thoracofrenolaparotomy is the preferred approach for very extensive disease with possible tumour thrombus in the inferior vena cava. As a rule, partial nephrectomy is performed via lumbotomy. It may be generally said that, in addition to the extent of the tumour, the preference and experience of the urologist can determine they choice of incision.		
		Recommendation: The working group is of the opinion that radical nephrectomy, as described by Robson, is no longer the gold standard for the treatment of small (< 7 cm) renal cell carcinomas.		Expert opinion

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		The choice between a transperitoneal and extraperitoneal (translumbar) radical nephrectomy is determined largely by the extent and size of the tumour, as well as the preference and experience of the urologist.		
Laparoscopic radical nephrectomy				
EAU 2014[1]	2013	**Conclusions:**		
		Laparoscopic radical nephrectomy has lower morbidity compared to open surgery.	2 meta-analyse 4 RCTs 20 comparative studies	1b
		Oncological outcomes for T1-T2a tumours are equivalent between laparoscopic and open radical nephrectomy.		2a
		Recommendations:		
		Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.		B
		Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.		A
IKNL 2010[4]	2009	**Conclusions:**		
		Laparoscopic radical nephrectomy is associated with less morbidity than open surgical nephrectomy.	2 case series 7 comparative studies	Level 2
		With sufficient expertise, laparoscopic radical nephrectomy is as effective as open surgical nephrectomy for localised tumours (T1 and T2), and possibly T3 tumours.		Level 2
		Considerations:		
		Given the limited expertise with laparoscopic tumour nephrectomy in the Netherlands at this time, this less invasive approach is preferably performed in a specialised treatment centre. The use of laparoscopic nephrectomy should be		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		promoted in the Netherlands, so that more patients may be treated with a lower risk of morbidity.		
		Recommendations: Laparoscopic nephrectomy is recommended for T1, T2, and possibly T3 tumours. Preferably, this less invasive approach is performed in a specialised treatment centre.		

Partial nephrectomy

Table 22 – Evidence table: Guidelines Surgery – Partial nephrectomy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
Radical nephrectomy versus partial nephrectomy				
EAU 2014[1]	2013	**Conclusion:**		
		Partial nephrectomy achieves similar oncological outcomes of radical nephrectomy for clinically localized renal tumours (cT1)	3 SR 1 RCT 23 comparative studies	1b
		Partial nephrectomy can be performed, either with an open, pure laparoscopic or robot-assisted approach, based on surgeon's expertise and skills.		2b
		Recommendations:		
		Nephron-sparing surgery is recommended in patients with T1a tumours.		A
		Nephron-sparing surgery should be favoured over radical nephrectomy in patients with T1b tumour, whenever technically feasible.		B
IKNL 2010[4]	2009	**Conclusions:**		
		Radical nephrectomy versus nephron-sparing treatment		
		There are indications that the chance of a local recurrence after medically necessary nephron-sparing treatment is 4-6%.	2 case series	Level 3
			2 case series	

		There are indications that the chance of a local recurrence after an elective nephron-sparing treatment is 2-4%.	1 comparative study 2 comparative studies	Level 3
		There are indications that survival results after nephron-sparing treatment and radical nephrectomy with tumours <4 cm are comparable.	2 case series 2 comparative study	Level 3
		There are indications that the chance of recurrence and disease-free survival is comparable for radical nephrectomy and nephron-sparing treatment for tumours with a cross-section of up to 4 cm.		
		Open partial nephrectomy There are indications that the surgical margin of unaffected tissue around the tumour is not associated with the chance of recurrence in the case of renal cell carcinoma.	2 case series	Level 3
		Recommendations: Nephron-sparing (partial) nephrectomy is the preferred treatment for T1a tumours (<4 cm). The surgical margin of unaffected tissue should consist of a layer of macroscopically normal-appearing parenchyma. After nephron-sparing treatment, it is recommended to conduct polyclinical follow-up aimed at detecting a possible local recurrence. It is recommended that nephron-sparing treatment is performed (if technically possible) in the case of a (functional) monokidney with renal cell carcinoma. The threshold of 4 cm is not applied here.		
Laparoscopic partial nephrectomy				
IKNL 2010[4]	2009	**Conclusions:** There are indications that, from a technical perspective, partial nephrectomy can be performed completely laparoscopically.	2 case series 2 comparative study	Level 3
		Considerations: Laparoscopic versus open partial nephrectomy. It is advised that laparoscopic technique is only applied by urologists with extensive laparoscopic experience		Professional perspective

	Recommendation: The guideline development group is of the opinion that a laparoscopic partial nephrectomy should only be performed in centres with extensive experience and expertise with the relevant treatment.		
See chapter on ablative techniques			

4.1.2.1.2. Associated procedure

Adrenalectomy

Table 23 – Evidence table: Guidelines Surgery – Adrenalectomy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusions:** Ipsilateral adrenalectomy during radical or partial nephrectomy does not provide a survival advantage	1 comparative study	3
		Recommendations: Ipsilateral adrenalectomy is not recommended when there is no clinical evidence of invasion of the adrenal gland.		B
IKNL 2010[4]	2009	**Conclusions:** Nearly one-half of all adrenal metastases are associated with primary tumours in the upper pole of the kidney. There is evidence that adjuvant adrenalectomy is indicated if the adrenal gland is found to be suspicious by preoperative CT or by macroscopic assessment during surgery. Adrenalectomy has no effect on prognosis for patients with advanced stage disease.	2 case series 1 comparative study 3 case series 3 comparative study 1 case series 3 comparative studies	Level 3 Level 3 Level 3
		Recommendations: Routine removal of the adrenal gland during radical tumour nephrectomy is no longer justifiable. Adrenalectomy may be beneficial only in cases of abnormal findings by CT or large, upper-pole tumours.		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		However, it is doubtful whether adrenalectomy improves survival in these settings		

Lymphadenectomy

Table 24 – Evidence table: Guidelines - Lymphadenectomy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusions:**		
		In patients with localized disease and no clinical evidence of lymph-node metastases, no survival advantage of a lymph-node dissection in conjunction with a radical nephrectomy was demonstrated.	2 SR 2 narrative review 7 case series 4 comparative studies	1b
		In patients with localized disease and clinically enlarged lymph nodes the survival benefit of lymph node dissection is unclear. In these cases lymph node dissection can be performed for staging purposes.		3
		Recommendations:		
		Lymph node dissection is not recommended in localized tumour without clinical evidence of lymph node invasion.		A
		In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.		C
IKNL 2010[4]	2009	**Conclusions:**		
		The addition of extensive lymph node dissection to radical tumour nephrectomy does not improve survival.	3 comparative studies 2 cases series	Level 2
		Preoperative CT scan appears insufficiently accurate in detecting lymph node metastases. Less than one-half of enlarged nodes are histologically positive.		Level 3

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		There is some evidence that the presence of lymph node metastases substantially worsens the prognosis of a patient with renal cell carcinoma.		Level 3
		Considerations: Prospective randomised studies with a long follow-up period are needed before a definitive judgement can be made regarding the therapeutic value of adjuvant lymphadenectomy. The incidence of positive lymph nodes, however, is extremely low (3.3%) in patients with non-metastatic renal cell carcinoma		
		Recommendations: At this time, lymphadenectomy has only diagnostic value in patients with renal cell carcinoma. Consequently it is useful for prognostic purposes only. Lymphadenectomy should not be performed routinely		

Embolization

Table 25 – Evidence table: Guidelines Ablative techniques – Embolization

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusions:** In patients unfit for surgery and suffering from massive haematuria or flank pain, embolization can be a beneficial palliative approach.	7 comparative studies	3
IKNL 2010[4]	2009	**Conclusions:** It is highly doubtful that preoperative embolization is of clinical value. Embolization may be indicated for the palliative treatment of massive haematuria and marked local pain in patients with inoperable or metastatic renal cell carcinoma, and in patients with poor physical condition.	2 case series 2 case series	Level 3 Level 3
		Considerations:		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Preoperative embolization of bone metastases prior to orthopaedic surgery is an effective and approved treatment option.		
		Recommendations: Embolization can be considered for the palliative treatment of massive haematuria and marked local pain in patients with inoperable or metastatic renal cell carcinoma, and for patients with poor physical condition.		

4.1.2.1.3. Management of RCC with thrombus

Table 26 – Evidence table: Guidelines Surgery – Thrombectomy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusions:** Low quality data suggests that tumour thrombus in the setting of non-metastatic disease should be excised. Adjunctive procedures such as tumour embolization or IVC filter do not appear to offer any benefits.		3 3
		Recommendations: Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC.		C
IKNL 2010[4]	2009	**Conclusions:** The prognosis of patients with a tumour thrombus in the inferior vena cava appears to be relatively good if no metastases are present and total surgical extirpation is possible. Renal cell carcinomas with a tumour thrombus generally have a higher stage and grade. Metastasis occurs at least twice as often in these patients. The biologically aggressive behaviour of these tumours influences the prognosis more than the cranial extent of the tumour thrombus.		B B

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Considerations: The higher the thrombus extends, the greater the likelihood it is inoperable. The surgical approach and technique used for the removal of a thrombus of the inferior vena cava is determined by the cranial extent of the tumour thrombus. If the thrombus has extended above the diaphragm, treatment must take place in a treatment centre with expertise in cardiopulmonary surgical protocols.		
		Recommendations: To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols.		

4.1.2.1.4. Alternative

Active surveillance

Table 27 – Evidence table: Guidelines Surgery – Active surveillance

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusion:** Population-based analyses show a significantly lower cancer-specific mortality for patients treated with surgery compared to non-surgical management. However, the same benefit in cancer-specific mortality is not confirmed in analyses focusing on older patients (> 75 years old). In active surveillance cohorts, the growth of small renal masses is low in most cases and progression to metastatic disease is rare (1-2%).		3 3
		Recommendations: In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation and cryoablation can be offered.		C

Cryoablation and Radiofrequency ablation

Table 28 – Evidence table: Guidelines Ablative techniques – Radiofrequency

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusion:**		
		The quality of the available data does not allow any definitive conclusions regarding morbidity and oncological outcomes of cryoablation and radiofrequency ablation.	9 comparative studies 1 case series	3
		Low quality studies suggest a higher local recurrence rate for minimally invasive therapies compared to partial nephrectomy.		3
		Recommendations:		
		Due to the low quality of the available data no recommendation can be made on radiofrequency ablation and cryoablation.		C
		In the elderly and/or comorbid patients with small renal masses and limited life expectancy, active surveillance, radiofrequency ablation and cryoablation can be offered.		C
IKNL 2010[4]	2009	**Conclusions:**		
		There are indications that radiofrequency cryoablation of renal cell carcinomas is a technique that is still in development.	1 comparative study 1 case series 1 narrative review	3
		Considerations:		3
		There is no long-term follow-up data (safety) available for laparoscopic and percutaneous cryoablation and radiofrequency ablation.		
		The result of cryoablation and radiofrequency ablation is partly dependent on the expertise and experience of the operator (professional perspective). It is recommended that this treatment is performed by an urologist (or together with a radiologist) who performs this intervention multiple times per year.		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		If the nephron-sparing treatment for a renal tumour involves a single functional kidney, the centre should also have a unit in which kidney function replacement therapy can be performed (organisation).		
		Recommendations: Cryoablation or radiofrequency ablation is recommended with tumours <4 cm where partial nephrectomy does not seem technically possible, renal-sparing treatment is necessary and/or when the co-morbidity of the patient is a risk factor for other surgery. The guideline development group is of the opinion that a laparoscopic partial nephrectomy, cryoablation and radiofrequency ablation should only be performed in centres with extensive experience and expertise with the relevant treatment.		

4.1.2.2. Adjuvant treatment

Table 29 – Evidence table: Guidelines Ablative techniques – Adjuvant treatment

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusion:** Adjuvant therapy with cytokines does not improve survival after nephrectomy.	5 RCT	1b
		Recommendations: Outside controlled clinical trials, there is no indication for adjuvant therapy following surgery.		A

4.1.2.3. Treatment of local recurrence

Table 30 – Evidence table: Guidelines Ablative techniques – Treatment of local recurrence

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL 2010[4]	2009	**Conclusions:**		
		There are indications that the incidence of isolated recurrences in the renal fossa after nephrectomy is low.		3
		There are indications that surgical resection of a local recurrence after nephrectomy is followed by a high frequency of further metastasis and cancer-specific mortality.		3
		If the recurrence is small, a complete resection can be achieved, the sarcomatoid subtype is not known and the patient has a good performance status, there are indications that a resection of the local recurrence may have a favourable influence on survival.		3
		There is no data available on the role of systemic therapy in the treatment of the isolated recurrence.		4
		Considerations:		

Items	*A) Formulate if it is of importance and how*	*B) Prioritisation in relation to the importance of 1-6*	*C) Include in formulating the recommendation?*	*D) If incorporating in the recommendation: Does the consideration strengthen or weaken the conclusion?*
1. Safety	Yes, resections of recurrences have a high morbidity	1	Yes	Weakened conclusion performing recurrence surgery
2.Patient perspective	Yes, patients put their hopes on complete resection of recurrence	3	Yes	Neutral
3. Professional perspective	Yes, recurrence surgery requires experience. The intervention can therefore not simply be performed at any location	2	Yes	Weakened conclusion performing recurrence surgery
4. Cost efficacy				
5. Organisation				
6. Society				

		Recommendations:		
		If the recurrence is small, a complete resection can be achieved, the sarcomatoid subtype is not known and the patient has a good performance status, the guideline development group is of the opinion that a resection of the local recurrence may be performed.		
		The guideline development group is of the opinion that radiotherapy or ablative therapies such as RFA may be considered as an alternative if a resection cannot be conducted due to the performance status.		

4.1.2.4. Treatment of metastatic RCC

4.1.2.4.1. Cytoreductive surgery

Table 31 – Evidence table: Guidelines Ablative techniques – Cytoreductive surgery in metastatic RCC

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusion:**		
		Cytoreductive nephrectomy in combination with interferon-alpha (IFN-α) improves the survival of patients with mRCC and good performance status.		1a
		Cytoreductive nephrectomy for patients with simultaneous complete resection of a single metastasis or oligometastases may improve survival and delay systemic therapy.		3
		Recommendations:		
		Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC.		C
IKNL 2010[4]	2009	**Conclusions:**		
		It is plausible that a tumour nephrectomy in combination with IFN- α leads to an improvement in survival for patients with metastatic renal cell carcinoma and a good performance status.		2
		There is no evidence as yet that tumour nephrectomy is of added value in the application of tyrosine-kinase inhibitors or monoclonal antibodies against the VEGF pathway or other forms of targeted therapy. Most patients who participated in phase III studies in which the efficacy of angiogenesis inhibitors and mTOR inhibitors were demonstrated did undergo a nephrectomy.		4
		Recommendations:		
		A tumour nephrectomy should be performed with patients with metastatic renal cell carcinoma treated with immunotherapy if the performance status of the patient allows it.		

4.1.2.4.2. Local therapy

Table 32 – Evidence table: Guidelines Ablative techniques – Local therapy in metastatic RCC

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
EAU 2014[1]	2013	**Conclusion:**		
		All included studies were retrospective non-randomized comparative studies, resulting in a high risk of bias associated with non-randomization, attrition, and selective reporting.		3
		With the exception of brain and possibly bone metastases, metastasectomy remains by default the most appropriate local treatment for most sites.		3
		Retrospective comparative studies consistently point towards a benefit of complete metastasectomy in mRCC patients in terms of overall survival, cancer-specific survival and delay of systemic therapy.		3
		Radiotherapy to bone and brain metastases from RCC can induce significant relief from local symptoms (e.g. pain).		3
		Recommendations:		
		No general recommendations can be made. The decision to resect metastases has to be taken for each site, and on a case-by-case basis; performance status, risk profiles, patient preference and alternative techniques to achieve local control, must be considered.		C
		In individual cases, stereotactic radiotherapy for bone metastases, and stereotactic radiosurgery for brain metastases can be offered for symptom relief.		C
IKNL 2010[4]	2009	**Conclusions:**		
		<u>Surgical decompression</u>		
		In the event of myelum compression as a result of limited vertebral metastasis (e.g. max. 3 vertebrae, not specifically the result of renal cell carcinoma), there are indications that surgical decompression followed by radiotherapy (10 x 3 Gray) is preferable to radiotherapy only for selected patients with a relatively favourable prognosis.		3
		<u>Palliative radiotherapy</u>		2

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		It is plausible that painful bone metastases of a renal cell carcinoma may respond well to palliative radiotherapy or surgical resection with osteosynthetic stabilisation followed by postoperative radiotherapy.		4
		In relation to palliative irradiation with a limited prognosis, it is the opinion of the guideline development group that a short irradiation series of 1 to 5 times is the treatment of choice (for example, 1x8 Gy or 5x4 Gy). In relation to palliative irradiation with a limited prognosis, it is the opinion of the guideline development group that a short irradiation series of 1 to 5 times is the treatment of choice (for example, 1x8 Gy or 5x4 Gy).		4
		Stabilising surgery prior to the radiotherapy may be considered in the case of an instable fracture or risk of fracture.		3
		<u>Metastasectomy</u>		
		There are indications that metastasectomy in patients with solitary metastasis improves survival after response to immunotherapy and in the case of solitary or limited multiple metachronous metastases.		3
		There are indications that a solitary metastasis of a renal cell carcinoma, with a patient in a good overall condition (KS>70%), may be irradiated with a local higher dosis (for example: 13 x 3 Gy, 16 x 2.5 Gy) or by means of radiosurgery/stereotactic radiotherapy. This applies to both bone and soft tissue metastases.		3
		<u>Whole Brain Radiotherapy (WBRT)</u>		
		There are indications that total cranial irradiation leads to less complaints in patients with >4 brain metastases and a Karnofsky performance status of at least 60 to 70%.		2
		The median survival of untreated patients is 1 month, with corticosteroids 2 months and after treatment with WBRT 3-6 months. Surgical extirpation of a solitary brain metastasis followed by WBRT, extends median survival to 6-12 months with select patients.		
		<u>Radiosurgery/stereotactic radiotherapy</u>		
		There are indications that radiosurgery/stereotactic radiotherapy cannot be given to select patients (≤ 3 metastases, KS >70%, maximum brain metastasis diameter 3-3.5 cm, no progressive extracranial tumour activity).		3
		The development group is of the opinion that surgery followed by radiotherapy may be considered in patients with a solitary brain		4

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		metastasis (confirmed by MRI), no metastases elsewhere, a good general condition and a long disease-free interval, depending on the location.		
		Considerations: Surgical decompression There is a chance of surgical morbidity and mortality with surgical decompression (safety). In addition, surgical decompression cannot be performed by every surgeon (professional perspective) and this intervention acutely requires an operation room (organisation). Palliative radiotherapy Palliative radiotherapy or surgical resection with osteosynthetic stabilisation followed by postoperative radiotherapy has a rapid palliative effect, and a limited toxicity (safety); it can be administered in a short and powerful dose, improves quality of life (patient perspective) and is cost-effective (cost-efficacy). In the case of longer survival, stereotactic radiotherapy probably has a higher success rate in the long-term, and results in less recurrence and morbidity (patient perspective). However, palliative radiotherapy, stereotactic radiotherapy or stabilising surgery must be performed in a centre with possibilities and expertise (organisation). Metastasectomy Metastasectomy is relatively safe (safety). Metastasectomy does require an experienced surgeon and suitable infrastructure. Radiosurgery/stereotactic radiotherapy Irradiation or radiosurgery/stereotactic radiotherapy in the case of solitary metastasis of a renal cell carcinoma is associated with little toxicity and high efficacy (safety) and meets the requirements and expectations of the patient. However, the facilities and experience do need to be available to be able to offer this (organisation). Whole Brain Radiotherapy Total cranial irradiation is safe (safety); provides palliation of neurological complaints (patient perspective). However, it must be performed in a radiotherapeutic centre (organisation) and side effects may occur, such as alopecia (safety).		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Radiosurgery/stereotactic radiotherapy The value of WBRT after radiosurgery/stereotactic radiotherapy should be discussed individually with the patient. The advantage of a WBRT after resection or after radiosurgery/stereotactic radiotherapy is higher efficacy and/or tumour follow-up (patient perspective), low toxicity (safety) and only a limited number of fractions are required (cost-efficacy). The disadvantage of WBRT is a period of total alopecia (safety). Stereotactic facilities and experience do need to be available (organisation and professional perspective).		
		Recommendations: Surgical decompression No recommendations can be made in relation to surgical decompression for patients with renal cell carcinoma and spinal metastases on the basis of available literature. The guideline development group is of the opinion that a direct surgical decompression followed by radiotherapy may be considered for patients with renal cell carcinoma who are in a good condition with myelum compression as a result of solitary spinal metastasis. Palliative radiotherapy If it only concerns eradication of local complaints, it is recommended that radiotherapy be applied (dependent on the extent of the metastases and the condition of the patient). Metastasectomy The development group is of the opinion that a metastasectomy can be considered for patients with a long disease-free interval after nephrectomy in the case of: • a solitary pulmonary metastasis/metastases or one with good access, or • a resectable solitary or limited intra-abdominal metastasis/metastases The development group is of the opinion that a metastasectomy may be considered for patients who are in good condition with a partial response of a limited number of metastases after immunotherapy. Radiosurgery/stereotactic radiotherapy		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		It is recommended that a high dose of external irradiation or radiosurgery/stereotactic irradiation is applied in the case of solitary non-resectable metastases or solitary metastases that cannot be fully resected. The morbidity associated with surgery and/or radiotherapy should be discussed with the patient and any survival advantage weighed up for each individual patient. Whole Brain Radiotherapy (WBRT) In patients with renal cell carcinoma and multiple (>4) brain metastases and a reasonable to good Karnofsky performance status, irradiation of the entire brain (whole brain radiotherapy) is advised. Radiosurgery/stereotactic radiotherapy It is recommended that radiosurgery/stereotactic radiotherapy is administered to patients with a favourable risk profile (≤ 3 metastases, KS>70%, maximum diameter 3-3.5 cm, no progressive extracranial tumour activity), possibly supplemented with WBRT. The benefits and disadvantages of WBRT should be discussed with the individual patient.		

4.2. Additional evidence for treatment

4.2.1. Treatment of localized renal cancer

4.2.1.1. Surgery

4.2.1.1.1. Systematic reviews

Table 33 – Evidence table - SR - Laparoscopic versus open partial nephrectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Zheng 2013[24]	• Design: Meta-analysis • Sources of funding: not mentioned • Search date: January 1990 to April 2012 • Searched databases: Medline, Embase and Cochrane library • Included study designs: Case-control studies and cohort studies • Number of included studies: 6 • Included studies: Springer 2012 Ching 2011 Jeon 2011 Lane 2010 Marszalek 2009	• Eligibility criteria: patients who underwent a LPN or OPN with at least 5-year follow-up • Patients characteristics: Patients are similar between the two groups for age, sex, BMI, ASA and laterality but differ for tumour size (MD=0.64, 95% CI (-1.09, _0.19) • Median FU: 5 years (except for one publication 7 years)	• Intervention: LPN • Comparator: OPN	• 5-year OS: Number of studies: 4 OR=1.83, 95% CI (0.80, 4.19), I^2=32%, p=0.15 • 5-year CSS Number of studies: 4 OR=1.09, 95% CI (0.62, 1.92), I^2=0%, p=0.75 • 5-year RFS Number of studies: 5 OR=0.68, 95% CI (0.37, 1.26), I^2=0%, p=0.22		Results critical appraisal: • Only cohort studies and case-control studies included into meta-analysis (low level of evidence), no RCT available • Small number of patients studied, the efficiency of statistical test may be inadequate • No subgroup analysis by tumour characteristic (i.e. TNM classification, tumour anatomic complexity) • All data came from Europa and North America, findings cannot

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Permpongkosl 2006					be applicable to the rest of the world

Table 34 – Evidence table - SR - Robotic versus laparoscopic partial nephrectomy for small renal tumours (T1a)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Froghi 2013[15]	• Design: Meta-analysis • Sources of funding: not mentioned: • Search date: 2000-2012 • Searched databases: Medline, Embase, Pubmed, Cochrane database • Included study designs: comparative studies • Number of included studies: 6 • Included studies: Hillyer 2011 Lavery 2011 Williams 2011 Seo 2011 Kural 2009 Aron 2008	• Eligibility criteria: Patients with small renal masses (4 cm) undergoing laparoscopic or robotic partial nephrectomy • Patients characteristics: • Median FU: not mentioned	• Intervention: robotic partial nephrectomy (RPN) • Comparator: Laparoscopic partial nephrectomy (LPN)	**Operative outcomes** • Estimated blood loss (ml) Weighted mean difference (WMD) =46.13, 95% CI (-12.01 to 104.26), I^2=87%, p=0.12 • Operative time (min) WMD =0.5, 95% CI (-24.02 to 25.02), I^2=59%, p=0.97 • Warm ischemia time (min) WMD =-5.76, 95% CI (-15.22 to 3.70), I^2=96%, p=0.23 **Postoperative outcomes** • Length of stay (days) WMD =-0.15, 95% CI (-0.38 to 0.09), I^2=0%, p=0.22 **Overall complications rate** WMD =-0.01, 95% CI (-0.05 to 0.06), I^2=0%, p=0.84 *Note: Operative time is based on 5 studies (Hillyer 2011 did not report this*		Results critical appraisal: • Low level of evidence: lack of RCT, only comparative study mostly retrospective (5/6 studies) • Lack of standardization in variables reporting such as anatomical features of renal tumours, scoring for tumour complexity • Lack of medium to long-term follow-up • Lack of data on tumours margins • Variation in inclusion and exclusion criteria, treatments protocols, operative

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				outcome). The other outcomes are based on all the 6 studies		techniques and outcome assessment • Learning curve of the surgeons is not taken into account

Table 35 – Evidence table – SR - Partial versus radical nephrectomy for localized renal function

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Kim 2012[17]	• Design: Meta-analysis • Sources of funding: Healthcare Delivery Research Scholars Program, Mayo Clinic • Search date: inception to February 2011 • Searched databases: Medline, Embase, Cochrane Central Register of Controlled Trials, Scopus, Web of Science • Included study designs: RCT, cohort studies, case-control	• Eligibility criteria: not mentioned • Patients characteristics: not mentioned • Median FU: not mentioned	• Intervention: Partial nephrectomy (PN) • Comparator: Radical nephrectomy (RN)	• All causes of mortality Number of studies: 21 HR =0.81, 95% CI (0.76 to 0.87), I^2=49%, p<0.00001 • Cancer specific mortality Number of studies: 21 HR =0.71, 95% CI (0.59 to 0.85), I^2=63%, p<0.0002	• Chronic kidney disease Number of studies: 9 HR =0.39, 95% CI (0.33 to 0.47), I^2=87%, p<0.00001	Results critical appraisal: • Low level of evidence. • Great heterogeneity between studies;

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Number of included studies: 36 • Included studies: Hellenthal 2001 Van Poppel 2011 Breau 2010 Kim 2001 Huang 2009 Thompson 2009 Miler 2008 Thompson 2008 Donat 2006 Huang 2006 Weight 2010 Weight 2010 Zini 2009 Barbalias 1999 Becker 2006 Bedke 2008 Crepel 2010 D'Armiento 1997 Jeldres 2009 Leibovich 2004 Margulis 2007 Patard 2004 Barlow 2010 Jeon 2009 Malcolm 2009 Snow 2008 Robson 1969 Novick 1991 Zincke 1985 Murad 2011 Swiglo 2008 Joudi 2007 Van Poppel 2007					

Table 36 – Evidence table – SR - Transperitoneal versus Retroperitoneal laparoscopic partial nephrectomy for renal cell carcinoma

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Ren 2014[21]	• Design: Meta-analysis • Sources of funding: no support or funding • Search date: 2004- 2013 • Searched databases: Medline, Embase, Cochrane database • Included study designs: retrospective comparative studies • Number of included studies: 8 • Included studies: Wright 2005 NG 2005 Kieran 2007 Marszalek 2010 Tugcu 2011 Ouzaid 2012 Hughes-Hallett 2013	• Eligibility criteria: Patients with clinical stage of T1 confirmed by CT or MRI • Patients characteristics: not mentioned • Median FU: not mentioned	• Intervention: Retroperitoneal laparoscopic partial nephrectomy (RLPN) • Comparator: Transperitoneal laparoscopic partial nephrectomy (TLPN)	**Perioperative variables** • Operative time (min) Number of studies: 7 SMD (standardized mean difference) =1.001, 95% CI (0.609 to 1.393), I^2=81.8%, p<0.001 • Estimated blood loss (ml) Number of studies: 5 SMD =0.403, 95% CI (0.015 to 0.791), I^2=74.9%, p=0.042 • Warm ischemia time (min) Number of studies: 7 SMD =0.302, 95% CI (-0.340 to 0.945), I^2=93.6%, p=0.356 **Postoperative variables** • Length of stay (days) Number of studies: 6 WMD =0.936, 95% CI (0.609 to 1.263), I^2=46.3%, p<0.001 • Serum creatine level (mg/dl) Number of studies: 2 WMD =0.02, 95% CI (-0.08 to 0.11), I^2=14%, p=0.68 **Surgical complications** • Overall complication rate Number of studies: 6 OR =0.849, 95% CI (0.576 to 1.250), I^2=0%, p=0.406 • Intraoperative complication Number of studies: 4 OR =2.30, 95% CI (0.83 to 6.4), I^2=16%, p=0.11		Results critical appraisal: • Low level of evidence: lack of RCT, only retrospective studies with varying protocols and surgeons' experience • Great heterogeneity between studies in terms of inclusion, exclusion criteria, operating techniques and outcomes assessment; • Mean and SD are derived from studies using median and range. It may cause bias • Lost to follow-up not always reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				• Postoperative complications Number of studies: 4 OR =1.33, 95% CI (0.73 to 2.41), I²=3%, p=0.35 • Open conversion rate Number of studies: 5 OR =2.14, 95% CI (0.85 to 5.39), I²=0%, p=0.11 **Oncological variables** • Positive margin Number of studies: 4 OR =1.29, 95% CI (0.48 to 3.46), I²=0%, p=0.61 • Recurrence rate and survival rates No study reported these outcomes		

RCTs

Table 37 – Evidence table - RCT – Surgery for localized renal cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
Scosyrev 2014[33]	• Design: RCT • Sources of funding: Fond Cancer (FOCA)-Belgium • Setting: 45 centres in Belgium, Italy, Austria, Poland, France, Turkey, Spain, Canada, Netherlands,	• Eligibility criteria: solitary renal mass suspicious for RCC ≤5 cm, radiographically normal contralateral kidney, WHO performance status of 0-2 • Patients characteristics: Mean age, yr (Q1, Q3)*: RN 60,4 (53-69) vs NSS	• Intervention(s): Nephron-sparing nephrectomy (NSS) • Comparator(s): Radical nephrectomy (RN)	**At lowest eGFR£** • At least moderate renal dysfunction stage A (eGFR<60) RN 85.7% vs NSS 64.7%, p<0.001 • At least moderate renal dysfunction stage B (eGFR45) RN 49.0% vs NSS 27.1%, p<0.001	**Subject-specific annual eGFR rate** ml/min per 1.73m² per year (Q1, Q3): RN=+0.3 (-0.4, +1.5) vs NSS=0.0 (-1.4, +1.2), p=0.007	Results critical appraisal: • Lack on detailed information on baseline kidney function (only eGFR measurement) • Target sample not reached

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
	Hungary, Germany, United Kingdom, Switzerland, Rep. of Georgia, Slovak Republic, USA • Sample size: RN (n=259), NSS (n=255) • Duration: Enrolment period: from 1992 to January 2003	60,9 (53-69); Sex (% of male): RN: 66.0 vs NSS 67.5; WHO performance status (%): status 0 RN 84.2% vs NSS 87.5, status 1 RN 13.9 vs NSS 12.1, status 2 RN 1.9 vs NSS à.4; Chronic disease (%): no RN 64.1 vs NSS, cardiovascular RN 22.8 vs NSS 20.8, pulmonary 5.0 vs NSS 3.1, other 8.1 vs 12.6, Serum creatinine: ≤1.25 x ULN[$] RN 93.4 vs NSS 92.9, 1.26-2.5 x ULN RN 6.2 vs NSS 6.7, 2.6-5.0 x ULN RN 0.4 vs NSS à, missing RNN à vs NSS 0.4 • Median FU: 6.7 yr		• Advanced kidney disease (eGFR<30) RN 10.0% vs NSS 6.3%, ns • Kidney failure (eGFR15) RN 1.5% vs NSS 1.6%, ns **At last eGFR[£]** • At least moderate renal dysfunction stage A (eGFR<60) RN 58.7% vs NSS 38.4%, p<0.001 • At least moderate renal dysfunction stage B (eGFR45) RN 24.7% vs NSS 13.3%, p<0.001 • Advanced kidney disease (eGFR<30) RN 6.6% vs NSS 3.5%, ns • Kidney failure (eGFR15) RN 1.2% vs NSS 0.8%, ns		• Lost to follow-up: 5% • Imperfect compliance with assigned intervention due to reassessment of patients tumour status but crossover did not affect the findings
Guan[34]	• Design: RCT • Sources of funding: Not mention • Setting: 1 centre in China • Sample size: PN (n=54), MWA (n=48) • Duration:	• Eligibility criteria: solitary, unilateral, solid renal mass up to 4 cm • Patients characteristics: Mean age yr (SD): PN 46.4 (±13.2) vs MWA 45.5 (±14.4); Sex (% of male): PN: 51.9 vs MWA 39.6; Mean ASA	• Intervention(s): Open or laparoscopic Microwave Ablation (MWA) • Comparator(s): Open or laparoscopic Partial Nephrectomy (PN)	**Perioperative data** • Mean operative time, min (range) MWA 148 (117-273) vs PN 154 (60-277), p=0.0955 • Mean estimated blood loss, ml (SD) 138.3±69.4 vs PN 465.9 ± 577.1, p=0.0002		Results critical appraisal: • Unclear blinding • Baseline serum creatinine, tumour site, and localisation were different between groups • Single centre study design

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
	Enrolment period: from December 2004 to June 2008	score (SD): PN 2.5±0.6 vs MWA 2.4±0.7; Mean Body Mass Index µmol/l (SD): PN 23.5±2.0 vs MWA 23.1±2.8, Mean preoperative Serum creatinine (SD): PN 69.6±29.6 vs MWA 55.6±12.7, Mean preoperative eGFR (SD): PN 113.0±36.4 vs MWA 130.5±31.7 • Median FU: 36 months		• Median length of stay, days (range) MWA 15 (13-26) vs PN 19 (10-47), p=0.7566 • Complication rate MWA 6/48 vs PN 18/54, p=0.0187 **Oncological outcomes** • 3-year recurrence-free survival rate PN 96.6% (95% CI: 78.0-99.6) vs MWA 90.4% (95% CI: 65.3-97.6), p=0.4650 • Disease-specific survival PN 100% vs MWA 100% **Renal function data** • Mean serum creatinine, µmol/l (SD) MWA 58.9 ± 9.7 vs PN 90.1 ± 29.2, p<0.0001 • Mean (eGFR), ml/min/1073 m² (SD) MWA: 120.6 ± 28.4 vs PN 107.5 ± 53.4, p=0.1320		

4.2.1.2. Associated procedures

4.2.1.2.1. Systematic reviews

Table 38 – Evidence table – SR – associated procedures in localized renal cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Su 2012[22]	• Design: Meta-analysis • Sources of funding: no support or funding • Search date: up to March 2012 • Searched databases: Pubmed • Included study designs: observational study • Number of included studies: 21 • Included studies: Siemer 2004 Xu 1998 Kobayashi 2003 Lane 2009 Weight 2011 Robey 1986 Kozak 1996 Leibovitch 1995 Komai 2010 Autorino 2003 Marois 1995 Tsui 2000	• Eligibility criteria: Patients with RCC • Patients characteristics: not mentioned • Median FU: not mentioned	• Intervention: Ipsilateral adrenalectomy radical nephrectomy Comparator: Adrenal-sparing radical nephrectomy	**Overall survival** Number of studies: 4 HR =0.89, 95% CI (0.67 to 1.19), I^2=80%, p=0.43 **5 year cancer specific survival** Number of studies: 8 OR =1.06, 95% CI (0. 79 to 1.44), I^2=73%, p=0.69 **Tumour localisation in upper pole kidney** Number of studies: 9 OR =1.11, 95% CI (0.83 to 1.47), I^2=16%, p=0.50		Results critical appraisal: • Sensibility analysis was performed and do not change the conclusions • Great heterogeneity between studies • No RCT available

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Moudouni 2002 Catalano 2003 Klestcher 1996 Gill 1994 Sawai 2002 Kardar 1998 Alamdali 2005 Paul 2001 Sandock 1997					

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Klatte 2014 [18]	• Design: Meta-analysis • Sources of funding: no support or funding • Search date: up to September 2013 • Searched databases: Medline, Web of Science • Included study designs: comparative study • Number of included studies: 13 • Included studies: Desai 2005 Emara 2014	• Eligibility criteria: Patients with RCC • Patients characteristics: not mentioned • Median FU: not mentioned	• Intervention: Laparoscopic cryoablation • Comparator: Laparoscopic partial nephrectomy	**Local tumour progression** Number of studies: 10 RR =9.39, 95% CI (3.83 to 22.99), I^2=0%, p<0.0001 **Metastatic progression** Number of studies: 10 RR =4.68, 95% CI (1.88 to 11.64), I^2=0%, p=0.001	**Operative time (min)** Number of studies: 12 WMD =35.45, 95% CI (17.01 to 53.88), I^2=93.1%, p<0.001 **Evaluated blood loss (ml)** Number of studies: 12 WMD =130.11, 95% CI (94.57 to 165.66), I^2=84.8%, p<0.001 **Length of stay (days)** Number of studies: 12 WMD =1.22, 95% CI (0.58 to 1.86), I^2=90.8%, p<0.001 **Overall complication (rate)** Number of studies: 12 RR =1.82, 95% CI (1.22 to 1.72), I^2=59.2%, p=0.003 **Urological complication (rate)**	Results critical appraisal: • Sensibility analysis was performed and do not change the conclusions • Great heterogeneity between pooled studies • No RCT available • Non English literature was included to reduce publication bias • Selection bias suspected by the authors

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Guillotreau 2012 Haber 2012 Haramis 2012 Hruby 2006 Kim 2007 Lian 2010 Lugghezzani 2009 O'Malley 2007 Turna 2009 Nisbet 2009				Number of studies: 10 RR =1.99, 95% CI (1.10 to 3.63), I^2=45.2%, p=0.024 **Non-urological complication (rate)** Number of studies: 10 RR =2.33, 95% CI (1.42 to 3.84), I^2=6.5%, p=0.001	

4.2.2. Adjuvant therapy

4.2.2.1. RCTs

Table 39 – Evidence table - RCT – Adjuvant therapy in RCC with or without metastases

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Aitchison-2014[35]	• Design: RCT • Sources of funding: Cancer Research UK, Roche; Chiron for supporting, EORTC Charitable Trust. • Setting: UK, Belgium, the Netherlands, Austria, Hungary, Italy • Sample size: Adj n=154, obs. n=155 • Duration: 9 years	Eligibility criteria: surgical resection of the primary RCC tumour, no metastatic disease or macroscopic residual disease, histologically proven stage T3b, T3c, T4 tumour or any pT stage and nodal status pN1 or 2, or any pT stage (TNM classification) and microscopic positive margins or presence of any microscopic vascular invasion, age ≤75 years, WHO performance status 0 or	• Intervention(s) (Adj): sc IL-2 (20 MIU/m² 3x week 1+4 and 5 MIU/m² 3x week 2-3) sc INF-α (6 MIU/m² 1x week 1+4, 3x week 2-3, 9 MIU/m² 3x week 5-8) 5-FU (750 mg/m² 1x week 5-8) • Comparator(s): observation	**Disease free survival (DFS)** • DFS time: results reported in graph (p=0.233) • Median DFS (95% CI): Adj 5.4 years (3.4-7.4) vs obs. 3.0 years (1.7-4.4) • 3-year DFS % (95% CI) Adj 61.3% (53.5%-69.0%) vs obs. 50.4% (42.5%-58.4%) (HR=0.84 ; 95% CI 0.63-1.12 ; p=0.233)	**Overall survival (OS)**: • OS time: results reported in graph (p=0.403) • 5-year DFS % (95% CI) Adj 69.7% (62.2%-77.3%) vs obs. 62.8% (54.8%-70.8%) (HR=0.87 ; 95% CI 0.61-1.23 ; p=0.428) **Toxicity:** • Treatment was stopped in 34.7% due to toxicity	• Dropouts: 11 in each arms • Results critical appraisal: - Due to sample size, the power of statistic tests was reduced to 87% - Some results are reported in graph and the text did not reported the values of some parameters

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		1, adequate organ function • Patients characteristics: Median age (IQR) Adj: 57(49-64), obs.: 55 (51-61), Gender (% female): Adj 30,5%, obs.: 34.4%, pT categories: pT1/2 Adj 22,1%, obs.: 20.1%, Pt3/4 Adj 77,8%, obs.: 79.8%, pN category pN0 Adj 66,2%, obs.: 65.2%, pN1 Adj 6,5%, obs.: 7.7%, pN2 Adj 9,1%, obs.: 8.4%, pNx Adj 18,2%, obs.: 18.1%, microscopic vascular invasion Adj 65,2%, obs.: 65.4% • Median follow-up (95% CI): 7 years (6.4-7.6)			**QoL (QLQC-30):** • No statistical significant differences between group	
Amato-2010[36]	• Design: RCT • Sources of funding: not mentinoed • Setting: 11 centres in France, Germany, Israel, Poland, Romania, Spain, UK, Ukraine, USA • Sample size: Vaccine n=365, placebo n=367	• Eligibility criteria: RCC cancer patients who had undergone nephrectomy for locally advanced or metastatic disease, no cerebal metastasis • Patients characteristics: age >18 y, Karnofsky performance status ≥80%, MSKCC performance status= 0-2, life expectancy > 12 weeks	• Intervention(s): MVA-5T4 vaccine + IL-2 or INF-α or Sunitinib (vaccine) • Comparator(s): Placebo + MVA-5T4 vaccine + IL-2 or INF-α or Sunitinib (placebo)	**Overall survival** • Median OS: vaccine 20.1 vs placebo: 19.2 HR (95%CI: 0.86-1.32), p=0.55): 1.07 • Subanalysis for geographic region, MSKCC grade, standard of care showed not significant differences **Response rate** • Complete response	**Safety**: • Serious adverse events vaccine 19.7 % vs placebo 20.8% • Life threatening or caused death: vaccine 1.7 % vs placebo 2.0%	• Dropouts: early termination of the trial because no benefit • Results critical appraisal: - only 13 patients (5%) received the complete course of injections - early termination

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Duration: early termination after 6 months			Vaccine: n=2 vs placebo n=5 • Partial response Vaccine: n=47 vs placebo n=46 • Stable disease Vaccine: n=164 (44.9%) vs placebo n=173 (47.1%)		
Atzpodien 2005[37]	• Design: RCT • Sources of funding: Deutsche Krebshilfe, Wilhelm-Sander-Stiftung and Deutsche Gesellschaft zur Förderung immunologischer Krebstherapien e.V. • Setting: 1 center in Hannover (Germany) • Sample size: arm A n=135, obs. n=68 • Duration: 9 years	• Eligibility criteria: histologically confirmed RCC (pT3b/c pN0 or pT4pN0; pN+; R0), age between 18 and 80 years; adequate organ function; Karnofsky performance status ≥80%; no evidence of cardiac disease, no HIV, hepatitis, no concomitant corticosteroid therapy, tumour nephrectomy. • Patients characteristics: Median age (range): arm A: 59 (31-77), obs.: 60 (38-77), Gender (% female): arm A 28%, obs.: 21%, Staging pT3b/c pN0 or pT4pN0: arm A 37%, obs.: 21%, pN+: arm A 21%, obs.: 12% , R0: arm A 42%, obs.: 48%	• Intervention(s): sc rIFN-α2a (5x106 IUm^{-2}, day 1, weeks 1+4; days 1, 3, 5, weeks 2+3; 10x106 IUm^{-2}, days 1, 3, 5, weeks 5–8), sc rIL-2 (10x106 IUm^{-2}, twice daily days 3–5, weeks 1+4; 5x106 IUm^{-2}, days 1, 3, 5, weeks 2 + 3) and iv 5-FU (1000 mgm^{-2}, day 1, weeks 5–8). (arm A) • Comparator(s): observation	**Overall survival** • Survival rate: arm A: 61% vs obs.: 75% • 2-year survival probability: arm A 81% vs obs.: 91% • 5-year survival probability: arm A 58% vs obs.: 76% • 8-year survival probability: arm A 58% vs obs.: 66% • Arm A: range 0.2-8.4 years vs obs.: range 0.3-9.7, log rank p=0.0278 • No difference in subgroups analysis related to stage (pT3b/c pN0 or pT4pN0, pN+ and R0) **Relapse-free survival** • Progression rate: arm A: 57% vs obs.: 50% • 2-year relapse free probability: arm A 54% vs obs.: 62%		• Dropouts: none reported • Results critical appraisal: - long period of recruitment - toxicity was not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		• Median follow-up: 4.3 years (range 0.2-9.7 years)		• 5-year relapse free probability: arm A 42% vs obs.: 49% • 8-year relapse free probability: arm A 39% vs obs.: 49% • Median relapse survival (years, range) arm A: 2.75 y (0-8.2) vs obs.: 4.25y (0-9.7), log rank p=0.2398 • No difference in subgroups analysis related to stage (pT3b/c pN0 or pT4pN0, pN+ and R0) for median relapse free survival		
Clarck 2003[38]	• Design: RCT • Sources of funding: educational grant from Chiron Corp • Setting: 15 institutions in USA • Sample size: IL-2: n=33; observation: n=36 • Duration: 5 years	• Eligibility criteria: patients older than 16 years, completely resected advanced high-risk RCC (T3b-c, T4, N1-3 or M1 disease resected to no evidence of disease), excellent performance status (ECGOG= 00 or 1), no cardiac disease, normal pulmonary function and adequate organ function • Patients characteristics: median age (range): IL-2: 49.5 (31-64) vs obs.: 49 (25-64); Gender (% of female):	• Intervention(s): high dose IL-2 600,000 U/Kg as an iv. Bolus over 15 min every 8 hours on days 1 to 5 and again on days 15 to 19 (max. 28 doses) • Comparator(s): Observation (obs.)	**Disease free survival** • Median (months): IL-2 19.5 vs obs. 36, ns • 2-year OS (%, 95% IC): IL-2 48% (32-74) vs obs. 55% (40-76), ns • 3-year OS (%, 95% IC): IL-2 32% (16-66) vs obs. 45% (29-69), ns	**Overall survival**: • 2-year OS (%, 95% IC): IL-2 86% (73-100) vs obs. 86% (74-100), ns • 3-year OS (%, 95% IC): IL-2 80% (63-100) vs obs. 86% (74-100), ns **Toxicity**: • 88% of IL-2 group experienced at least one grade 3 or 4 toxicity • 3 most common grade 3 or 4 toxicity were Hypotension (52%), GI (nausea, vomiting, diarrhea	• Dropouts: trial was stopped during the intermediate analysis because the expected reduction in disease free survival was not reached • Results critical appraisal: - Sponsoring by industry - Early termination because projected improvement not reached - small sample size

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		IL-2: 33% vs obs.: 33%, Performance status (% of PS=0): IL-2: 88% vs obs.: 83%, stratification: locally advanced : IL-2: n=21 vs obs.: n=23, M1 resected to NED : IL-2: n=12 vs obs.: n=13, • Median follow-up: 22 months			(27%) and serum electrolyte abnormalities (↓ PO_4, ↓ Na, ↓ Ca, ↑K))	
Figlin 1999[39]	• Design: RCT • Sources of funding: Chiron therapeutics • Setting: 19 centres in US and 7 centres in Europe • Sample size: TIL n=81, control n= 79 • Duration: not mentioned	• Eligibility criteria: patients with mRCC, ECOG Ps=0 or 1, age ≥ 18 years no significant renal or hepatic dysfunction, no cardiac disease, adequate blood counts, no HIV, no hepatitis, no CNS disease • Patients characteristics: median age (range): TIL: 56 (20-77) vs obs.: 55 (16-85); Gender (% of female): TIL: 13.6% vs obs.: 32.9%, ECOG performance status (% of PS=0): TIL: 46.9% vs obs.: 44.3%, Staging: T2: TIL 19.8% vs obs. 24.1%, T3a 46.9% vs 53.2%,	• Intervention(s): iv infusion of $5x10^7$ to $3x10^{10}$ CD8+ Tumour-infiltrating lymphocytes + rIL-2 (TIL group) • Comparator(s): Placebo + rIL-2 (control group) rIL-2 was delivered via a pump with a daily dose of $5x10^6$IU/m² for 4/ week during 4 weeks followed by 2 weeks of rest.	**Overall survival** • Not statistical difference between group OR= 0.851 (p=0.753) • ECOG PS was not predictive of response OR= 1.07 (p=0.894) • 1-year survival: TIL 55% vs control 47%, p=0.551 • Median survival time: 12.8 months (38 patients censored) vs control 11.5 months (35 patients censored)	**Safety**: • No side effects specially associated with TIL therapy • No death was directly related to treatment	• Dropouts: 20 patients not treated because surgical complication, death during surgery, ineligible for rIL-2 after surgery and 33 additional patients not treated with TIL because of cell processing failure • Results critical appraisal: - 166 patients were needed to adequate power of statistic tests only 160 were randomized but only 87% received actually the first cycle of treatment. This percentage is lower in cycle 2 and 3. - Quality of preparation of TIL

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		T4 30.9% vs obs. 21.5%				was not standard between centres - Study was terminated early because of the lack of efficacy - Characteristics of patients are not well balanced for % of female - No RCC patients were included
Galliglioni 1996[40]	• Design: RCT • Sources of funding: not mentioned • Setting: Centro di Referimento Oncologico of Aviano (Italy) • Sample size: ASI n=60, Control n=60 • Duration: 4 years	• Eligibility criteria: patients radical nephrectomy for Stage I-II or Stage III (TNM staging system) with staging lymphadenectomy, performance status (ECOG) of 0 to 1, tumour cells available for preparation of autologous vaccine • Patients characteristics: Median age (years, range): ASI 57 (25-75) vs control 61 (32-85), Gender (% of female): ASI 33% vs control 40%, primary tumour T1 ASI n=2 vs control n=1, T2 ASI n=23 vs control n=24, T3a ASI n=23 vs control n=23, T3b ASI n=8 vs control n=10; stage I	• Intervention(s): Active specific immunotherapy (ASI) (vaccine preparation using tumour cells and normal renal tissue) • Comparator(s): no treatment	**Disease Free survival** • 5 years DFS: ASI 63% vs control group 72%, ns **Number of relapses** • ASI n=25 vs control group n=20 • No significant differences in pattern of relapse were observed between the 2 groups **Overall survival** • 5-year survival ASI 69% vs control group 78%, ns		• Dropouts: 54/60 patients were evaluable • Results critical appraisal: - no blinding possible because control group did not receive treatment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		ASI n=2 vs control n=1, stage 2 ASI n=23 vs control n=24, stage 3 ASI n=35 vs control n=35 • Median follow-up: 61 months (range, 43-99 months)				
Hinotsu 2013[41]	• Design: RCT • Sources of funding: not mentioned • Setting: 53 institutions in Japan • Sample size: IFN: n=50, obs.: n=49 • Duration: 5 years	• Eligibility criteria: Stage II or III renal cell carcinoma; prior open or laparoscopic nephrectomy, no lung metastasis, no hepatic metastasis or retroperitoneal node metastasis, and no bone metastasis, aged between 20 and 75 years; performance status (ECOG) of 0–2; adequate organ function, no administration UFT, chemotherapeutic agents such as vinblastine, and cytokines such as glucocorticoids,IL-2, and IFN γ • Patients characteristics: Gender (% of female): IFN 36% vs obs. 39%, Age < 50 years: IFN : 18% vs obs: 16%, performance status	• Intervention(s): IF-α 3 to 6 million units IM 3 times a week for 1 year • Comparator(s): observation (obs.)	**Progression Free Survival** • No difference between the two groups (results reported in graph, p=0.456, log-rank test) • Peak hazards of progression in IFN group were delayed for about 6-10 months compared to obs. group	**Overall survival** • No difference between the two groups (results reported in graph, p=0.150, log-rank test) • Subgroup analysis according T1-T2 and T3 factors, no difference was shown No death was caused by treatment toxicity	• Dropouts: 7 patients withdrew before the start of treatment. • Results critical appraisal: - Treatment was suspended in 44/50 subjects (15 after 1 year, 1 after 5 years, 7 due to self-withdrawal and 21 for adverse events) - Small sample size leading to insufficient power for statistical tests

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		(ECOG): PS=0: IFN:86%, obs.: 92%, PS=1: IFN:12%, obs.: 8%, PS=2: IFN:2% • Median follow-up: 4.6 years				
Jocham 2004[42]	• Design: RCT • Sources of funding: LipoNova • Setting: 55 institutions in Germany • Sample size: vaccine group (n=177), control (n=202) • Duration: 1 year	• Eligibility criteria: Patients with primary RCC stage pT2-3b pN0-3 M0 (1993 UICC classification) ECOG performance status 0 to 2, no cardiac disease, no pulmonary disease, no chronic infection • Patients characteristics: Age (Median, IQR): vaccine 58 (53-64) vs control 59 (53-64), Gender (% of female): vaccine 36% vs control 66%, ECOG status: PSO vaccine 85% vs control 84%, PS1 vaccine 13% vs control 13%, PS2 vaccine 2% vs control 2%, PS unknown vaccine 0.% vs control 1%, Tumour stage pT2 vaccine 67% vs control 72%, pT3 vaccine 33% vs control 28% • Median follow-up: not mentioned	• Intervention(s): Autologous cells incubated with IFN-γ 1500 IE per vaccine dose and tocopherol acetate 750 µg per vaccine dose. Tumours cells were then washed to remove IFN-γ and tocopherol acetate. A physiological saline tumour cells solution was then frozen (-82°c) to devitalize the cells. 6 intradermal applications at 4 weeks intervals • Comparator(s): no adjuvant treatment	**Risk of tumour progression** • HR (1.58 (95% CI 1.05-2.37) in favour of vaccine, p=0.0204 log-rank test **Progression-free survival (PSF)** • 5-year PSF: vaccine 77.4% vs control 67.8%, p=0.0204 • In T2 tumour, 5-year PSF: vaccine 81.3% vs control 74.6%, p=0.216, log-rank test) • In T3 tumour, 5-year PSF: vaccine 67.5% vs control 49.7%, p=0.039, log-rank test)	**QoL**: • No difference between groups	• Dropouts: 36 withdrew due to protocol violation • Results critical appraisal: - partial blinding of patients and personnel

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Kjaer 1987[43]	• Design: RCT • Sources of funding: not mentioned • Setting: 2 oncological departments in Denmark • Sample size: Rx n=32 obs. n=33 • Duration: 5 years	• Eligibility criteria: renal adenocarcinoma stage II or III patients that underwent nephrectomy *en bloc*, age < 75 years, no other malignancy, postoperative normal bone marrow, renal-, liver function, ECOG performance status = 0 or 1 • Patients characteristics: Age (Median, range): Rx: 62 y (32-75) vs obs.: 62 y (34-75); Gender (% of female): Rx: 34% vs obs.: 33%; Stage: Rx: stage I (n=17) stage II (n=15) vs obs.: stage I (n=17) stage II (n=16); • Median follow-up (range): Rx: 1404 days (609-2293) obs.: 1281 days (631-2309)	• Intervention(s): Nephrectomy *en bloc* + adjuvant radiotherapy 50 Gy, 1650 reu, 90 TDF ± 15% in 20 fractions of 2.5 Gy with 4 fractions per week (Rx) • Comparator(s): Nephrectomy *en bloc* + no further treatment	**Relapse rate** • Rx: 15/32 vs obs.: 13/33, ns **Survival** • Median survival: Rx: 26 months obs.: no reached • 2-year survival, log rank test ns	**Complication rate**: • Rx: 44%	• Dropouts: 7 patients excluded because of protocol violations • Results critical appraisal: - Small sample size - Protocol violations - Variations in Rx treatment between 2 included centres leading to separate reporting for mortality and morbidity
Margulis 2009[44]	• Design: RCT • Sources of funding: not mentioned • Setting: Anderson Cancer Center (Texas – USA) • Sample size: intervention n=23, comparator n= 23	• Eligibility criteria: completely resected locally advanced high-risk RCC defined as: pT2 (Fuhrman grade 3 or 4), pT3a-c, T4 or N1-2 disease (TNM classification) • Patients characteristics: median age (y) ± SD	• Intervention(s): RN + Thalidomide (100 mg/d for 2 weeks, then 200 mg/d for 2 weeks, followed by 300 mg/d) • Comparator(s): RN + observation	**Recurrence-free survival (RFS):** • Median RFS (95% IC): Thalidomide (n=18) 18.5 months (0.0-37.8) vs observation (n=8) not reached, p=0.022 • % 2-year probability of RFS (SD):	**Cancer-specific survival (CSS):** • % 2-year CSS (SD): Thalidomide 82.6% (7.9) vs observation 82.4% (8.0) • % 3-year CC (SD): Thalidomide 76.7% (9.3) vs	• Dropouts: not clearly reported • Results critical appraisal: - Small sample size leading to insufficient power - CSS is not clearly reported - Total of patients that discontinued

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Duration: 4 years	58.0 ± 11.6; Gender (% of female) 12%; T stage: T2 15.2%, T3a 41.3%, T3b/c 43.5%; Stage: N0/Nx 71.7%, N1 15.2%, N2 13.1%; Fuhrman grade: grade2 8.7%, grade3 50.0%, grade4 41.3% • Median follow-up: 43.9 months (range 9.7-74.2 months)		Thalidomide 47.8% (10.4) vs observation 69.3% (9.7), p=0.022 • % 3-year probability of RFS (SD): Thalidomide 28.7% (9.7) vs observation 69.3% (9.7), p=0.022 **Recurrence site** • Distant metastases: Thalidomide 72% vs observation 78%, p=0.613 • Regional nodal or isolated local recurrences Thalidomide 28% vs observation 22%, p=0.787	observation 75.5% (9.9) **Tolerability:** Most common adverse events • Pain : Thalidomide 100% vs observation 4.3% • Neuropathy: Thalidomide 78.3% vs observation 4.3% • Fatigue / malaise: Thalidomide 6.9% vs observation 4.3% • Constipation: Thalidomide 6.9% vs observation 0% **Safety**: • There was no treatment-related mortality	the treatment is not clearly reported
Messing 2003[45]	• Design: RCT • Sources of funding: National Cancer institute, National Institutes of Health, Department of Health and Human Services, Bethesda • Setting: not mentioned	• Eligibility criteria: patients who had undergone radical nephrectomy for unilateral locally advanced (T3-4a) and/or node-positive RCC without metastasis, no prior radiation, no chemotherapy, no other malignancy, no cardiac disease, adequate bilirubin,	• Intervention(s): RN + IFNα (12 cycles of 5 days every 3 weeks: day 1: $3x10^6$ U/m², day 2: $5x10^6$ U/m², days 3-5: $20x10^6$ U/m²) (IFNα) • Comparator(s): RN + observation (obs.)	**Overall survival :** • Median, years: IFNα.5.1 vs obs. 7.4, p=0.09 • % 2-year survival probability: IFNα.70% vs obs. 77%, p=0.09 • % 5-year survival probability: IFNα.51% vs obs. 62%, p=0.09	**Toxicity :** • 11.4% of IFNα treated patients experienced grade 4 toxicity • No patient died from toxicity	• Dropouts: 10 patients were excluded because of presence of exclusion criteria, 1 was lost to follow-up • Results critical appraisal: - No blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Sample size: IFNα n=140, obs. n=143, • Duration: 5 years	creatinine level and WBC counts, ECOG performance status 0-1 • Patients characteristics: Gender (% of female) IFNα 29.0% vs obs. 30.8%; Age (% of 70-79): IFNα 30.4% vs obs. 30.1%; Stage: pT3a-c, N0 IFNα 64.7% vs obs. 65.7%, pT4a, N0-3, IFNα 5.3% vs obs. 4.2% pT3a-c, N1-3, IFNα 17.3% vs obs. 16.8%, pT1-2, N1-3 IFNα 12.7% vs obs. 13.3%; Performance status 0-1 (% of level 1): IFNα 33.4% vs obs. 30.1%; • Median follow-up: 10.4 months		**Recurrence-free survival :** • Median, years: IFNα.2.2 vs obs. 3.6, p=0.33 • % 2-year survival probability: IFNα.51% vs obs. 56%, p=0.33 • % 5-year survival probability: IFNα.37% vs obs. 41%, p=0.33		
Naito 1997[46]	• Design: RCT • Sources of funding: not mentioned • Setting: 1 centre in Japan • Sample size: UFT: n=33, control n=33 • Duration: 2 years	• Eligibility: Stage I or II RCC (Robson's classification) patients that underwent transperitoneal RN, life expectancy > 3 months, no other previous treatment, no metastasis, no other neoplasm, no disturbance in heart, kidney, liver, bone marrow functions	• Intervention(s): 3 to 6 capsules of UFT (300 to 600 mg as tegafur) • UFT= combination of tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) and 5-fluorouracil • Comparator(s): No adjuvant treatment (control)	**Non-recurrence rate (%):** 5-year non-recurrence rate: UFT: 80.5 % vs control 77.1 %, ns **RCC-specific survival rate (%)** 5-year RCC-specific survival rate: UFT: 90.6 % vs control 82.1 %, ns	**Adverse effects:** • Gastrointestinal disturbance was the most frequent toxicity • No grade 3 or 4 adverse effects **Risk factors of recurrence:** • Tumour grade (1/2, 3): HR (95% CI) 3.10 (0.86-11.14), p=0.0834	• Dropouts: 2 patients received immunotherapy in combination with UFT • Results critical appraisal: - Small sample size

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		• Patients characteristics: Age (% < 60 years): UFT: 60% vs control 42%, Gender (% of female): UFT: 33% vs control: 33%, WHO performance status (%):PS0: UFT: 82% vs control: 79%, PS1: 18% vs control: 18%%, PS2: 0% vs control: 3%; pT stage(%): pT0: UFT 3% vs control: 6%, pT1: UFT 82% vs control: 82%, pT2 UFT 15% vs control: 12%, Tumour grade (%): grade1: UFT 55% vs control: 42%, grade2: UFT 39% vs control: 55%, grade3 UFT 3% vs control: 3%, unknown: UFT 3% vs control: 0% • Median follow-up: 112.9 months (range, 8.1 – 133.1)			• UFT (+/-), Age (<60 years), sex (male/female), Ps (0/1,2) pT stage (1/2, 3), cell type (clear/others) are ns risk factors	
Pizzocaro 1987[47]	• Design: RCT • Sources of funding: Italian National Research Council • Setting: 5 centres in Italy • Sample size: MPA n=58, control n=62	• Eligibility criteria: Radically resected renal cancer without distant metastases, no previous hormonal therapy, no disease contraindication for high dose MPA, age ≤ 70 years	• Intervention(s): MPA 500 mg 3/weeks for 1 years (i.m. During 2 months than per os.) (MPA) • Comparator(s): No adjuvant treatment (control)	**Relapse rate** • MPA 32.7% vs control 33.9%, ns • Median interval to relapse: MPA 11 months vs control 20 months, ns	**Complication rate** • 56.9 % in MPA group	• Dropouts: 11.7% (n=16), excluded (4 early cardiovascular deaths, 9 inadequate follow-up, 3 discontinuation of MPA) • Results critical appraisal:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Duration: 4 years	• Patients characteristics: Gender (% of female): MPA 38 % vs control 34 % • Median follow-up: not mentioned		**5-year disease free-survival** • MPA 20/58 vs control 19/62, ns		- No ITT reporting - Same sample size - Partial result reporting: no range provided with medians
Pizzocaro 2001[48]	• Design: RCT • Sources of funding: Italian National Research Council • Setting: 21 urological units in Italy • Sample size: rIFN-α2b (n=123), obs. (n=124) • Duration: 5 years	• Eligibility criteria: radical nephrectomy for RCC with lymph node dissection, age < 70 years, ECOG <2, no cardiac disease, renal, hepatic hematologic disorders, no other malignancy • Patients characteristics: Gender (% of female): rIFN-α2b 29% vs obs. 35%, Age (% of <60 years): rIFN-α2b 50% vs obs. 55%, T category: pT2 rIFN-α2b n=8 vs obs. n=8, pT3a rIFN-α2b n=75 vs obs. n=72, pT3b rIFN-α2b n=40 vs obs. n=44, N category pN0 rIFN-α2b n=102 vs obs. n=102, pN1 rIFN-α2b n=8 vs obs. n=9, pN2 rIFN-α2b n=10 vs obs. n=12, pN3 rIFN-α2b n=3 vs obs. n=1	• Intervention(s): rIFN-α2b 6 million IU im. 3x/week for 6 months • Comparator(s): No adjuvant treatment (obs.)	**5-year overall survival probability** • rIFN-α2b: 0.660 vs obs. : 0.665 HR [IFN/obs (95% CI)]= 1.04 (0.671-1.613), p*=0.891 **5-year event-free survival** • rIFN-α2b: 0.567 vs obs. : 0.671 HR [IFN/obs (95% CI)]= 1.04 (0.927-2.149), p*=0.107 * log-rank test	**Toxicity** • 55.3% of rIFN-α2b patients develops signs of toxicity • 28 % of rIFN-α2b patients had a dose reduction and/or suspension of IFN therapy	• Dropouts: 15 patients because poor collaboration of 6 participating centres, and 2 were lost of follow-up • Results critical appraisal: - slightly underpowered

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		• Median follow-up (range): 62 months (-99 months)				
Wood 2008[49]	• Design: RCT • Sources of funding: antigenics • Setting: 118 centres in North America and Europe • Sample size: Vaccine: n=361, obs. : n=367 • Duration: not mentioned (extension of the trial from 2005 to 2007)	• Eligibility criteria: resectable RCC without metastasis, tumour stage cT1b-T4 No M0 or cTany N1-2 M0, performance status ≤ 1, age ≥ 18 y, life expectancy ≥ 3 months, no other malignancy, adequate bone marrow, renal, hepatic and cardiac function • Patients characteristics: Age (Median, range): Vaccine 57.0 (29-81) vs obs.: 60.0 (35-86), Gender (% of female) Vaccine 37% vs obs. 38%, ECOG performance status: Vaccine: 77% PS0, 23% PS1 vs obs: PS0 78%, PS1 22% AJCC* stage: • Median follow-up: 1.9 years (IQR 0.9-2.5 *AJCC: American Joint Committee on Cancer*	• Intervention(s): autologous vaccine prepared with vitespen (HSPPC-96 protein) derived tumour cells (vaccine) *Preparation of vaccine failed in 8%* • Comparator(s): No further treatment (Obs.)	**Recurrence** In ITT • Recurrence rate: Vaccine: 37.7% vs 39.8%, p=0.506 • Recurrence-free survival Results reported in graph, p=0.506 **Overall survival** • Results reported in graph, p=0.896	**Adverse events**: • Discontinued treatment because of adverse events : 2% among whom 0.9% were treatment-related • Most commonly reported: injection-site erythema (vaccine: 49.7% vs obs. 0%, p<0.05), injection-site induration (vaccine: 48.1% vs obs. 0%, p<0.05), back pain (vaccine: 12.3% vs obs. 5.0%, p<0.05), headache (vaccine: 12.3% vs obs. 2.5%, p<0.05), fatigue (vaccine: 10.4% vs obs. 3.3%, p<0.05)	• Dropouts: 17% dropouts because metastatic/residual disease • Results critical appraisal: - Small sample size (85% power in ITT but this % is not reached in full analysis set) - Discrepancy between investigators and external assessor's reading of outcomes - Sponsored trial with a large implication of the sponsor in design and in data analysis - Difference in follow-up frequency between group - Not accurate checking of inclusion criteria - One patient received another patient's vaccine

4.2.3. Treatment of local recurrence/ metastases

4.2.3.1. Surgery

Table 40 – Evidence table - RCT – Surgery in metastatic RCC

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Flanigan 2001[50]	• Design: RCT • Sources of funding: National Cancer institute • Setting: 80 institutions in US • Sample size: nephrectomy n= 120, IFNα-2b n=121 • Duration: 7 years	• Eligibility criteria: metastatic RCC patients SWOG performance status 0 to 1 without prior chemotherapy, immunotherapy or other biologic-modifiers, no radiotherapy, adequate bilirubin and creatinine level, cardiac arrhythmias, no previous cancer • Patients characteristics: Mean age (range): IFNα-2b: 59.0 (29-87) vs nephrectomy 58.8 (37-80); Gender (% of female): IFNα-2b: 24.8% vs nephrectomy 30.8%; SWOG performance status 0-1 (% of level 1): IFNα-2b: 58.1% vs nephrectomy 45.0%*, only lung metastases (%): IFNα-2b: 66.9% vs nephrectomy 45.0%, • Median follow-up: 368 days	• Intervention(s): nephrectomy + IFNα-2b (escalation from 1.25 to 3.75 million IU/m²) (nephrectomy) • Comparator(s): IFNα-2B (escalation from 1.25 to 3.75 million IU/m²) (IFNα-2b)	**Median survival** in months (95% CI) • Nephrectomy 11.1 (9.2-16.5) vs IFNα-2b 8.1 (5.4-9.5), p=0.012 **1-year survival probability** • Nephrectomy 49.7% vs IFNα-2b 36.8%, p=0.012 The primary analysis based on the stratified log-rank test found a significant advantage associated with nephrectomy (p=0.05)	**Adverse events** • Surgical complications : 22/98 patients **Response rate (SWOG)** • Partial or complete response [% (95%CI)] : nephrectomy: 3.3% (1-9) vs IFNα-2b 3.6% (1-10), ns **Toxicity** • Severe complication (n) : nephrectomy: 10 vs IFNα-2b 13 • One patient died from myocardial infraction attributed to IFN (IFNα-2b group)	• Dropouts: 17 patients did not undergo the planned surgery, 2 patients declined interferon therapy • Results critical appraisal: - Blinding of intervention is difficult - Short follow-up due to a low survival rate at 1 year

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		**p=0.04, however this unbalanced parameter did not affect the results*				
Mickisch 2001[51]	• Design: RCT • Sources of funding: National Cancer institute • Setting: 3 centres in Europe (Netherlands, Russia, Belgium) • Sample size: nephrectomy n=42, IFNα-2b n=43 • Duration: 3 years	• Eligibility criteria: metastatic RCC patients SWOG performance status 0 to 1 without prior chemotherapy, immunotherapy or other biologic-modifiers, no radiotherapy, adequate bilirubin and creatinine level, cardiac arrhythmias, no previous cancer • Patients characteristics: Median age (range): IFNα-2b: 56 (29-74) vs nephrectomy 61 (36-76); Gender (% of female): IFNα-2b: 36% vs nephrectomy 21%; WHO performance score 0-1 (% of level 1): IFNα-2b: 60% vs nephrectomy 52%, lung metastases (%): IFNα-2b: 81% vs nephrectomy 79%, • Median follow-up (range): 16 weeks (1-90)	• Intervention(s): nephrectomy + IFNα-2b 5 x 10^6 million IU/m² 3X/week during 52 weeks (nephrectomy) • Comparator(s): IFNα-2b 5 x 106 million IU/m² 3X/week	**Survival time** in months • HR (95%CI) 0.54 (0.31-0.94) p=0.03 • Median survival: nephrectomy: 17 months vs IFNα-2b 7 months **Time to progression** • HR (95%CI) 0.60 (0.36-0.97) p=0.04	**Overall response rate (complete or partial response)** • Partial or complete response (%): nephrectomy: 19% vs IFNα-2b 12%, p=0.38 **Toxicity** • Perioperative surgical complications (n=6)	• Dropouts: No data available for one control patient • Results critical appraisal: - Blinding of intervention is difficult - Short follow-up - Small sample size leading to underpowered statistical test

4.2.3.2. Systemic treatment

4.2.3.2.1. Immunotherapy

Systematic reviews

Table 41 – Evidence table - SR – Immunotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Coppin 2006[13]	• Design: SR • Sources of funding: BC Cancer (Canada), Prostate Disease and Urologic Malignancies CRG (USA), Department of Veterans Affairs Health Services Research and Development HSRD office (USA), Cochrane Urological Cancers Subgroup, Velindre NHS Trust, Cardiff, UK • Search date: CENTRAL, MEDLINE, EMBASE, American Urologic Association,	• Eligibility criteria: Patients with histologically verified metastatic or locally inoperable RCC. The majority of studies excluded patients with brain metastases and set limits on organ dysfunction. • Patients' characteristics: In most studies, patients' ECOG was 0 to 2 but when intensive therapy arm was used, ECOG was 0 to 1 with lack of comorbidity. Age range was most commonly 18 to 75 years. A few studies required nephrectomy. • Median FU: not mentioned	• Intervention: immunotherapy agent • Comparator: placebo or other immunotherapy agent or chemotherapy or hormone therapy, lectin, cimetidine or nephrectomy	**Remission rate#** *Partial or complete remission* (56 studies) 6% in placebo arm, 2.4% in unblinded non-immunotherapy arms, 12.4% in immunotherapy arms **Median survival** (27 studies) 15.7 months in placebo arm, 9.5 month on active non-immunotherapy arms and 13.0 months on immunotherapy arms **Correlation of remission and survival rate** For the individual arms by treatment type, no correlation between remission rate and median survival or between remission rate and one-year survival # Dose effect and route of administration issues were not reported here because	**High dose IL-2 vs other treatment option** • Remission - IL-2 (hd)* vs IL-2 (ld)$ iv 2 studies (n=306) Peto OR (95% CI) 1.82 (1.00 to 3.30),I²=0%, p=0.049 - IL-2 (hd) vs IL-2 (ld) sc 1 study (n=154) Peto OR (95% CI) 2.67 (1.06 to 6.71), p=0.037 - IL-2 (hd) vs IFN-α + IL-2 (ld) sc 1 study (n=192) Peto OR (95% CI) 2.70 (1.26 to 5.82), p=0.011 • One-year mortality - IL-2 (hd)* vs IL-2 (ld)$ iv 2 studies (n=305) Peto OR (95% CI) 0.95 (0.59 to 1.53), I²=0%, p=0.84 - IL-2 (hd) vs IL-2 (ld) sc 1 study (n=187)	Results critical appraisal: • Narrative quality assessment of the included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	American Society of Clinical Oncology, ECCO, European Society of Medical Oncology • Searched databases: 1966 through to the end of June 2005 • Included study designs: RCT including phase II and phase III randomized trials but not phase I. • Number of included studies: 58 RCT including 6 published as meeting abstracts • Included studies: Aass 2005 Adler 1987 Atzpodien 2001 Atzpodien 2004 Boccardo 1998 Borden 1990 Brinkmann 2001 Bromwich 2002			considered as out-of-scope of our review. In addition, adjuvant effect of IFN-α for the nephrectomy is reported in the dedicated section. Coppin et al. did not find any additional references. Finally, hierarchy of cytokine therapies was also reported.	Peto OR (95% CI) 1.00 (0.55 to 1.83), p=1.0 - IL-2 (hd) vs IFN-α + IL-2 (ld) sc 1 study (n=192) Peto OR (95% CI) 0.71 (0.40 to 1.26), p=0.24 **IFN-α vs control [4 studies vs MPA, 1 study vinblastine, 3 studies IL-2 (ld)]** • Remission - IFN-α vs non-immuno controls 4 studies (n=644) OR (95% CI) 7.61 (3.02 to 19.18), I^2=0%, p=0.000017 - IFN-α vs non-immuno control (intermed. prognosis) 1 study (n=245) OR (95% CI) 1.71 (0.40 to 7.32), p=0.47 - IFN-α vs IL-2 (ld) 3 studies (n=576) OR (95% CI) 0.93 (0.47 to 1.84), I^2 = 0%, p=0.84 • One-year mortality - IFN-α vs non-immuno control 4 studies (n=614)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Buzogany 2001 Creagan 1991 DeMulder 1995 Dexeus 1989 Donskov(i) 2005 Donskov(ii) 2005 Edsmyr 1985 Figlin 1999 Flanigan 2001 Foon 1988 Fossa 1992 Fujita 1992 Gleave 1998 Henriksson 1998 Jayson 1998 Kinouchi 2004 Kirkwood 1985 Kriegmair 1995 Law 1995 Lissoni 1993 Lissoni 2000 Lummen 1996 McCabe 1991 McDermott 2005 Mickisch 2001 Motzer 2000 Motzer 2001 MRCRCC 2000 Muss 1987 Naglieri 1998 Negrier 1998 Negrier 2000 Negrier 2005 Neidhart 1991 Osband 1990 Pedersen 1980 Porzsolt 1988 Pyrhonen 1999				OR (95% CI) 0.56 (0.40 to 0.77), I², p=0.00049 - IFN-α vs non-immuno control (intermed. prognosis) 1 study (n=230) OR (95% CI) 0.86 (0.51 to 1.46), p=0.57 - IFN-α vs IL-2 (ld) 3 studies (n=559) OR (95% CI) 0.93 (0.66 to 1.31) **IFN-α +/- hormone** • Remission 2 studies (n=183) Peto OR (95% CI) 0.98 (0.37 to 2.62), I²=0%, p=0.97 • One-year mortality 1 study (n=63) Peto OR (95% CI) 1.58 (0.47 to 5.30), p=0.46 **IFN-α +/- chemotherapy** • Remission 3 studies (n=455) Peto OR (95% CI) 1.36 (0.80 to 2.32), I²=52%, p=0.26 • One-year mortality 2 studies (n=343)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Quesada 1985 Radosavljevic 2000 Rosenberg 1993 Sagaster 1995 Scardino 1997 Steineck 1990 Tannir 2004 Tsavaris 2000 Weiss 1992 Witte 1995 Yang 1995° Yang (i) 2003 Yang (ii) 2003 ° not reported because melanoma and RCC patients mixed. Other RCTs with only RCC patients are available				Peto OR (95% CI) 0.81 (0.53 to 1.25), I²=0%, p=0.34 **IFN-α +/- IFN-γ** • Remission 2 studies (n=170) Peto OR (95% CI) 0.42 (0.13 to 1.40), I²=0%, p=0.16 • One-year mortality 1 study (n=58) Peto OR (95% CI) 0.98 (0.34 to 2.81), p=0.97 **IFN-α +/- 13-cis-retinoic acid** • Remission 2 studies (n=387) Peto OR (95% CI) 2.28 (1.17 to 4.45), I²=0%, p=0.016 • One-year mortality 2 studies (n=592) Peto OR (95% CI) 0.88 (0.63 to 1.21), I²=0%, p=0.43 **IFN-α +/- other agents** (cimetine, aspirine, coumarin) • Remission 3 studies (n=395) Peto OR (95% CI) 0.96 (0.53 to 1.73), I²=45%, p=0.88	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					• One-year mortality 2 studies (n=287) Peto OR (95% CI) 0.94 (0.58 to 1.53), I²=0%, p=0.79 **IFN-α + IL-2 ± 5 FU vs control** (tamoxifen, lectin, IFN-γ) • Remission 4 studies (n=442) OR (95% CI) 12.06 (4.79 to 30.34), I²=31%, p< 0.00001 • One-year mortality 3 studies (n=243) OR (95% CI) 0.82 (0.50 to 1.37), I²=73%, p=0.45 **IFN-γ vs placebo** • Remission 1 study (n=197) OR (95% CI) 0.66 (0.18 to 2.41), p=0.53 • One-year mortality 1 study (n=150) OR (95% CI) 1.00 (0.53 to 1.91), p=0.99 $ ld = low-dose * hd= high-dose	
Tang 2013[23]	• Design: Meta-analysis • Sources of funding: Key	• Eligibility criteria: patients with metastastic RCC	• Intervention: Adoptive Cellular Immunotherapy* : autolymphocyte +	**Objective response** (4 studies) RR (95%CI)	**Toxicity** • Most of ACI-related adverse reactions: grade 1 or 2	Results critical appraisal:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	New Drug Creation, Manufacturing Program of the "Twelfth Five-year Plan' • Search date: from inception to December 12, 2012 • Searched databases: Pubmed • Included study designs: RCT • Number of included studies: 4 • Included studies: Osband 1990 Law 1995 Figlin 1999 Liu 2012	• Patients' characteristics: only reported by study and by study arms • Median follow-up: not mentioned	cimetidine, LAK, $CD8^+$ TIL + IL-2, CIK (ACI) • Comparator: various control: cimetidine, IL-2, IL-2+IFN-α-2a (control) * LAK = Lymphokine Activated Killer; TIL = Tumour Infiltrating lymphocytes; CIK = Cytokine Induced Killer	1.65 (1.15-2.38), I^2=49%, p=0.007 (n=454) **1-year mortality** RR (95%CI) 1.30 (1.12-1.52), I^2=0%, p=0.0008 (n=469) **3-year mortality** RR (95%CI) 2.76 (1.85-4.14), I^2=46%, p<0.00001 (n=309) **5-year mortality** RR (95%CI) 2.42 (1.21-4.83), I^2=28%, p=0.01 (n=219)	• LAK+IL-2: more pulmonary toxicity (p=0.008), hypotensive episodes (p=0.051) compared to IL-2 • At least twice more embolus, apnea, dyspnea caused by IL-2 + TIL cell in comparison with IL-2	• Difference in ACI protocols and comparators • Two studies added IL-2 to ACI • Low quality of included studies • Various histology types, one study restricted to clear cell renal carcinoma

RCTs

Table 42 – Evidence table - RCT – Immunotherapy in metastatic RCC

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Gore 2010[52]	• Design: RCT • Sources of funding: National Cancer Institute, EORTC,	• Eligibility criteria: Advanced metastatic RCC older than 18 years, measurable lesion, WHO performance status 0	• Intervention(s): IFN-α2a subcutaneously 3X/week 9 or 10 million IU (IFN-α2a)	**Overall survival (OS):** • OS probability* HR (95% CI) 1.05 (0.90-1.21), p=0.55 • 1-year OS probability	**Progression-free survival (PFS)**: • Overall PFS probability* HR (CI95%)	• Dropouts: all analyses were on ITT. However, only 1% of IFF group received the

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Schering-Plough, Chiron, Roche, UK National Health Service • Setting: 50 centres across UK, Holland, Slovakia, Germany, Belgium, Denmark • Sample size: IFN-α2a n=502, IIF n=504 • Duration: 5 years	or 1, normal haematological and creatinine measures, life expectancy > 12 weeks, no previous chemotherapy, endocrine therapy or radiotherapy, no brain metastasis, no cardiac disease, no active infection, no previous malignant disease < 5 years • Patients characteristics: Median age (range): IFN-α2a 58 (23-82) vs IIF 57 (20-81), Gender (% of female): IFN-α2a 28% vs IIF 23%, WHO performance status 0-1 (% of level 1): IFN-α2a 46% vs IIF 40%, Nephrectomy (%): IFN-α2a 89% vs IIF 90%, Metastases (% only in one site): IFN-α2a 28% vs IIF 32%, MSKCC risk group: low IFN-α2a 7% vs IIF 8%; medium IFN-α2a 58% vs IIF 60%; high IFN-α2a 19% vs IIF 17%; unknown IFN-α2a 17% vs IIF 15%, • Median follow-up: 37.2 months (24.8-52.3)	• Comparator(s): Combined treatment composed of IFN-α2a, IL-2 and fluorouracil (IIF)	IFN-α2a (95% CI): 67% (62-71) vs IIF 67% (63-71), ns • 3-year OS probability IFN-α2a (95% CI): 30% (26-35) vs IIF 26% (22-30), ns • Median survival time IFN-α2a (95% CI): 18.8 months (17.0-23.2) vs IIF 18.6 (16.5-20.6), ns * Adjustment for confounding variables leads to similar results: HR (CI95%) 1.12 (0.96-1.30), p=0.14	1.02 (0.89-1.16), p=0.81 • Median PFS time IFN-α2a (95% CI): 5.5 months (4.3-6.2) vs IIF 5.3 (4.8-6.0), n **Toxicity** • Grade 3 and 4 probability IFN-α2a: 53% vs IIF 36%, p<0.0001 **Quality of life** Rotterdam Symptom Checklist, the Hospital Anxiety and Depression Scale, and the EuroQol Five Dimensions questionnaire • No difference between group in score **Overall response rate** • IFN-α2a: 23% vs IIF 16%, p=0.0045 * Adjustment for confounding variables leads to similar results: HR (CI95%) 1.03 (0.90-1.17), p=0.69	third cycle of treatment • Results critical appraisal: - Predefined sample size was not exactly reached but a huge number of events was collected - No blinding - Difference dosage if INF-α2a in the two group - Important rate of treatment break and dose modification - Confounding factors are taken into account

4.2.3.2.2. Targeted therapies

Systematic review

Table 43 – Evidence table - SR – Targeted therapies in metastatic renal cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Coppin 2010[14]	• Design: SR • Sources of funding: • Search date: • Searched databases: January 2000 to June 2010 • Included study designs: RCTs • Number of included studies: 16 RCTs reported in 33 publications • Included studies: **1. TARGET** Bukowki (2) 2007 Eisen 2008 Escudier 2007 Escudier (3) 2009 **2. AVOREN** Escudier 2007 Escudier(3) 2010 Melichar 2008	• Eligibility criteria: Adult patients with metastatic or locally inoperable RCC, histologically verified at presentation or relapse. Patients characteristics: Adult men and women in ratio for renal cancer (2:1). Age range was broad. Patients with brain metastases were usually excluded. Good performance status excepted in Hudes 2010. Vast majority undergone prior nephrectomy. Histology restricted to renal cancers with clear-cell component. Extent of prior systemic treatment (systemically untreated, second-line after cytokine therapy, second-line	• Intervention: 13 targeted agents (inhibitor of VEGF, EGFR, mTOR) • Comparator: Placebo, cytokines or other targeted agents	**Objective response rate** See overview of results in main report **Progression free survival** See overview of results in main report **Overall survival** See overview of results in main report	**Toxicity** See overview of results in main report	Results critical appraisal: • Adequate search • Quality appraisal performed, and reported • Only RCTs were included but some were reported as abstracts. Only peer reviewed journal publications are considered here • No pooling of results was performed due to the heterogeneity in the interventions

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	3. **Escudier(4) 2009** 4. **Hudes 2007** Dutcher 2009 Zbrozek 2010 5. **Jonasch 2010** 6. **Lee 2006** 7. **Motzer 2007** Cella 2008 Cella 2009 Cella 2010 Castellano 2009 Motzer 2008 Motzer 2009_3 8. **RECORD-1** Motzer 2008 White 2010 9. **Bukowski 2007** 10. **Propopio 2010** 11. **Ratain 2006** 12. **Ravaud 2008** 13. **Rini 2004** Rini 2008 14. **Stadler 2005** 15. **Sternberg 2010** Hutson 2006 16. **Yang 2003** Elaraj 2004	after targeted therapy • Median follow-up: not mentioned				

RCTs

Table 44 – Evidence table - RCT – Targeted therapies in metastatic renal cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Rini 2012[53]	• Design: RCT • Sources of funding: Amgen Incorporated • Setting: 41 centres in North America and Europe • Sample size: 152 patients (50 arm A, 51 arm B, 51 arm C) • Duration: 1 year	• Eligibility criteria: untreated mRCC with clear-cell component, good/intermediate risk MSKCC, ≥1 unidimensionnally measurable lesion (RECIST), ECOG ≤ 1, no previous systemic treatment, no brain metastases • Patients characteristics: Gender (% of female): arm A 18%, arm B 31%, arm C 25%, Median (range) age in years: arm A 60 (39-80), arm B 58 (28-84), arm C 59 (38-84), > 3 sites of metastases: arm A 22%, arm B 24%, arm C 12%, ECOG=1 arm A 38%, arm B 43%, arm C 45% • Median follow-up: 75 (1-124) weeks	• Intervention(s): Sorafenib 400 mg orally 2/day + Intravenous infusion AMG 386 over 30 to 60 minutes • Comparator(s): Sorafenib 400 mg orally 2/day + Intravenous infusion placebo over 30 to 60 minutes (arm C)	**PFS** (months (95% CI)) • Arm A 9.0 (5.4-15.0), arm B 9.0 (5.4-14.4), arm C7.2 (5.4-12.8) • HR for arm A and B combined versus arm C: 0.88 (95% CI, 0.60-1.30; p= 0.52) **Objective response rate** % (95% CI) • Arm A 38 (25-53), arm B 37 (24-52), arm C 25 (14-40), • Comparison with placebo: arm A (-6.9 to 30.8), arm B (-7.5 to 30.0)	**Adverse events (AEs)**: • Serious AEs arm A 36%, arm B 49%, arm C 28% • Discontinuation because of AEs: arm A 12%, arm B 18%, arm C 8% **Pharmacodynamics biomarkers**: • Not reported (see publication for more details) **Pharmacokinetics**: • Not reported (see publication for more details)	• Dropouts: drop-pout arm A 41, Arm B 45, arm C 47 • Results critical appraisal: - Small sample size - Huge discontinuation rate (see dropout) - Independent centralized review for PFS and objective response rate
Motzer 2013[54]	• Design: RCT • Sources of funding: AVEO oncology	• Eligibility criteria: age ≥ 18 years, clear cell RCC + recurrence or metastases, measurable disease per RECIST,	• Intervention(s): Tivozanib (orally) at 1.5mg 1x/day every day for 3 weeks followed by 1 week off	**PFS** • Overall PFS (months): HR (95% CI): 0.797 (0.639-0.993), p=0.042	**OS** • HR (95% CI) 1.245 (0.954-1.624), p=0.105 **ORR (% (95% CI))**	• Dropouts: tivozanib 154/259 vs sorafenib 192/257

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Setting: 76 centres across 15 countries • Sample size: Tivozanib (n=260), sorafenib (n=257) • Duration: between February and August 2010	ECOG≤1, treatment-naïve patients or prior immunotherapy, chemotherapy or hormonal therapy, no significant cardiovascular disease, stable brain metastases (at least 3 months) • Patients characteristics: Median age (range): tivozanib 59 y (23-83) vs sorafenib 59 y (23-85), Gender (% of female): tivozanib 29% vs sorafenib 26%, ECOG PS (% of ECOG=0): tivozanib 45% vs sorafeib 54%, prior systemic therapy for metastatic (%): tivozanib 30 % vs sorafenib 30% Patients characteristics were well balanced between the 2 arms except for ECGO PS (More patients with favourable ECGOC of 0 in sorafenib arm compared with tovozanib (p=0.035) • Median follow-up:tivozaib 12.0	• Comparator(s): Sorafenib (orally) at a dose of 400 mg 2X/day continuously (one cycle is 4 weeks on).	• Stratified PFS by prior systemic therapy o No prior treatment HR (95% CI): 0.756 (0.580-0.985), p=0.037 o Prior systemic treatment for mRCC HR (95% CI): 0.877 (0.587-1.309), p=0.520 • Stratified PFS by ECOG PS o ECOG PS=0 HR (95% CI): 0.617 (0.442-0.860), p=0.004 o ECOG PS=1 HR (95% CI): 0.920 (0.680-1.245), p=0.588 • Stratified PFS by MSKCC prognosis group o Favorable HR (95% CI): 0.590 (0.378-0.921), p=0.018 o Intermediate HR (95% CI): 0.786 (0.601-1.028), p=0.076 o Poor HR (95% CI):	• Tivozanib 33.1% (27.4-39.2) vs sorafenib 23.3% (18.3-29.0), p=0.014 **HRQoL:** • No difference between baseline level and 12 month of treatment in both arms **AEs**: • % of patients experiencing at least 1 treatment-emergent AE: tivozanib 91 % vs sorafenib 97% • % of patients discontinuing therapy because of AE: tivozanib 4% vs sorafenib 5% • % of patients interrupting their treatment because of AE: tivozanib 19% vs sorafenib 36% • % of patients with dose reductions due to AE: tivozanib 14% vs sorafenib 43%, p<0.001 • Mortality o Due to disease progression (n): tivozanib 8 vs sorafenib 2 o Due to other causes (n) : tivozanib 12 vs sorafenib 12	• Results critical appraisal: - Cross-over allowed after progression disease in patients treated with sorafenib -> long-term OS impossible - High percentage of dropouts mainly because of disease progression

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		months and sorafenib 9.5 months		1.361 (0.546-3.393), p=0.504		
Motzer 2013b[55]	• Design: RCT • Sources of funding: GSK pharmaceuticals • Setting: 14 countries in North America, Europe, Australia and Asia • Sample size: pazopanib (n=554) and sunitinib (n=548) • Duration: 2 years	• Eligibility criteria: age≥ 18 years, advanced or metastatic clear-cell RCC, no prior systemic treatment, measurable disease by RECIST, Karnofshy performance-status score ≥ 70, no brain metastases, no poorly controlled hypertension, no cardiac and vascular conditions • Patients characteristics: Median age (range): pazopanib 61 (18-88) vs sunitinib 62 (23-86), gender (% of female): pazopanib 29% sunitinib 25%, prior nephrectomy (%) pazopanib 82% vs sunitinib 84%, prior X-ray pazopanib 8% vs sunitinib 8%, KPS<90 pazopanib 25% vs sunitinib 24%, MSKCC prognosis: favourable pazopanib 27% vs sunitinib 27%,	• Intervention(s): Pazopanib (orally) at 800 mg 1x/day, • Comparator(s): Sunitinib (orally) in 6-week cycles at 50 mg (1x/day) for 4 weeks, followed by 2 weeks without treatment.	**PFS** *Non-inferiority* • HR (95% CI): 1.05 (0.90-1.22) Similar results across ethnic groups, geographic regions	**OS** • HR (95%) 0.91 (0.76-1.08) **ORR** • Pazopanib 31% vs sunitinib 25%, p=0.03 **Safety** • Dose interruption of 7 days or more: pazopanib 44% vs sunitinib 49% • Discontinuation drug rate: pazopanib 24% vs sunitinib 20% **HRQoL** *Difference in mean change from baseline score with pazopanib vs sunitinib* • FACIT-F: 2.32, p< 0.001 • FKSI-19 (total score): 1.41, p=0.02 • CTSQ p < 0.001 excepted in dimension related to expectations of therapy (no difference between arms) • SQLQ p≤0.01 in all dimension	• Dropouts: discontinuation of intervention pazopanib 486/557 vs sunitinib 483/553 • Results critical appraisal: - High implication of the pharma sponsor in design trial, data collection and reporting - Open-label trial but blinding in outcome assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		intermediate pazopanib 58% vs sunitinib 59%, poor pazopanib 12% vs sunitinib 9% unknown pazopanib 3% vs sunitinib 4% • Median follow-up (range): pazopanib 8.0 months (0-40) vs sunitinib 7.6 months (0-38)				
Mulders 2012[56]	• Design: RCT • Sources of funding: AstraZeneca • Setting: 1 centre • Sample size: cediranib (53), placebo (18) • Duration: 11 months	• Eligibility criteria: Adult patients with metastatic or recurrent clear-cell RCC/ adenocarcinoma, measurable lesion(s) by RECIST, 0 <WHO PS> 2, no prior VEGF-signalling inhibitor therapy, max 1 prior immunotherapy, no prior cytotoxic chemotherapy • Patients characteristics: Median age (range): cediranib 60 (46-75) vs placebo 61 (45-79), gender (% of female): cediranib 25% placebo 17%, WHO PS=0 cediranib 72% vs placebo 56%, prior nephrectomy (%)	• Intervention(s): Cediranib 45mg/day • Comparator(s): placebo	**% change from baseline in tumour size** • Cediranib -20% versus placebo +20%, p<0.0001	**Response rate**: • Partial response Cediranib 34% versus placebo 0% • Stable disease Cediranib 47% versus placebo 22% **PFS** • HR (95% CI): 0.45 (0.26-0.76) **Safety and tolerability** • Dose reduction and/or pause 87% in cediranib patients • 75% of cediranib patients experienced CTCAE grade ≥3 (most frequent hypertension, fatigue and diarroea) • Discontinued treatment due to AEs 16% in cediranib patients • Severe hypertension: cediranib 32% vs placebo 1%	• Dropouts: cediranib (8) and placebo (4) • Results critical appraisal: - Sample sample size - Sponsor participated in data collection and analysis - No external assessment of response rate - Cross-over from placebo to cediranib before the completion of the trial leading to cause in interpretation of PFS

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		cediranib 87% vs placebo 83%, prior X-ray cediranib 11% vs placebo 17%, MSKCC prognosis: favourable cediranib 49% vs placebo 33%, intermediate cediranib 49% vs placebo 56%, poor cediranib 2% vs placebo 11% • Median follow-up: not reported			• Moderate hypertension: cediranib 45% vs placebo 5%	
INTORACT Rini 2014[57]	• Design: RCT • Sources of funding: Wyeth (Pfizer) • Setting: 124 sites in 29 countries • Sample size: Tem/Bev (n=400), IFN/Bev (n=391) • Duration: 30 months	• Eligibility criteria: Adult patients with advanced (stage IV or recurrent) clear cell RCC, no prior systemic treatment, Karnofsky PS≥ 70%, life expectancy ≥ 12 weeks, at least one lesion measurable by RECIST, no CNS metastasis, no thrombotic or bleeding episodes within 6 months, controlled hypertension, no surgery or X-ray therapy within 4 weeks, no use of antiplatelet agents or corticosteroids • Patients characteristics: Median age (range):	• Intervention(s): temsirolimus (25 mg IV weekly) + bevacizumab (10 mg/kg IV every 2 weeks) [Tem/Bev] • Comparator(s): IFN (9 million U sc thrice weekly) + bevacizumab (10 mg/kg IV every 2 weeks). [IFN/Bev]	**PFS** HR (95%CI): 1.1 (0.9 – 1.3), p=0.8 No clinical benefit for Tem/Bev after stratification by prior nephrectomy, MSKCC prognostic group, age, sex or geographic region	**ORR** RR adjusted (95% CI): 1.0 (0.8-1.3), p=1.0 **OS** HR (95%CI): 1.0 (0.9 – 1.3), p=0.6 **QoL** • FKSI-15 mean overall score Tem/Bev: 43.3 vs IFN/Bev 41.5, p=0.002 but not clinically meaningful difference threshold of 3-5 • FKSI-DRS mean overall score Tem/Bev: 29.2 vs IFN/Bev 28.0, p<0.001 but not clinically meaningful difference threshold of 2-3 • EQ-5D, Teem/Bev vs IFN/Bev, ns • EQ-VAS, Teem/Bev vs IFN/Bev, ns	Dropouts: number of patients that discontinued the treatment Tem/Bev: 372/400 vs IFN/Bev 354/391 • Results critical appraisal: - Open-label but blinding outcome assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		Tem/Bev 59 years (22-87), IFN/Bev 58 years (23-81), Gender (% of female): Tem/Bev 29%, IFN/Bev 31%, Karnofsky PS≥80%: Tem/Bev 95%, IFN/Bev 92%, favourable or intermediate MSKCC prognosis group: Tem/Bev 89%, IFN/Bev 90%, prior nephrectomy Tem/Bev 85%, IFN/Bev 86%,, prior X-ray Tem/Bev 11%, IFN/Bev 9% • Median follow-up: not mentioned			**Safety and tolerability** • Dose reduction owing to AEs Tem/Bev: 30% vs IFN/Bev 38% • Dose delay owing AEs Tem/Bev: 70% vs IFN/Bev 62% • Treatment-emergent AEs (all grades) Only significant differences (p<0.001) were reported - Hypercholesterolemia Tem/Bev: 32% vs IFN/Bev 10% - Rash Tem/Bev: 32% vs IFN/Bev 8% - Mucosal inflammation Tem/Bev: 27% vs IFN/Bev 10% - Stomatitis Tem/Bev: 26% vs IFN/Bev 10% - Hyperglycaemia Tem/Bev: 22% vs IFN/Bev 5% - Pyrexia Tem/Bev: 21% vs IFN/Bev 39% - Peripheral oedema Tem/Bev: 17% vs IFN/Bev 8% - Neutropenia	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					Tem/Bev: 5% vs IFN/Bev 17% - Myalgia Tem/Bev: 5% vs IFN/Bev 15%	
Nosov 2012[58]	• Design: randomized discontinuation trail • Sources of funding: AVEO pharmaceuticals • Setting: no mentioned • Sample size: Tivozanib (n=61), placebo (n=57) • Duration: 8 months	• Eligibility criteria: adult patients non-operable patients, Karnofsky PS≥ 70%, adequate bone narrow, hepatic and renal function, only one prior systemic treatment for RCC excepted VEGF targeted therapy, no CNS malignancies, no clinically symptomatic metastases or cardiovascular disease, tumour size reduction less than 25% after 16 weeks of tivozanib treatment • Patients characteristics: Median age (range): 56 years (26-79), Gender (% of female): 30%, ECOG PS=0 49% favourable or intermediate MSKCC prognosis group: 88%, prior nephrectomy 73%,	• Intervention(s): Tivozanib 1.5 mg/d orally for 3 weeks followed by 1-week break (one cycle=4 weeks) for 12 weeks • Comparator(s): placebo	**ORR** • Not reported by treatment group	**PFS**: • Proportion of patients without progression after 12 weeks (95% CI): tivozanib 49% (36-63) vs placebo 21% (11-34), p=0.001 • Median PFS in months (95% CI): tivozanib 10.3 (8.1-21.2) vs placebo 3.3 (1.8-8.0), p=0.01	• Dropouts: discontinuation rate: tivozanib 61/76 vs placebo 9/57 • Results critical appraisal: - Small sample size (underpowered study) - Cross-over from placebo to tivozanib leading to caution when interpreting PFS - Characteristics of patients and ORR not reported by treatment group

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		IFN/Bev 86%, treatment naïve 54% • Median follow-up: not reported				
Hutson 2013[59]	• Design: RCT • Sources of funding: Wyeth (Pfizer) • Setting: 13 countries • Sample size: Axitinib (n=192), sorafenib (n=96) • Duration: 10 months	• Eligibility criteria: Adult mRCC measurable disease per RECIST; ECOG PS 0 or 1; life expectancy ≥12 weeks; adequate hematologic, hepatic, and renal function. No previous systemic treatment, no brain metastases, no myocardial infarction, controlled hypertension, no cerebrovascular accident or transient ischaemic attack • Patients characteristics: Median age (range): axitinib 58 years (23-83), sorafenib 58 years (20-77), Gender (% of female): axitinib 30%, sorafenib 23%, ECOG PS=0: axitinib 57%, sorafenib 57%, favourable or intermediate MSKCC prognosis group: axitinib 93%, sorafenib 97%, prior nephrectomy axitinib 85%, sorafenib 90%	• Intervention(s): axitinib 5 mg orally twice per day • Comparator(s): sorafenib 400 mg orally twice per day	**PFS** HR (95% CI) 0.77 (0.56-1.05), one-sided p=0.038	**ORR** RR (95% CI) 2.21 (1.31-3.75, one-sided p=0.0006) **Safety** • All-causality serious adverse events: axitinib 34% vs sorafenib 25% • Treatment-related serious events: axitinib 5% vs sorafenib 7% **QoL** FKSI-15, FKSI-DRS, EQ-5D similar in both groups	• Dropouts: discontinuation rate axitinib 125/192, sorafenib 69/96 • Results critical appraisal: - Open-label but blinding outcome assessment - sponsor participated in study design and analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		• Median follow-up: not avalaible				
Hutson 2014[60]	• Design: RCT • Sources of funding: Wyeth (Pfizer) • Setting: 112 sites in 20 countries • Sample size: temsirolimus (n=259), sorafenib (n=253) • Duration: 3 years 7 months	• Eligibility criteria: Adult patients with confirmed mRCC while receiving first-line sunitinib during at least one 4-week cycle, at least one measurable (nonbone) target lesion per RECIST; ECOG PS, 0 or 1; life expectancy ≥12 weeks; adequate hematologic, hepatic, renal, and cardiac function, no brain metastases, stable coronary artery disease or no myocardial infarction, controlled hypertension, controlled diabetes mellitus • Patients characteristics: Median age (range): temsirolimus 60 years (19-82), sorafenib 61 years (21-80), Gender (% of female): temsirolimus 25%, sorafenib 24%, ECOG PS=0: temsirolimus 40%, sorafenib 45%, favourable or intermediate MSKCC prognosis group: temsirolimus 88%, sorafenib 87%, prior	• Intervention(s): temsirolimus 25 mg IV • Comparator(s): sorafenib 400 mg orally twice per day	**PFS** HR (95% CI) 0.87 (0.71-1.07), p=0.19 No significant difference between arms according to the duration of prior sunitinib exposure	**ORR** Temsirolimus 8% vs sorafenib 8% **OS** • Stratified HR (95% CI) 1.31 (1.05-1.63) in favour of sorafenib • Median OS (95% CI): Temsirolimus 12.3 months (10.1-14.8) vs sorafenib 16.6 months (13.6-18.7) • Subgroup analyses showed advantages for sorafenib Prior nephrectomy (p=0.02) ; clear-cell histology (p=0.01), MSKCC intermediate risk (p=0.002), prior treatment with more than 180 days of sunitinib (p=0.02) age <65 years (p=0.0005, male sex (p=0.02), normal hepatic function (p=0.007), normal baseline lactate dehydrogenase (p=0.01) **Safety** • Proportion of patients experienced at least one grade ≥ 3 AEs: temsirolimus 70% vs sorafenib 69% • Incidence of serious AEs: temsirolimus 41% vs sorafenib 34% • Incidence of fatal AEs: temsirolimus 8% vs sorafenib 8%	• Dropouts: discontinuation rate temsirolimus 241/259, sorafenib 246/253 • Results critical appraisal: - Open-label but blinding outcome assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		nephrectomy temsirolimus 86%, sorafenib 87%, Clear cell histologic type temsirolimus 83%, sorafenib 82% • Median follow-up: 9.2 months			• Dose reduction owing AEs: temsirolimus 16% vs sorafenib 33%	
Motzer 2014[61]	• Design: RCT • Sources of funding: Novartis Pharmaceuticals • Setting: Japan, Asia Pacific, Europe, Middle East, and Americas • Sample size: dovitinib (n=284) sorafenib (n=286) • Duration: 1 year 6 months	• Eligibility criteria: adult patients with clear-cell mRCC with progression despite VEGF-targeted or mTOR inhibitor therapy, other anticancer therapy was allowed, measurable disease with RECIST, Karnofsky PS≥ 70, adequate haematological, renal and hepatic functions, no brain metastasis, no uncontrolled hypertension or significant cardiac disease • Patients characteristics: Median age (range): dovitinib 61 years (29-89), sorafenib 62 years (18-81), Gender (% of female): dovitinib 25%, sorafenib 23%, Karnofsky PS≥80:	• Intervention(s): Dovitinib 500 mg orally according to a 5-days-on and 2-days-off schedule • Comparator(s): Sorafenib 400 mg orally twice daily	**PFS** HR (95% CI) 0.86 (0.72-1.04), p=0.063	**OS** HR (95% CI) 0.96 (0.75-1.22) **Median time to definitive worsening of Karnofsky PS** HR (95% CI) 1.12 (0.87-1.45) **Definitive deterioration by 10% of QoL score** • of the EORTC QLQ-C30 HR (95% CI) 1.08 (0.86-1.36) • of the FKSI-DRS HR (95% CI) 1.20 (0.91-1.58) **Adverse events** • AEs leading to dose changes or interruptions: dovitinib 51% vs sorafenib 49% • Treatment-emergent serious AEs dovitinib 48% vs sorafenib 39% • Death on study or within 30 days after last dose: dovitinib 14% vs sorafenib 15%	• Dropouts: discontinuation rate dovitinib 249/284, sorafenib 246/286 • Results critical appraisal: - Open label trial but blinded independent review for outcomes - Sponsor participated to data collection analysis and interpretation

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		dovitinib 88%, sorafenib 90%, favourable or intermediate MSKCC prognosis group: dovitinib 78%, sorafenib 77%, prior nephrectomy dovitinib 96%, sorafenib 91%, prior X-ray dovitinib 23%, sorafenib 32%, prior cytokines dovitinib 7%, sorafenib 8%, • Median follow-up: 11 months (IQR 7.9-14.6)				

4.2.4. What is the long term induced morbidity by type of surgery?

In this section, only long term outcomes were reported. A long term outcome is an oncological event occurring at more than 5 years after nephrectomy. Sooner outcomes were reported in the previous chapters.

Table 45 – Evidence table – non-randomized studies – long term induced morbidity by surgery

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Antonelli 2012[62]	• Design: retrospective cohort study • Sources of funding: not mentioned • Setting: 16 academic centres in Italy • Sample size: RN (n=2345), PN (n=1266)	• Eligibility criteria: T1N0M0 renal tumours registered in the database 'surveillance and treatment update renal neoplasms' • Patients characteristics: **cT1a** Age (mean ± SD): RN 62.7 y (±11.3) vs PN 60.5 y (±12.7);	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10-year cancer-specific survival:** • cT1a: RN 90.4% vs PN 94.9% (long-rank test p=0.01) • cT1b: RN 87% vs PN 90% (long-rank test p=0.89) • Nuclear grade IV CSS was significantly worse for PN compared		• Dropouts: not dropouts reported • Results critical appraisal: - Some patients were excluded from the survival analyses to balance the two groups. However significant differences are

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Duration: not mentioned	sex (% of female): RN 34.4 vs PN 30.1; Pathological tumour size (mean ± SD): RN 3.4 cm (± 1.1) vs PN 2.8 cm (± 1.1) Fuhrman nuclear grade (%) RN: grade 1-2: 77.8%, grade 3-4 :22.2%, PN: grade 1-2 85%, grade 3-4 15% **cT1b** Age (mean ± SD): RN 62.4 y (±11.6) vs PN 58.2 y (±14.8); sex (% of female): RN 36.7 vs PN 32.3; Pathological tumour size (mean ± SD): RN 5.7 cm (± 1.1) vs PN 5.0 cm (± 0.9) Fuhrman nuclear grade (%) RN: grade 1-2: 65.7%, grade 3-4 :35.2%, PN: grade 1-2 80%, grade 3-4 20% • Median follow-up (IQR): 47 (24-80) months		with RN (long-ran test: p=0.14)		observed between groups for patients' characteristics - Several surgeons, several institutions without prospective protocol - Retrospective design
Becker 2006[63]	• Design: retrospective cohort study • Sources of funding: not mentioned	• Eligibility criteria: patients with solid renal lesions treated in the institution Patients characteristics: Age (median (range): RN	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10-year cancer-specific survival:** RN 84.4% vs PN 95.8% (long-rank test p<0.05) **15-year cancer-specific survival:**		• Dropouts: not mentioned • Results critical appraisal: - No subgroup analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Setting: single institution in Germany • Sample size: PN (n=241) vs RN (n=369) • Duration:	59.0 y (32.0-84.0) vs PN 60.0 y 26.0-85.8); sex (% of male): RN 61.0 vs PN 62.2; Pathological tumour size (median (range)): RN 4.0 cm (1.0-9.2) vs PN 3.0 cm (0.5-8.0); Tumour grade (%) Grade 1: RN 20.3% vs PN 24.9%, grade 2 RN 67.5% vs PN 67.6%, grade 3 RN 12.2% vs PN 7.5%, histology subtype (%): clear cell RN 4.0 vs PN 5.4; papillary RN 6.0 vs PN 10.4; chromophobe RN 90.0 vs PN 84.2; tumour stage (%): pT1: RN 96.2 vs PN 96.7, pT2: RN 2.7 vs PN 2.1, pT3: RN 1 vs PN 1.2. • Median follow-up for PN: 66 months		RN 77.9% vs PN 95.8% (long-rank test p<0.05)		- Retrospective design
Capitanio 2015[64]	• Design: retrospective cohort study • Sources of funding: none • Setting: 4 European tertiary care centres	• Eligibility criteria: T1a-T1b N0 M0 renal mass with normal preoperative function • Patients characteristics: Age (median (range): RN 62 y (54-70) vs PN	• Intervention(s): Partial nephrectomy (PN) open, laparoscopic or robot-assisted surgery • Comparator(s): Radical nephrectomy (RN)	**10-year cardiovascular events** PN 20.2% vs RN 25.9% (p=0.001) After accounting for clinical characteristics and cardiovascular profile		• Dropouts: not mentioned • Results critical appraisal: - Long period of recruitment of patients - Groups are not well balanced for

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Sample size: PN (n=869), RN (n=462) • Duration: 1987-2013	62 y 53-70); sex (% of female): RN 22.9 vs PN 16.2; clinical tumour size (median (range)): RN 5.0 cm (4.0-6.0) vs PN 3.0 cm (2.3-4.0); clinical tumour stage (%) cT1a: RN 30.1 vs PN 75.9, cT1b: RN 69.9 vs PN 24.1 • Median follow-up: 52 months (IQR 24-90)		HR (95% CI): 0.57 (0.34-0.96, p=0.03)		clinical characteristics and cardiovascular profile - Retrospective study limiting the availability of adjustment for other potential confounders
Daugherty 2014[65]	• Design: retrospective cohort study • Sources of funding: not mentioned • Setting: USA • Sample size: RN (n=494) vs PN (n=222) • Duration: 1993-2003	• Eligibility criteria: patients aged from 20 to 44 years surgically treated for RCC ≤ 4 cm with known grade and histology, single tumour, no prior RCC, no metastatic or locally advanced disease • Patients characteristics: Age group (%): < 30 y RN 5.4 vs PN 7.2, 30-39 y RN 47 vs PN 42.4, 40-44 y RN 47.5 vs PN 50.5; Sex (% of female): RN 43.3 vs PN 37.8; tumour histology (%): clear cell RN 42.7 vs PN 42.8, papillary RN 4.3 vs PN 8.6,renal cell RN	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10-year cancer-specific survival** PN 100% vs RN 98.3%, HR (95% CI° 0.25 (0.047-1.32), p=0.10 **10-year overall survival** PN 94% vs RN 89.7%, HR (95% CI° 0.50 (0.28-0.92), p=0.025		• Dropouts: not mentioned • Results critical appraisal: - Long period of recruitment of patients - Groups were well balanced for patients' characteristics - Retrospective design adjustment for confounders is limited

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		50.4 vs PN 45.0, other RN 2.6 vs PN 2.8 • Median follow-up: PN 92 months (IQR 79-108) vs RN 99 months (IQR 82-117)				
Roos 2014[66]	• Design: retrospective cohort study • Sources of funding: not mentioned • Setting: six German tertiary care centres • Sample size: RN (n=2955), ePN (n=1108), iPN (263) • Duration: 1980-2010	• Eligibility criteria: patients that underwent surgery for localized RCC pT1-3a, no detectable metastasis • Patients characteristics: Age (mean ± SD) RN 61.6 y (±11.1) vs ePN 59.7 y (±11.6) vs iPN 62.8 y (±11.2); sex (% of female): RN 40.1 vs ePN 32.5 vs iPN 39.9; Tumour diameter (mean ± SD): RN 5.6 cm (± 2.7) vs ePN 3.4 cm (± 1.8) vs iPN 4.2 cm (± 2.2), Stage (%) pT1 RN 66.8 vs ePN 95.5 vs iPN 86.3, pT2 RN 16.5 vs ePN 2.3 vs iPN 5.7, pT3a RN 16.6 vs ePN 2.2 vs iPN 8.0; Grade (%) : grade 1-2: RN 87.6 vs ePN 93.6 vs iPN 93.6, grade 3-4 : RN	• Intervention(s): Elective Partial Nephrectomy (ePN) or Imperative Partial Nephrectomy (iPN) • Comparator(s): Radical nephrectomy (RN)	**10-year overall survival** RN 64.7% vs ePN 74.6% vs I PN 57.5% (log rank, p<0.001) *Multivariate by Cox regression* RN reference ePN HR (95% CI) 0.79 (0.66-0.94), p=0.008 iPN HR (95% CI) 1.07 (0.83-1.38), p=0.62		• Dropouts: not reported • Results critical appraisal: - Retrospective design - No adjustment for comorbidities, preoperative renal function - Selection bias because of no standardization of the choice for procedure - No central pathological review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		14.2 vs ePN 6.4 vs iPN 6.4; histology (% of clear cell RCC): RN 85.8 vs ePN 76.6 vs iPN 79.6 • Median follow-up: 63 months (IQR: 30-109)				
Stewart 2014[67]	• Design: retrospective cohort study • Sources of funding: National Institutes of Health • Setting: 1 institution • Sample size: PN (n=926), RN (=1255) • Duration: from 1970 to 2008	• Eligibility criteria: low risk patients with M0 sporadic RCC treated by surgery (pT1Nx-0) • Patients characteristics: not reported by treatment group • Median follow-up: 9.0 years (IQR 5.7 to 14.4)	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10 year recurrence rates (%)** • Any PN 12.4 vs RN 14.5, p= 0.074 • Abdomen PN 10.4 vs RN 6.3, p= 0.009 • Chest PN 1.1 vs RN 5.3, p < 0.001 • Bone, PN 0.8 vs RN 2.7, p=0.005 • Other PN 0.8 vs RN 2.5, p=0.003		• Dropouts: 3% of patients were lost to follow-up • Results critical appraisal: - Tumours were less aggressive in PN group than in RN group - Retrospective design - No standardized protocol for follow-up - Long duration of the data collection implying various imaging techniques and improvement of radiology techniques
Tan 2012[68]	• Design: retrospective cohort study • Sources of funding: Agency for Healthcare	• Eligibility criteria: Medicare patients with single renal tumour ≤ 4 cm (T1a) in early-stage treated by partial or	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**8 years overall survival difference** 15.5 (95% CI, 5.0-26.0) % points, p< 0.001 in favour of PN		• Dropouts: not mentioned • Results critical appraisal: - Patients are not balanced

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Research and Quality, the Edwin Beer Research Fellowship in Urology, New-York Academy of Medicine, and the University of Michigan Comprehensive Cancer Center • Setting: USA (nationally representative, population-based registry) • Sample size: PN (n=1925) vs RN (n=5213) • Duration: from 1992 to 2007	radical nephrectomy by either an open or laparoscopic approach • Patients characteristics: Age group categories (%): 65-69 years PN 32.8 vs RN 25.6, 70-74 years PN 29.7 vs RN 28.1, 75-79 years PN 24.7 vs RN 26.3, 80-84 years PN 10.7 vs RN 14.6, > 85 years PN 2.1 vs RN 5.4, Gender (% of female) PN 41.7 vs RN 46.4; Tumour histology (%): Clear cell PN 73.8 vs RN 84.2, Papillary PN 14.7 vs RN 7.7, Chromophobe PN 6.5 vs RN 3.7, Oncocytoma PN 0.6 vs RN 0.4, Other histology PN 4.4 vs RN 4.0, Charlson Index score (CIS in %): CIS_0 PN57.6 vs RN 57.9, CIS_1 PN 24.3 vs RN 24.2, CIS_≥2 PN 18.1 vs RN 17.9 • Median follow-up: 62 months (IQR 39-92)				between groups (i.e. age, tumour type...) - Only early-stage small tumours were taken into account - Patients were all aged of ≥ 65 years (Medicare) - Retrospective design

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Van Poppel 2011[69]	• Design: RCT • Sources of funding: National Cancer Institute (USA) and Fonds cancer (FOCA – Belgium) • Setting: Europe, USA, Canada (17 countries) • Sample size: RN (n= 273) PN (n=268) • Duration: from 1992 to 2003	• Eligibility criteria: solitary T1-T2 N0 M0 renal tumour ≤ 5 cm suspicious for RCC, normal contralateral kidney WHO performance status of 0_2 • Patients characteristics: Age (median (range) RN 62.0 years (23.0-84.0) vs PN 62.0 (29.0-+82.0), Gender (% female) RN 33.3 % vs PN 32.5, WHO performance status (% of PS=0) RN 83.2 vs PN 85.4, no chronic disease (%) RN 63.7 vs PN 61.9 • Median follow-up: not mentioned	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10-year Overall Survival Rate** PN 75.2 % vs RN 79.4% **10-year Progression rate** In % (95% CI) PN 4.1% (1.7-6.5) vs RN 3.3% (1.2-5.4), Gray's test p=0.48		• Dropouts: analysis realised in Intention-to-treat • Results critical appraisal: - Shifting in treatment allocation - Underpowered study because of slow accrual - Tumour size limit from 4 to 5 cm in this study - Selective reporting (i.e. duration of follow-up)
Zini 2009[70]	• Design: retrospective matched analyses • Sources of funding: not mentioned • Setting: USA (national database) • Sample size: unmatched for Fuhrman grade PN 2153 vs RN 5616 matched for	• Eligibility criteria: adult patients localized renal masses up to 4.0 cm (T1aN0M0) • Patients characteristics: UNMATCHED FOR FUHRMAN GRADE age (mean): PN 59.8 years vs RN 61.1 years, sex (% of male) PN 61.8 vs RN 59.4, tumour size PN 2.4cm vs	• Intervention(s): Partial nephrectomy (PN) • Comparator(s): Radical nephrectomy (RN)	**10-year overall survival** • UNMATCHED PN 71.3% vs RN 68.2% HR 1.23, p=0.001 • MATCHED PN 70.9% vs RN 68.8% HR 1.19, p=0.048 **10-year non-cancer-related mortality** • UNMATCHED PN 27.1% vs RN 31.6%		• Dropouts: not mentioned • Results critical appraisal: - Large data collection 16 years period but matching for year of surgery - Matching for age, tumour size, year of surgery and Fuhrman grade but no matching

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Fuhrman grade PN 1283 vs RN 3166 • Duration: from 1988 to 2004	RN 2.7 cm, pathologic subtype (%): clear cell PN 79.8 vs RN 84.6, papillary PN 9.2 vs RN 5.3 other PN 10.9 vs RN 10.2, Fuhrman grade (%) grade 1-2 PN 42.8 vs RN 47.4 grade 3-4 PN 9.5 vs RN 8.8 MATCHED FOR FUHRMAN GRADE age (mean): PN 59.6 years vs RN 61.3 years, sex (% of male) PN 59.6 vs RN 61.3, tumour size PN 2.5 cm vs RN 2.8 cm, pathologic subtype (%): clear cell PN 81.6 vs RN 85.2, papillary PN 8.1 vs RN 4.8 other PN 10.3 vs RN 9.9, Fuhrman grade (%) grade 1-2 PN 84.7 vs RN 86.0 grade 3-4 PN 15.2 vs RN 14.0 • Median follow-up: PN 35 months, RN 46 months		• MATCHED PN 27.1% vs RN 30.6%		for co-morbidity or surgical techniques (open vs laparoscopic) - Fuhrman grade was available only for 62.3% in PN group and 56.0% in RN group

5. GRADE PROFILES

During the grading process, the evaluation of a RCT begins from high level of evidence and non-randomized studies (NRS) begin from low level whatever the design (cohort studies, case-series, etc). The level of evidence can be downgraded when methodological limitations are observed. This section presents the grading of the evidence used in this report.

5.1. Treatment

5.1.1. Primary treatment

5.1.1.1. Surgical treatment

5.1.1.1.1. Nephrectomy

Radical nephrectomy vs partial nephrectomy (nephron-sparing surgery)

Table 46 – GRADE profiles - Radical versus partial nephrectomy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
All cause of mortality HR =0.81, 95% CI (0.76 to 0.87), I²=49%, p<0.00001	1 RCT 20 NRS	-2	0	0	0	0	1: only one RCT included. This RCT was stopped early for methodological reason.	Low
Cancer specific mortality HR =-0.71, 95% CI (0.59 to 0.85), I²=63%, p<0.0002	21 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
Chronic kidney disease HR =-0.39, 95% CI (0.33 to 0.47), I²=87%, p<0.00001	9 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
At lowest eGFR **At least moderate renal dysfunction stage A (eGFR<60)** RN 85.7% vs NSS 64.7%, p<0.001	1 RCT	-1	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At lowest eGFR **At least moderate renal dysfunction stage B (eGFR45)** RN 49.0% vs NSS 27.1%, p<0.001	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
At lowest eGFR **Advanced kidney disease (eGFR<30)** RN 10.0% vs NSS 6.3%, ns	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At lowest eGFR **Kidney failure (eGFR15)** RN 1.5% vs NSS 1.6%, ns	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At last eGFR **At least moderate renal dysfunction stage A (eGFR<60)** RN 58.7% vs NSS 38.4%, p<0.001	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At last eGFR **At least moderate renal dysfunction stage B (eGFR45)** RN 24.7% vs NSS 13.3%, p<0.001	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At last eGFR **Advanced kidney disease (eGFR<30)** RN 6.6% vs NSS 3.5%, ns	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low
At last eGFR **Kidney failure (eGFR15)** RN 1.2% vs NSS 0.8%, n	1 RCT	-2	-1	0	0	0	1: very serious limitations 2: only one study	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Techniques of partial nephrectomy

Table 47 – GRADE profiles - Laparoscopic versus open partial nephrectomy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
5-year overall survival OR=1.83, 95% CI (0.80, 4.19), I^2=32%	4 NRS	0	0	0	0	0		Low
5-year cancer specific survival OR=1.09, 95% CI (0.62, 1.92), I^2=0%	4 NRS	0	0	0	0	0		Low
5-year recurrence free survival OR=0.68, 95% CI (0.37, 1.26), I^2=0%	5 NRS	0	0	0	0	0		Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 48 – GRADE profiles - Transperitoneal versus Retroperitoneal laparoscopic partial nephrectomy for renal cell carcinoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Perioperative outcomes								
Operative time (min) *SMD (standardized mean difference)* 1.001, 95% CI (0.609 to 1.393), I^2=81.8%, p<0.001	7 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
Estimated blood loss (ml) SMD =0.403, 95% CI (0.015 to 0.791), I^2=74.9%, p=0.042	5 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
Warm ischemia time (min) SMD =0.302, 95% CI (-0.340 to 0.945), I^2=93.6%, p<0.001	7 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
Postoperative outcomes								
Length of stay (days)	6 NRS	0	0	0	0	0		Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
WMD =0.936, 95% CI (0.609 to 1.263), I²=46.3%, p<0.001								
Serum creatine level (mg/dl) WMD =0.02, 95% CI (-0.08 to 0.11), I²=14%, p=0.68	2 NRS	0	0	0	0	0		Low
Surgical complications								
Overall complication rate OR =0.849, 95% CI (0.576 to 1.250), I²=0%, p=0.406	6 NRS	0	0	0	0	0		Low
Intraoperative complication OR =2.30, 95% CI (0.83 to 6.4), I²=16%, p=0.11	4 NRS	0	0	0	-1	0	2: high imprecision due to a large 95% CI	Very low
Postoperative complication OR =1.33, 95% CI (0.73 to 2.41), I²=3%, p=0.35	4 NRS	0	0	0	-1	0	2: high imprecision due to a large 95% CI	Very low
Open conversion rate OR =2.14, 95% CI (0.85 to 5.39), I²=0%, p=0.11	5 NRS	0	0	0	-1	0	2: high imprecision due to a large 95% CI	Very low
Oncological outcomes								
Positive margin OR =1.29, 95% CI (0.48 to 3.46), I²=0%, p=0.61	4 NRS	0	0	0	-1	0	2: high imprecision due to a large 95% CI	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 49 – GRADE profiles - Robotic versus laparoscopic partial nephrectomy for small renal tumours (T1a)

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Operatives outcomes								
Estimated blood loss (ml) *Weighted mean difference (WMD)* 46.13, 95% CI (-12.01 to 104.26), I^2=87%, p=0.12	6 NRS	0	-1	0	-1	0	1: only comparative studies included 2: high heterogeneity 4: high imprecision due to a large 95% CI	Very low
Operative time (min) WMD =0.5, 95% CI (-24.02 to 25.02), I^2=59%, p=0.97	5 NRS	0	-1	0	-1	0	1: only comparative studies included 2: moderate heterogeneity 4: high imprecision due to a large 95% CI	Very low
Warm ischemia time (min) WMD =-5.76, 95% CI (-15.22 to 3.70), I^2=96%, p=0.23	6 NRS	0	-1	0	-1	0	1: only comparative studies included 2: high heterogeneity 4: high imprecision due to a large 95% CI	Very low
Postoperative outcomes								
Length of stay (days) WMD =-0.15, 95% CI (-0.38 to 0.09), I^2=0%, p=0.22	6 NRS	0	0	0	0	0	1: only comparative studies included	Low
Overall complications rate								
Both intra and postoperative complications WMD =0.01, 95% CI (-0.05 to 0.06), I^2=0%, p=0.84	6 NRS	0	0	0	0	0	1: only comparative studies included	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

5.1.1.1.2. Associated procedures

Adrenalectomy

Table 50 – GRADE profiles - Adrenalectomy versus adrenal sparing in radical nephrectomy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Blood transfusion OFF-PN (15.3%) vs ON-PN (6.3%) WMD =1.54, 95% CI (1.07 to 2.21), I^2=19%, p=0.02	8 NRS	0	0	0	0	0		Low
Conversion OFF-PN (1.7%) vs ON-PN (1.7%) WMD =1.00, 95% CI (0.38 to 2.62), I^2=47%, p=0.99	4 NRS	0	0	0	-1	0	4: Large 95% IC	Very low
Positive margin OFF-PN (2.4%) vs ON-PN (3.2%) WMD =0.49, 95% CI (0.26 to 0.90), I^2=0%, p=0.02	9 NRS	0	0	0	0	0		Low
Postoperative complication OFF-PN (12.5%) vs ON-PN (18%) WMD =0.61, 95% CI (0.44 to 0.83), I^2=4%, p=0.002	6 NRS	0	0	0	0	0		Low
Urinary leakage OFF-PN (3.5%) vs ON-PN (3.8%) WMD =0.71, 95% CI (0.35 to 1.45), I^2=33%, p=0.35	5 NRS	0	0	0	0	0		Low
Decreased eGFR (mL/min) WMD =5.81, 95% CI (1.80 to 9.81), I^2=96%, p=0.005	5 NRS	0	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low
Operative time (min) WMD =-10.02, 95% CI (-37.43 to 17.39), I^2=99%, p=0.47	6 NRS	0	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low
Estimated blood loss (ml) WMD =60.74, 95% CI (-5.84 to 127.33), I^2=99%, p=0.07	7 NRS	0	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low
Length of stay (days) WMD =0.37, 95% CI (-0.78 to 1.51), I^2=100%, p=0.53	5 NRS	-1	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low

5.1.1.1.3. Ablative therapy

Cryoablation and Radiofrequency ablation

Table 51 – GRADE profiles - Laparoscopic cryoablation versus laparoscopic (robot-assisted) partial nephrectomy for renal cell carcinoma

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Local tumour progression RR =9.39, 95% CI (3.83 to 22.99), I^2=0%, p<0.0001	10 NRS	0	0	0	-1	0	4: large 95% IC	Very low
Metastatic progression RR =4.68, 95% CI (1.88 to 11.64), I^2=0%, p=0.001	10 NRS	0	0	0	-1	0	4: large 95% IC	Very low
Operative time (min) WMD =35.45, 95% CI (17.01 to 53.88), I^2=93.1%, p<0.001	12 NRS	0	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low
Evaluated blood loss (ml) WMD =130.11, 95% CI (94.57 to 165.66), I^2=84.8%, p<0.001	12 NRS	0	-1	0	-1	0	2: high heterogeneity 4: large 95% IC	Very low
Length of stay (days) WMD =1.22, 95% CI (0.58 to 1.86), I^2=90.8%, p<0.001	12 NRS	0	-1	0	0	0	2: high heterogeneity	Very low
Overall complication (rate) RR =1.82, 95% CI (1.22 to 1.72), I^2=59.2%, p=0.003	12 NRS	0	-1	0	0	0	2: moderate heterogeneity	Very low
Urological complication (rate) Number of studies: 12 RR =1.99, 95% CI (1.10 to 3.63), I^2=45.2%, p=0.024	10 NRS	0	-1	0	0	0	2: moderate heterogeneity	Very low
Non-urological complication (rate) Number of studies: 12 RR =2.33, 95% CI (1.42 to 3.84), I^2=6.5%, p=0.001	10 NRS	0	0	0	0	0		Low

Table 52 – GRADE profiles - Thermal ablation versus surgical nephrectomy for small renal cell tumours

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Operative time (min) Median (range) MWA 148 (117-273) vs 154 (60-277), p=0.0955	1 RCT	-1	-1	0	-1	0	1: blinding is not clear 2: only 1 study 4: imprecise, difference not statistically different	Very low
Estimated blood loss Mean ± SD MWA 138.3±69.4 vs PN 465.9±577.1, p=0.0002	1 RCT	-1	-1	0	0	0	1: blinding is not clear 2: only 1 study	Low
Length of stay (days) Mean (range) MWA 15 (13-26) vs 19 (10-47), p=0.7566	1 RCT	-1	-1	0	-1	0	1: blinding is not clear 2: only 1 study 4: imprecise, difference not statistically different	Very low
Complication rate MWA 6/48 vs PN 20/54, p=0.0187	1 RCT	-1	-1	0	0	0	1: blinding is not clear 2: only 1 study	Low
3-year recurrence free survival rate MWA 90.4% (95% IC 65.3-97.6) vs PN 96.6% (95% CI: 78.0-99.6), p=0.4650	1 RCT	-1	-1	0	-1	0	1: blinding is not clear 2: only 1 study 4: imprecise, equivalence not proven	Very low

5.1.2. Adjuvant treatment

5.1.2.1.1. Immunotherapy and adoptive immunotherapy

Table 53 – GRADE profiles – Adjuvant treatment immunotherapy versus adoptive immunotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
OS and DFS	5 RCT	-1		-1	-1		1: lack of allocation concealment 3: heterogeneous interventions of whom it is not clear if they are still applicable in the current context 4: no-inferiority not proven.	Very low

5.1.2.1.2. Immuno-chemotherapy

Table 54 – GRADE profiles – Adjuvant treatment immune-chemotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
OS and DFS	2 RCT	-1			-1		1: lack of allocation concealment 4: no inferiority not proven.	Low

5.1.2.1.3. Vaccine

Different Vaccines were tested in single underpowered studies, the last study was terminated prematurely. We did not grade.

5.1.3. Treatment of local recurrence/metastasis

5.1.3.1. Surgery

Table 55 – GRADE profiles – Nephrectomy in metastatic RCC patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Remission rate Peto OR (95%CI) 1.45 (0.56-3.75), I^2=0%, p=0.44 (n=331)	2 RCTs	-1	0	-1	-2	0	1. no allocation concealment 3. Comparison not current standard of care 4. CI both includes benefit and harm	Very low
1-year mortality Peto OR (95%CI) 0.53 (0.34-0.83), I^2=0%, p=0.0060 (n=306)	2 RCTs	-1	0	-1	0	0	1. no allocation concealment 3. Comparison not current standard of care	Low

5.1.3.2. Systemic treatment

Table 56 – GRADE profiles – First-line treatment: targeted therapy vs cytokine in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Sorafenib vs IFN								
PFS HR (95% CI)=0.88 (0.61-1.27); p=0.50 Escudier 2009a[71]	1 RCT	-1	-1	0	-1	0	1. No blinding: open-label study 2. Only one study 4. CI both includes benefit and harm	Very low
ORR (%) 5.2 vs 9.7; ns Escudier 2009a[71]	1 RCT	-1	-1	0	-1	0	1. No blinding: open-label study 2. Only one study 4. CI both includes benefit and harm	Very low
Sunitinib vs IFN								
PFS HR (95% CI)=0.54 (0.45-.64); p<0.001 SUTENT[72]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS HR (95% CI)=0.82 (0.67-1.00); p=0.049 SUTENT[72]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
ORR (%) 31 vs 6; p<0.05 SUTENT[72]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
Temsirolimus vs IFN								
Median progression free survival in months (95% CI) Temsirolimus 5.5 (3.9-7.0) vs IFN 3.1 (2.2-3.8) p <0.05 Hudes 2007[73]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS HR (95% CI)= 0.73 (0.58-0.92); p=0.008	1 RCT	0	-1	0	0	0	2. Only one study	Moderate

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Hudes 2007[73]								
ORR (%) IFN 4.8 (1.9-7.8) vs Temsirolimus 8.6 (4.8-12.4) Hudes 2007[73]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
Bevacizumab + IFN vs Placebo + IFN								
PFS HR (95% CI)=0.66 (0.57-0.77); p<0.00001, I^2=37% AVOREN[74], Rini 2004[75]	2 RCT	0	0	0	0	0		High
OS HR (95% CI) = 0.86 (0.76-0.97); p=0.01, I^2=0% AVOREN[74], Rini 2004[75]	2 RCT	0	0	0	0	0		High

Table 57 – GRADE profiles – First-line treatment: targeted therapy vs other targeted therapy in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Pazopanib vs Sunitinib								
PFS HR (95% CI): 1.05 (0.90-1.22) Motzer 2013b[55]	1 RCT	0	-1	0	-1	0	2: Only one study 4. CI both includes benefit and harm	Low
OS HR (95%) 0.91 (0.76-1.08) Motzer 2013b[55]	1 RCT	0	-1	0	-1	0	2: Only one study 4. CI both includes benefit and harm	Low
ORR Pazopanib 31% vs sunitinib 25%, p=0.03 Motzer 2013b[55]	1 RCT	0	-1	0	0	0	2: Only one study	Moderate

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Axitinib vs Sorafenib								
PFS HR (95% CI) 0.77 (0.56-1.05), one-sided p=0.038 Hutson 2013[59]	1 RCT	0	-1	0	-1	0	2: Only one study 4. CI both includes benefit and harm	Low
ORR RR (95% CI) 2.21 (1.31-3.75), one-sided p=0.0006) Hutson 2013[59]	1 RCT	-1	-1	0	0	0	2: Only one study	Moderate

Table 58 – GRADE profiles – First-line treatment: targeted therapy combined with cytokine vs targeted therapy alone in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Sorafenib + IFN vs Sorafenib								
PFS HR (95% CI)=0.85 (0.51-1.42); p=0.53 Jonasch 2010[76]	1 RCT	-1	-1	0	-1	0	1. No blinding: open-label study 2. Only one study 4. CI both includes benefit and harm	Very low
OS univariate: HR (95% CI)=1.94 (0.84-4.52); p=0.0764 multivariate: HR (95% CI)= 2.172 (0.92-5.12); p= 0.1219 Jonasch 2010[76]	1 RCT	-1	-1	0	-1	0	1. No blinding: open-label study 2. Only one study 4. CI both includes benefit and harm	Very low
Sorafenib + IL-2 vs Sorafenib								
1-year PFS Sorafenib + IL-2: 30% (20.2-44.6) vs Sorafenib: 22.5% (21.5-45.1) ROSORC[77, 78]	1 RCT	-2	-1	0	0	0	1. No allocation concealment, no blinding of participants and outcome assessment 2. Only one study	Very low
2-year PFS	1 RCT	-2	-1	0	0	0	1. No allocation concealment, no blinding of participants and outcome assessment	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Sorafenib + IL-2: 31.1% (14.1-35.9) vs Sorafenib: 11.3 (5.3-23.7) ROSORC[77, 78]							2. Only one study	
5-year OS Sorafenib + IL-2: 26.3% (CI 15.9-43.5) vs Sorafenib: 23.1% (CI 13.2-40.5) ROSORC[77, 78]	1 RCT	-2	-1	0	0	0	1. No allocation concealment, no blinding of participants and outcome assessment 2. Only one study	Very low

Table 59 – GRADE profiles – First-line treatment: combined targeted therapy vs targeted therapy alone in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Bevacizumab + Erlotinib vs Bevacizumab								
PFS 9.9 vs 8.5 months; p=0.58 Bukowski 2007a[79]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS 20 months vs not reached; p= 0.16 Bukowski 2007a[79]	1 RCT	0	-1	0	-1	0	2. Only one study 4. median OS not reached in control group	Low
Bevacizumab + temsirolimus vs sunitinib								
PFS At 48 weeks Bevacizumab + temsirolimus: 29.5% (CI 20.0-39.1) Sunitinib: 35.7% (CI 21.2-50.2) TORAVA[80]	1 RCT	0	-1	0	0	0	2. only one study	Moderate

Table 60 – GRADE profiles – First-line treatment: combination of targeted therapy and angiopoietin/Tie2 inhibitor vs target therapy alone in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Sorafenib + AMG 386 vs Sorafenib								
PFS HR: 0.88 (95% CI, 0.60-1.30; p= 0.52) Rini 2012[53]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low
ORR % (95% CI) Mean difference Comparison with placebo: arm high dose (-6.9 to 30.8), arm low dose (-7.5 to 30.0) Rini 2012[53]	1 RCT	0	-1	0	0	0	2. Only one study 4. CI both includes benefit and harm	Moderate

Table 61 – GRADE profiles – First-line treatment: combination of targeted therapies vs combination of targeted therapy and cytokine in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Bevacizumab + temsirolimus vs Bevacizumab + IFN								
PFS At 48 weeks Bevacizumab + temsirolimus: 29.5% (CI 20.0-39.1) vs IFN: 61.0% (CI 46.0-75.9) TORAVA[80]	1 RCT	0	-1	0	0	0	2. only one study	Moderate
Temsirolimus + Bevacizumab vs IFN + Bevacizumab								
PFS HR (95%CI): 1.1 (0.9 – 1.3), p=0.8	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
INTORACT[57]							4. CI both includes benefit and harm	
OS HR (95%CI): 1.0 (0.9 – 1.3), p=0. 6 INTORACT[57]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low
ORR RR $_{adjusted}$ (95% CI): 1.0 (0.8-1.3), p=1.0 INTORACT[57]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low

Table 62 – GRADE profiles – Second-line treatment: targeted therapy vs placebo in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Sorafenib vs placebo								
PFS 5.5 vs 1.4 months; p=0.0087 Ratain 2006[81] HR (95%) 0.78 (0.62-0.97, p=0.029) TARGET[82]	2 RCT	0	0	0	0	0		High
PFS Elderly patients ≥ 70 years: HR (95% CI) 0.43 (0.26-0.69) < 70 years: HR (95% CI) 0.55 (0.47-0.66) TARGET[83]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
PFS Prior cytokine therapy: HR 0.54, CI 0.45-0.64 No prior cytokine therapy: *:* HR (95% CI) 0.48 (0.32-0.83)	1 RCT	0	-1	0	0	0	2. Only one study	Moderate

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
TARGET[84]								
CBR Elderly patients ≥ 70 years: sorafenib 84.3% vs placebo 62.2% < 70 years: sorafenib 98.6% vs placebo 53.8% TARGET[83]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
CBR Prior cytokine therapy: sorafenib 83.0% vs placebo 54.3% No prior cytokine therapy: : sorafenib 85.7% vs placebo 56.0% TARGET[84]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
HRQoL FKSI-15 time to deterioration ≥ 70 years: HR (95% CI) 0.55 (0.43-1.03) < 70 years: HR (95% CI) 0.69 (0.59-0.81) TARGET[83]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
Pazopanib vs placebo								
PFS All patients HR (95%) =0.46 (0.34-0.62) First-line treatment: HR (95%) =0.40 (0.27-0.6) Second-line treatment HR (95%) =0.54 (0.35-0.84) VEG105192[85]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS (Sternberg 2013) ITT analysis HR (95%) =0.91 (0.71-1.16)	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Inverse probability of censor weighting HR (95%) =0.50 (0.31-0.76) Rank-preserving structural failure time HR (95%) =0.43 (0.21-1.39) VEG107769[86]								
Response rate (95% CI) All patients Pazopanib 30% (25.1-35.6) vs placebo 3% (0.5-6.4) First-line treatment: Pazopanib 32% (24.3-38.9) vs placebo 4% (0-8.1) Second-line treatment Pazopanib 29% (21.2-36.5) vs placebo 3% (0-7.1) VEG105192 [85]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
HRQoL *HR (95% CI) for time to 20% HRQoL deterioration* EORTC QLQ-C30 global health status/QoL scale All patients 0.77 (0.57-1.03), p= 0.0817 First-line treatment 0.75 (0.50-1.13), p=0.1698 Second-line treatment 0.75 (0.48-1.18), p=0.2141 VEG105192[87]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low

Cediranib vs placebo								
% change from baseline in tumour size Cediranib -20% versus placebo +20%, p<0.0001 Mulders 2012[56]	1 RCT	-1	-1	0	0	0	1. Unclear allocation concealment, unclear blinding of participants, no blinding of the outcome assessment 2. Only one study	Low
Response rate: Partial response Cediranib 34% versus placebo 0% Stable disease Cediranib 47% versus placebo 22% Mulders 2012[56]	1 RCT	-1	-1	0	0	0	1. Unclear allocation concealment, unclear blinding of participants, no blinding of the outcome assessment 2. Only one study	Low
PFS HR (95% CI): 0.45 (0.26-0.76) Mulders 2012[56]	1 RCT	-1	-1	0	0	0	1. Unclear allocation concealment, unclear blinding of participants, no blinding of the outcome assessment 2. Only one study	Low
Tivozanib vs placebo								
PFS: Proportion of patients without progression after 12 weeks (95% CI): Tivozanib 49% (36-63) vs placebo 21% (11-34), p=0.001 Nosov 2012[58]	1 RCT	-1	-1	0	0	0	1. Unclear allocation concealment, high risk of incomplete outcome data and selective reporting 2. Only one study	Low
PFS: Median PFS in months (95% CI): tivozanib 10.3 (8.1-21.2) vs placebo 3.3 (1.8-8.0), p=0.01 Nosov 2012[58]	1 RCT	-1	-1	0	0	0	1. Unclear allocation concealment, high risk of incomplete outcome data and selective reporting 2. Only one study	Low
Bevacizumab (10 mg/kg or 3 mg/kg) vs placebo								
PFS *Time to progression of disease* Bevacizumab 10 mg/kg vs placebo	1 RCT	0	-1	0	0	0	2. Only one study	Moderate

HR 2.55, p<0.001 Bevacizumab 3 mg/kg vs placebo HR 1.96 p=0.053 Yang 2003[88]								
OS p>0.20 for all comparison Yang 2003[88]	1 RCT	0	-1	0	-1	0	2. Only one study 4. p value non-significant	Low
Everolimus vs placebo								
PFS HR (95%) 0.33 (0.25-0.43) 2nd-line: HR (95%) 0.32 (0.19-0.54) 3rd-line: HR (95%) 0.32 (0.09-0.55) *All*: HR (95% CI) 0.32 (0.13-0.77) *Intolerance to previous sunitinib:* HR (95% CI) 0.28 (0.07-1.18) *Intolerance to previous sorafenib:* HR (95% CI) 0.29 (0.09-0.91) ≥ 65 years: HR (95% CI) 0.33 (0.21-0.51) ≥ 70 years: HR (95% CI) 0.19 (0.09-0.37) Record-1[89-92]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS HR (95%) 0.87 (0.65-1.15) ≥ 65 years: HR (95% CI) 1.07 (0.69-1.67) ≥ 70 years: HR (95% CI) 0.85 (0.47-1.55) Record-1[91, 92]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Moderate

Table 63 – GRADE profiles – Second-line treatment: targeted therapy vs other targeted therapy in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Axitinib vs Sorafenib								
PFS HR (95% CI): 0.66 (0.55-0.78) in favour of axitinib AXIS[93]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
OS HR (95%) 0.97 (0.80-1.17) AXIS[93]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low
QoL FKSI-15, FKSI-DRS, EQ-5D, EQ-VAS not statistical difference AXIS[87]	1 RCT	0	-1	0	0	0	2. Only one study	Moderate
Tivozanib vs Sorafenib								
PFS Overall PFS (months): HR (95% CI): 0.797 (0.639-0.993), p=0.042 No prior treatment HR (95% CI): 0.756 (0.580-0.985), p=0.037 Prior systemic treatment for mRCC HR (95% CI): 0.877 (0.587-1.309), p=0.520 ECOG PS=0 HR (95% CI): 0.617 (0.442-0.860), p=0.004	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm in subgroup analysis	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
ECOG PS=1 HR (95% CI): 0.920 (0.680-1.245), p=0.588 Favorable HR (95% CI): 0.590 (0.378-0.921), p=0.018 Intermediate HR (95% CI): 0.786 (0.601-1.028), p=0.076 Poor HR (95% CI): 1.361 (0.546-3.393), p=0.504 TIVO-1[54]								
OS HR (95% CI) 1.245 (0.954-1.624), p=0.105 TIVO-1[54]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low
ORR (% (95% CI)) Tivozanib 33.1% (27.4-39.2) vs sorafenib 23.3% (18.3-29.0), p=0.14 TIVO-1[54]	1 RCT	-1	-1	0	0	0	1. No allocation concealment 2. Only one study	Low
HRQoL: No difference between baseline level and 12 month of treatment in both arms TIVO-1[54]	1 RCT	-1	-1	0	0	0	1. No allocation concealment 2. Only one study	Low
Temsirolimus vs Sorafenib								
PFS HR (95% CI) 0.87 (0.71-1.07), p=0.19 Hutson 2014[60]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
OS HR (95% CI) 1.31 (1.05-1.63) in favour of sorafenib Hutson 2014[60]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low
ORR Temsirolimus 8% vs sorafenib 8% Hutson 2014[60]	1 RCT	-1	-1	0	0	0	1. No allocation concealment 2. Only one study	Low

Table 64 – GRADE profiles – Second-line treatment: targeted therapy vs hormones in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Lapatinib vs hormones								
PFS HR (95% CI)=0.94 (0.75-1.18); p=0.60 Ravaud 2008[94]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low
OS HR (95% CI)=0.88 (.69-1.12); p=0.29 Ravaud 2008[94]	1 RCT	0	-1	0	-1	0	2. Only one study 4. CI both includes benefit and harm	Low

Table 65 – GRADE profiles – Third-line treatment: targeted therapy vs targeted therapy in metastatic renal cancer patients

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Dovitinib vs Sorafenib								
PFS HR (95% CI) 0.86 (0.72-1.04), p=0.063 Motzer 2014[61]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
OS HR (95% CI) 0.96 (0.75-1.22) Motzer 2014[61]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low
Median time to definitive worsening of Karnofsky PS HR (95% CI) 1.12 (0.87-1.45) Motzer 2014[61]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low
Definitive deterioration by 10% of QoL score of the EORTC QLQ-C30 HR (95% CI) 1.08 (0.86-1.36) of the FKSI-DRS HR (95% CI) 1.20 (0.91-1.58) Motzer 2014[61]	1 RCT	-1	-1	0	-1	0	1. No allocation concealment 2. Only one study 4. CI both includes benefit and harm	Very low

6. FOREST PLOTS

6.1. Treatment

6.1.1. Combination of immuno(chemo)therapy vs control in metastatic renal cancer

Figure 9 – Combination of immuno(chemo)therapy vs control - remission

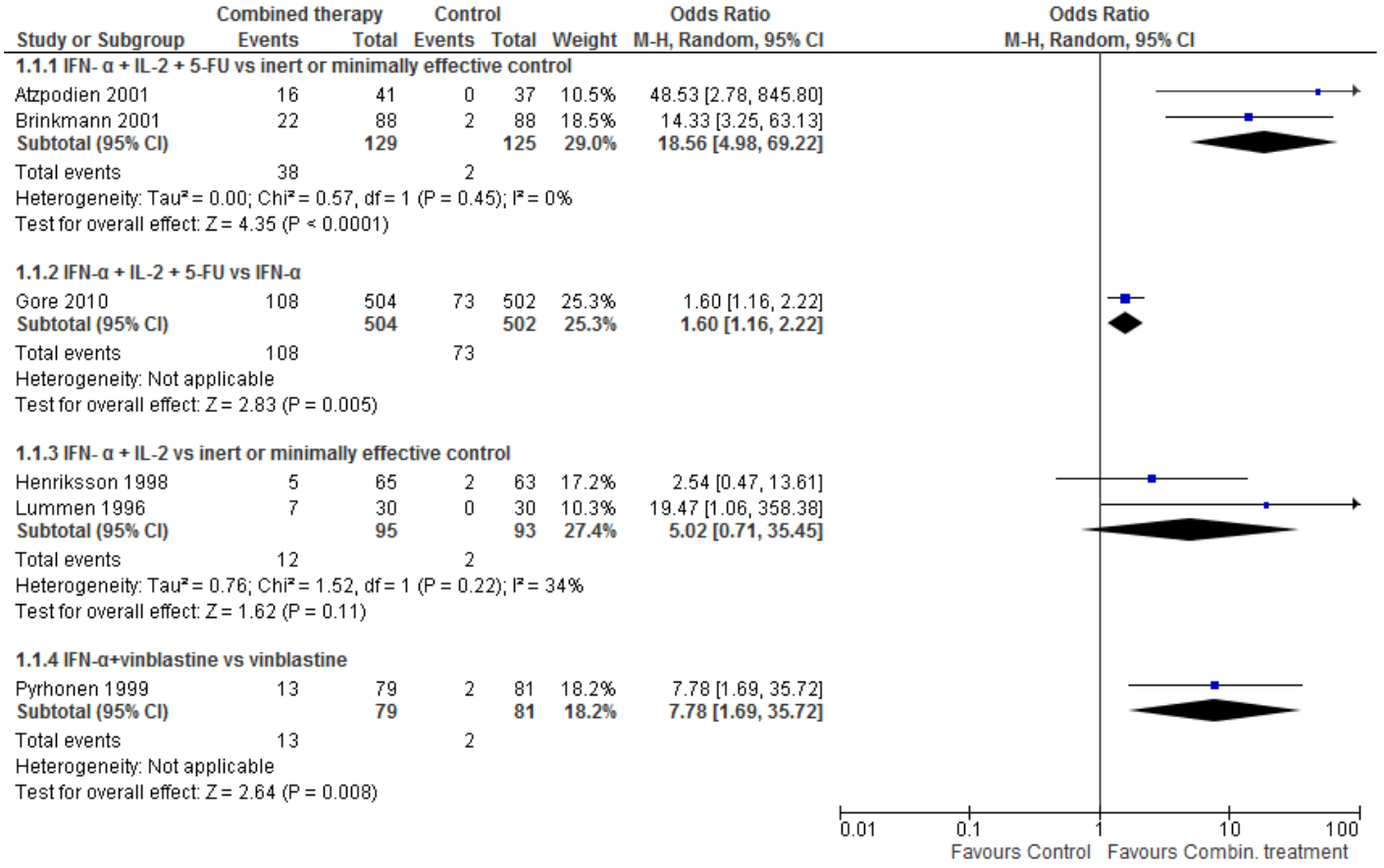
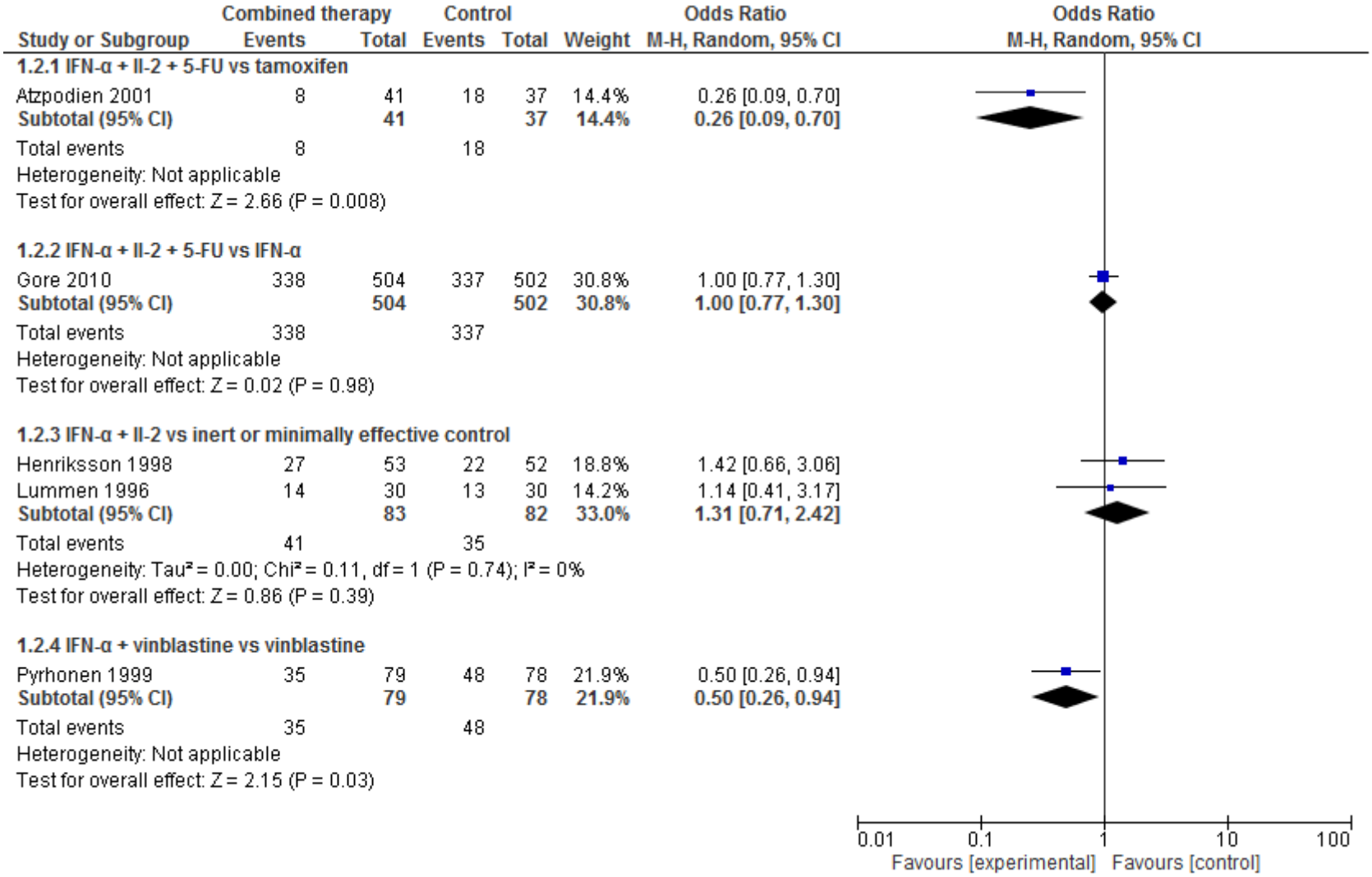


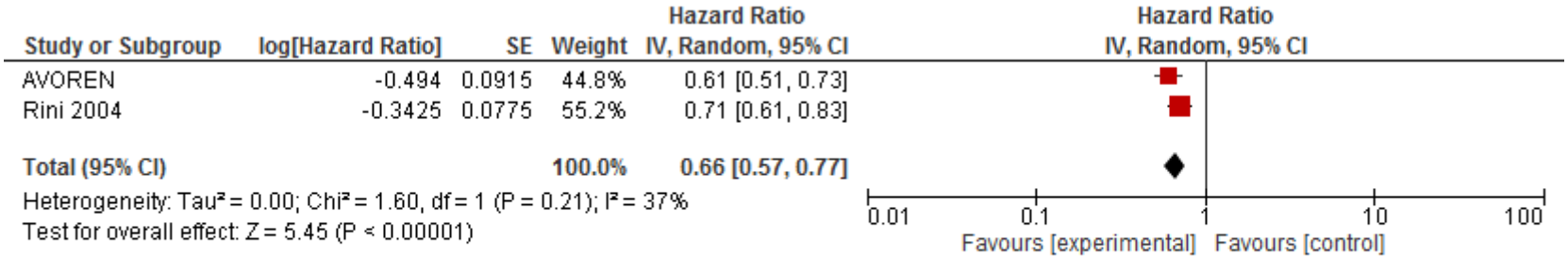
Figure 10 – Combination of immuno(chemo)therapy vs control – one-year mortality



6.1.2. *Bevacizumab + IFN versus IFN*

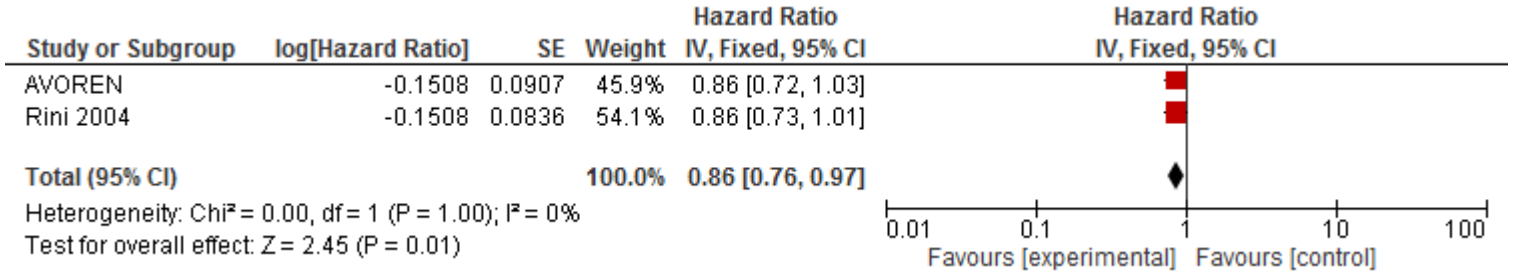
- **Progression-free survival**

Figure 11 – Combination of bevacizumab + IFN vs IFN – progression-free survival



- **Overall survival**

Figure 12 – Combination of bevacizumab + IFN vs IFN – Overall survival



7. ADDITIONAL EVIDENCE

7.1. Chemotherapy in metastatic renal cancer

7.1.1. Chemotherapy

The search strategy performed from 2009 did not retrieve any additional meta-analysis, systematic review or RCTs dealing with chemotherapy alone.

EAU guideline retrieved one systematic review[13] that compared, amongst others, chemotherapy with cytokine agents (IFN-α or IL-2). The following sections described the evidence related to chemotherapy retrieved from this systematic review. All details are provided in evidence tables presented above (see section 5). IKNL did not provide any additional evidence.

7.1.2. Chemotherapy as enhancement agents for cytokine therapies

Three RCTs tested IFN-α alone against IFN-α plus vinblastine.[95-97] No statistical significant advantage in favour of enhanced treatment was found for remission rate [Peto Odd ratio (95%CI): 1.36 (8.80 – 2.32)] or for survival rate [Peto Odd ratio (95%CI): 1.36 (8.80 – 2.32)].[13]

7.1.3. Chemotherapy combined with cytokine agents versus other controls

Kriegmair 1995 compared medroxyprogesterone with a combination of IFN-α2b and vinblastine.[98] Brinkmass 2001 compared lectin with a combination of IFN-α2b, IL-2 and 5 FU.[99] Results were reported and discussed in the section dedicated to immunotherapy.

Conclusions

- Immuno-chemotherapies provided better remission rate and one-year survival than chemotherapy alone in 2 studies. This advantage was not confirmed in a third RCT.
- IFN-α alone has equivalent efficacy to a combination of IFN-α + interleukine-2 (IL-2) + vinblastine

7.2. Immunotherapy in metastatic renal cancer

The search strategy retrieved two systematic reviews. A Cochrane Systematic Review[13] addressed immunotherapy in RCC and one additional RCT[52] was found as update from the literature search. A second review focused on adoptive immunotherapy.[23] It included 4 RCTs of which one was previously discussed in adjuvant therapy section.[39] EAU and IKNL guidelines did not provide any additional evidence.

Definitions:

In the Coppin 2006, 'high dose' interleukine-2 (IL-2 (hd)) is defined as the American standard dose and regimen namely more than intravenous bolus 600,000 IU/m² per 8 hours. In European, the standard regimen is different namely 18 MU/m²/day by continuous infusion.[13]

7.2.1. Interferon-α (IFN-α)

7.2.1.1. IFN-α versus control

- **IFN-α vs medroxyprogesterone (non-immunotherapy controls)**

  In Coppin 2006, four studies comparing IFN-α with medroxyprogesterone (MPA) were retrieved.[13] These studies used recombinant IFN-α either IFN-α2a form[100] or IFN-α2b.[98, 101] One study added vinblastine to IFN-α2b.[98] Subcutaneous injection was the route of administration for all studies with the exception of the oldest study[100] that used intramuscular injection.

  A pooling of three RCTs was performed and showed a clear advantage for IFN- α in comparison with MPA in terms of remission rate (IFN-α: 11.2 % vs MPA: 1.2%) and in one-year mortality (IFN-α: 56.0 % vs MPA: 69.0%). One study was excluded of the pooling because of the restriction in entry to intermediate prognosis patients.[102] However, if this study is combined with the others, the pooled estimation for remission and for one-year mortality is still improved when IFN-α is used in comparison of MPA. [Remission OR (95% CI): 8,73 (2.85-26.75) based on 3 RCTs, OR (95% CI): 5,37 (2.30-12.53) including the 4 RCTs. One-year mortality OR (95% CI): 0,58 (0.39-0.85) based on 3 RCTs and OR (95% CI): 0,66 (0.49-0.90) including the 4 RCTs]. [13] A subgroup analysis was conducted by Coppin 2006 for studies using recombinant subtypes IFN-α2a and IFN-α2b.The authors concluded that there was

no evidence of heterogeneity by subtype for remission rate or one-year mortality.

- **IFN-α vs IL-2 (ld) (immunotherapy control)**

  Coppin 2006 retrieved 3 studies[103-105] that performed a three-arm comparison between IFN-α, IL-2 (ld) and the combination of both. [13] There is no difference in remission rate and in one-year mortality when those 3 studies are pooled [Remission OR (95% CI): 0,93 (0.47-1.84), One-year mortality OR (95% CI): 0,93 (0,66 (0.49-1.31)]. [13] However, IL-2 (ld) presented a subtantially greater toxicity than IFN-α (Grade 3 or 4 adverse events: IL-2 (ld): 281/607 vs IFN-α: 151/287).

7.2.1.2. Enhancement of IFN-α with drugs

Coppin 2006 reported 12 studies using various enhancement agents.[13] Hormones was used as enhancement agent in 2 studies,[106, 107] vinblastine was used in 3 studies,[95-97] interferon-γ in 2 studies,[108, 109] 13-cis-retinoic acid (13CRA) in 2 studies,[110, 111] and finally miscellaneous agents including aspirin, cimetidine alone or with coumarin[112-114] in three studies. None of these agents provided an improvement in remission rate or in one-year mortality (Coppin 2006) except for 13CRA that showed an increased remission rate [IFN-α+ 13CRA: 13.5% vs IFN-α alone: 6.1%, Peto OR (95 CI): 2.28 (1.17-4.45)] but no difference in one-year mortality [Peto OR (95% CI): 0.88 (0.63-1.21)] and a greater toxicity. [13]

7.2.2. Interleukine-2 (IL-2)

7.2.2.1. High dose IL-2 versus other treatment option

Yan (2003) is a 2 arm RCT completed by a 3rd arm in the continuation of the study.[115] IL-2 dosage was 2.16 MU/kg/day i.v., 0.216 MU/kg/day i.v. and 0.125 MU/kg s.c. When compared to the 2 lower dosage regimen, high dose showed a marginally higher remission rate (n=306, Peto OR (95% CI) 1.82 (1.00 to 3.30), I^2=0%, p=0.049) and equal overall survival (n=305, Peto OR (95% CI) 0.95 (0.59 to 1.53), I^2=0%, p=0.84). However, the gain in remission rate was not balanced by the toxicity of IL-2 (hd).

In 193 patients with RCC, McDermott (2005) compared IL-2 (hd) i.v. with a subcutaneous combined treatment composed by IFN-α with IL-2 (ld).[116] High dose arm showed a higher remission rate than patients treated by the combined therapy (Peto OR (95% CI) 2.70 (1.26 to 5.82), p=0.011). In full intention-to-treat analysis, no advantage was found in progression-free survival or overall survival for IL-2 (hd) treatment. However, one-year survival was improved with IL-2 (hd) for patients with liver or bone metastases or for those with primary tumour in place (Liver-bone metastases: IL-2 (hd): 60% vs IFN-α + IL-2 (ld): 25%, p=0.001; Primary tumour: in place 51% vs resected 32%, p=0.04).

Weiss (1992) shown similar remission rate in 94 patients treated by either IL-2 4-5 MU/m²/day + Lymphokine Activated Killer (LAK) cells in infusion or IL-2 0.4 MU/kg/day + LAK cells in i.v. bolus.

7.2.2.2. Enhancement of high dose IL-2

Rosenberg (1993) tested IL-2 (hd) with or without LAK cells in in 97 patients with various cancers.[117] No significant difference was seen in terms of response rate or overall survival.

Law (1995) and McCabe (1991) also used LAK cells to enhance IL-2 (ld) but with similar lack of success.[118, 119] Enhancement of IL-2 (ld) was also tried with tumour infiltrating lymphocytes[39], IFN-β[120], histamine[121] or melatonin[122] leading to the same failure.

7.2.3. Interferon-γ

Coppin (2006) identified in his review one placebo-controlled study that examined interferon-γ (Gleave 1998)[123] in 197 patients. No advantage was found in terms of remission rate [OR (95%CI): 0.66 (0.18-2.41)] or in one-year deaths rate [OR (95%CI): 1.00 (0.53-1.91)].

7.2.4. Combination of immunotherapy or immuno-chemotherapy

In the systematic review related to immunotherapy for advanced renal cell cancer[13], IFN-α combined with IL-2 ± 5-FU is compared with 3 different control types: tamoxifen (2 studies already discussed in chemotherapy chapter)[124, 125], Lectin (1 study)[99] or interferon-gamma[126]. In addition, one RCT using IFN-α as control was retrieved during the update process of this review[52]. Finally, a combination of IFN-α and vinblastine was compared with vinblastine alone to in 1 RCT[127].

Gore (2010) randomly assigned 1006 untreated metastatic RCC patients either in IFN-α-2a treatment group or in combined treatment group (IFN-α-2a + IL-2 + fluorouracil)[52]. This trial showed that combined treatment did not

provide any advantage compared with IFN-α-2a in terms of overall survival (HR (CI95%) 1.05 (0.90-1.21), p=0.55) or progression-free survival (HR (CI95%) 1.02 (0.89-1.16), p=0.81). The overall response rate was higher in combined treatment group (IFN-α2a: 23% vs combined treatment 16%, p=0.0045). However, combined treatment was associated with more severe toxic effects in comparison with IFN-α-2a (Grade 3 and 4 probability: IFN-α2a: 53% vs combined treatment 36%, p<0.0001).

Combined treatment improved the remission rate whatever the comparator (OR (95% CI): 2.29 (1.71-3.08), I^2=76%, p<0.00001). However, this effect is more important when comparator is an inert or minimally effective drug and when 5-FU is included in the combination. No advantage was seen in terms of one-year mortality (see appendix section 6).

7.2.5. Adoptive cellular immunotherapy

Adoptive cellular immunotherapy (ACI) is part of therapeutic arsenal that aims to enhance immune system response against cancer. Cells with anti-tumour activity are largely expended *in vitro* and administrated to patients to eradicate malignant cells. In the Tang 2013's review, 3 types of ACI were used in metastatic renal cell carcinoma patients: lymphokine – activated killer (LAK), tumour-infiltrating (TIL) and cytokine-induced killer (CIK). Four RCTs were pooled with different comparators (autolymphocyte + cimetidine vs cimetidine, LAK + IL-2 vs Il-2, $CD8^+$ TIL+ IL-2 vs IL-2 and CIK vs IL-2 + IFN-α2a). The pooling showed that objective response, 1-3 and 5-year survival were in favour of the ACI in comparison of controls[23]. However, these results have to be interpreted with caution because of the low quality of the primary studies.

Conclusions

- IFN-α provides better remission rate and one-year survival than hormones as MPA.
- No difference in remission rate and one-year survival is shown between IFN-α and IL-2 (ld).
- Enhancement agents such as hormone, vinblastine, IFN-γ do not improve remission rate or survival in metastatic RCC patients treated with IFN-α.
- Remission rate is marginally improved in metastatic RCC patients treated with IL-2 (hd) in comparison with those treated with IL-2 (ld) but survival is not improved.
- Addition of LAK cells to IL-2 to treat metastatic RCC patients does not improved survival or remission rate.
- Interferon-γ does not provide any advantage in comparison with placebo in terms of remission rate or survival of metastatic RCC patients.
- Combined immunotherapy with or without 5-FU improves remission rate in metastatic RCC patients in comparison with tamoxifen, lectine or interferon-γ. However, 1-year survival is not improved.
- Adoptive cellular immunotherapy seems to improve objective response rate and 1 to 5-year survival compared to cimetidine or cytokines.

7.3. Adverse events of targeted therapy

7.3.1. First-line treatment

7.3.1.1. Tyrosine kinase inhibitors

Table 66 – First-line treatment – Tyrosine Kinase inhibitors: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fatigue/Asthenia	Escudier 2009	CC mRCC	Sorafenib	42/97 (5/97)	IFN	39/90 (9/90)
Fatigue	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (18/40)	Sorafenib	NR (10/40)
Fatigue	ROSORC	All tumour types	Sorafenib + IL-2	12/66 (2/66)	Sorafenib	10/62 (1/62)
Fatigue	Hutson 2013	CC mRCc	Axitinib	62/189 (10/189)	Sorafenib	25/96 (1/96)
Fatigue	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 30% (2%) 24% (4%)	Sorafenib + placebo arm C	 22% (0%)
Fatigue	SUTENT	CC mRCC	Sunitinib	54/375 (11/375)	IFN	52/360 (13/360)
Fatigue	Motzer 2013b	CC mRCC	Pazopanib	302/554 (59/554)	Sunitinib	344/558 (94/558)
Fatigue	Mulders 2012	All tumour types	Cediranib	31/53 (10/53)	Placebo	9/18 (1/18)
Chills	Escudier 2009	CC mRCC	Sorafenib	0/97 (0/97)	IFN	11/90 (0/90)
Chills	SUTENT	CC mRCC	Sunitinib	7/375 (1/375)	IFN	29/360 (0/360)
Fever	Escudier 2009	CC mRCC	Sorafenib	3/97 (0/97)	IFN	29/90 (0/90)
Pyrexia	ROSORC	All tumour types	Sorafenib + IL-2	13/66 (0/66)	Sorafenib	1/62 (0/62)
Pyrexia	SUTENT	CC mRCC	Sunitinib	8/375 (1/375)	IFN	35/360 (0/360)
Pyrexia	Motzer 2013b	CC mRCC	Pazopanib	48/554 (2/554)	Sunitinib	88/558 (6/558)
Weight loss	Escudier 2009	CC mRCC	Sorafenib	14/97 (2/97)	IFN	18/90 (1/90)
Weight loss	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (0/40)
Weight loss	Hutson 2013	CC mRCc	Axitinib	69/189 (16/189)	Sorafenib	23/96 (3/96)
Weight loss	SUTENT	CC mRCC	Sunitinib	12/375 (0/375)	IFN	14/360 (0/360)
Weight loss	Motzer 2013b	CC mRCC	Pazopanib	84/554 (5/554)	Sunitinib	33/558 (1/558)
Insomnia	Escudier 2009	CC mRCC	Sorafenib	0/97 (0/97)	IFN	8/90 (0/90)
Insomnia	Rini 2012	CC mRCC	Sorafenib + AMG 386		Sorafenib + placebo	

			A: 10 mg/kg qw B: 3 mg/kg qw	24% (2%) 12% (0%)	arm C	2% (0%)
Syncope (fainting)	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (0/40)
Non-neuropathic infection	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (2/40)
Appendicitis	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Pancreatitis	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Dysphonia	Hutson 2013	CC mRCc	Axitinib	44/189 (2/189)	Sorafenib	10/96 (0/96)
Decreased appetite	Hutson 2013	CC mRCc	Axitinib	54/189 (4/189)	Sorafenib	18/96 (0/96)
Decreased appetite	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 38% (2%) 27% (0%)	Sorafenib + placebo arm C	 20% (0%)
Decreased appetite	SUTENT	CC mRCC	Sunitinib	10/375 (0/375)	IFN	11/360 (0/360)
Dysphonia	Mulders 2012	All tumour types	Cediranib	31/53 (0/53)	Placebo	1/18 (0/18)

Table 67 – First-line treatment – Tyrosine Kinase inhibitors: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Confusion	Escudier 2009	CC mRCC	Sorafenib	1/97 (0/97)	IFN	5/90 (0/90)
Dizziness	Escudier 2009	CC mRCC	Sorafenib	0/97 (0/97)	IFN	0/90 (0/90)
Mood alteration/depression	Escudier 2009	CC mRCC	Sorafenib	0/97 (0/97)	IFN	0/90 (13/90)
Sensory neuropathy	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (1/40)	Sorafenib	NR (1/40)
Asthenia	Hutson 2013	CC mRCc	Axitinib	39/189 (16/189)	Sorafenib	15/96 (5/96)
Asthenia	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 30% (2%) 22% (4%)	Sorafenib + placebo arm C	 20% (2%)
Asthenia	SUTENT	CC mRCC	Sunitinib	20/375 (7/375)	IFN	19/360 (4/360)

Table 68 – First-line treatment – Tyrosine Kinase inhibitors: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (2/40)
Hypertension	ROSOR	All tumour types	Sorafenib + IL-2	6/66 (1/66)	Sorafenib	10/62 (4/62)
Hypertension	Hutson 2013	CC mRCC	Axitinib	92/189 (26/189)	Sorafenib	28/96 (1/96)
Hypertension	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 42% (18%) 49% (20%)	Sorafenib + placebo arm C	 46% (14%)
Hypertension	SUTENT	CC mRCC	Sunitinib	30/375 (12/375)	IFN	4/360 (1/360)
Hypertension	Mulders 2012	All tumour types	Cediranib	34/53 (10/53)	Placebo	4/18 (0/18)
Cardiac ischemia/infraction	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Arterial thromboembolic events	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 8% (8%) 6% (4%)	Sorafenib + placebo arm C	4% (4%)
Venous thromboembolic events	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 4% (2%) 4% (4%)	Sorafenib + placebo arm C	0% (0%)
Cardiac toxicity	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 2% (2%) 0% (0%)	Sorafenib + placebo arm C	0% (0%)
Haemorrhagic events	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 12% (0%) 14% (2%)	Sorafenib + placebo arm C	20% (2%)
Impaired wound healing	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 4% (0%) 6% (2%)	Sorafenib + placebo arm C	2% (0%)
Decline in ejection fraction	SUTENT	CC mRCC	Sunitinib	13/375 (3/375)	IFN	3/360 (1/360)
Epistaxis	SUTENT	CC mRCC	Sunitinib	18/375 (1/375)	IFN	2/360 (0/360)
Epistaxis	Motzer 2013b	CC mRCC	Pazopanib	48/554 (1/554)	Sunitinib	97/558 (6/558)

Table 69 – First-line treatment – Tyrosine Kinase inhibitors: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Cough	Escudier 2009	CC mRCC	Sorafenib	3/97 (0/97)	IFN	5/90 (0/90)
Cough	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 26% (0%) 12% (0%)	Sorafenib + placebo arm C	10% (0%)
Dyspnoea	Escudier 2009	CC mRCC	Sorafenib	2/97 (0/97)	IFN	8/90 (0/90)
Dyspnoea	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (4/40)	Sorafenib	NR (4/40)
Dyspnoea	ROSORC	All tumour types	Sorafenib + IL-2	5/66 (0/66)	Sorafenib	1/62 (1/62)
Dyspnoea	SUTENT	CC mRCC	Sunitinib	11/375 (0/375)	IFN	8/360 (1/360)
Voice change	Escudier 2009	CC mRCC	Sorafenib	6/97 (0/97)	IFN	0/90 (0/90)
Pneumonitis	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Chest pain	ROSORC	All tumour types	Sorafenib + IL-2	3/66 (1/66)	Sorafenib	0/62 (0/62)

Table 70 – First-line treatment – Tyrosine Kinase inhibitors: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grade s (grade 3-4)	Control	All grades (grade 3-4)
Hypophosphatemia	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (5/40)	Sorafenib	NR (3/40)
Hypophosphatemia	ROSORC	All tumour types	Sorafenib + IL-2	4/66 (1/66)	Sorafenib	3/62 (0/62)
Hypophosphatemia	SUTENT	CC mRCC	Sunitinib	31/375 (6/375)	IFN	24/360 (6/360)
Hypophosphatemia	Motzer 2013b	CC mRCC	Pazopanib	193/554 (24/554)	Sunitinib	279/558 (49/558)
Proteinuria	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (2/40)	Sorafenib	NR (1/40)
Proteinuria	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 16% (2%) 14% (0%)	Sorafenib + placebo arm C	8% (0%)
Hyponatremia	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (1/40)	Sorafenib	NR (2/40)
Adrenal insufficiency	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (1/40)	Sorafenib	NR (0/40)
Blood creatine increased	ROSORC	All tumour types	Sorafenib + IL-2	166 (0/66)	Sorafenib	3/62 (0/62)

Increased creatine kinase	SUTENT	CC mRCC	Sunitinib	49/375 (3/375)	IFN	12/360 (1/360)
Peripheral oedema	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 18% (0%) 16% (0%)	Sorafenib + placebo arm C	 12% (0%)
Peripheral oedema	SUTENT	CC mRCC	Sunitinib	13/375 (1/375)	IFN	1/360 (0/360)
Peripheral oedema	Motzer 2013b	CC mRCC	Pazopanib	59/554 (1/554)	Sunitinib	91/558 (2/558)
Hypokalaemia	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 4% (2%) 8% (2%)	Sorafenib + placebo arm C	 4% (0%)
Infusion reactions	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 6% (0%) 2% (0%)	Sorafenib + placebo arm C	 8% (2%)
Increased uric acid	SUTENT	CC mRCC	Sunitinib	46/375 (14/375)	IFN	33/360 (8/360)
Hypomagnesaemia	Motzer 2013b	CC mRCC	Pazopanib	125/554 (1/554)	Sunitinib	128/558 (7/558)
Hypermagnesaemia	Motzer 2013b	CC mRCC	Pazopanib	62/554 (13/554)	Sunitinib	97/558 (25/558)

Table 71 – First-line treatment – Tyrosine Kinase inhibitors: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Anorexia	Escudier 2009	CC mRCC	Sorafenib	29/97 (0/97)	IFN	27/90 (2/90)
Anorexia	ROSORC	All tumour types	Sorafenib + IL-2	3/66 (0/66)	Sorafenib	1/62 (0/62)
Anorexia	SUTENT	CC mRCC	Sunitinib	34/375 (2/375)	IFN	28/360 (2/360)
Diarrhoea	Escudier 2009	CC mRCC	Sorafenib	53/97 (6/97)	IFN	11/90 (0/90)
Diarrhoea	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (21/40)	Sorafenib	NR (13/40)
Diarrhoea	ROSORC	All tumour types	Sorafenib + IL-2	15/66 (0/66)	Sorafenib	17/62 (0/62)
Diarrhoea	Hutson 2013	CCmRCc	Axitinib	94/189 (17/189)	Sorafenib	38/96 (5/96)
Diarrhoea	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 70% (8%) 67% (10%)	Sorafenib + placebo arm C	 56% (6%)
Diarrhoea	SUTENT	CC mRCC	Sunitinib	61/375 (9/375)	IFN	15/360 (1/360)

Diarrhoea	Mulders 2012	All tumour types	Cediranib	39/53 (4/53)	Placebo	5/18 (0/18)
Dry mouth	Escudier 2009	CC mRCC	Sorafenib	5/97 (0/97)	IFN	1/90 (0/90)
Dry mouth	SUTENT	CC mRCC	Sunitinib	12/375 (0/375)	IFN	6/360 (0/360)
Vomiting	Escudier 2009	CC mRCC	Sorafenib	13/97 (2/97)	IFN	13/90 (1/90)
Vomiting	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 20% (2%) 22% (2%)	Sorafenib + placebo arm C	 18% (2%)
Vomiting	SUTENT	CC mRCC	Sunitinib	31/375 (4/375)	IFN	12/360 (1/360)
Nausea and vomiting	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (1/40)
Nausea	Escudier 2009	CC mRCC	Sorafenib	18/97 (0/97)	IFN	25/90 (3/90)
Nausea	ROSORC	All tumour types	Sorafenib + IL-2	3/66 (0/66)	Sorafenib	3/62 (1/62)
Nausea	Hutson 2013	CC mRCc	Axitinib	37/189 (2/189)	Sorafenib	14/96 (1/96)
Nausea	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 30% (2%) 33% (2%)	Sorafenib + placebo arm C	 20% (2%)
Nausea	SUTENT	CC mRCC	Sunitinib	52/375 (5/375)	IFN	35/360 (1/360)
Nausea	Mulders 2012	All tumour types	Cediranib	17/53 (0/53)	Placebo	5/18 (0/18)
Constipation	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 24% (0%) 12% (0%)	Sorafenib + placebo arm C	 22% (2%)
Constipation	SUTENT	CC mRCC	Sunitinib	12/375 (0/375)	IFN	4/360 (0/360)
Constipation	Mulders 2012	All tumour types	Cediranib	16/53 (0/53)	Placebo	4/18 (0/18)
Constipation	Motzer 2013 (b)	CC mRCC	Pazopanib	94/554 (4/554)	Sunitinib	130/558 (5/558)
Gastrointestinal perforation	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 4% (2%) 0% (0%)	Sorafenib + placebo arm C	 2% (2%)
Hyperamylasemia or lipasemia	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (4/40)	Sorafenib	NR (5/40)
Increased lipase	SUTENT	CC mRCC	Sunitinib	56/375 (18/375)	IFN	46/360 (8/360)
Increased amylase	SUTENT	CC mRCC	Sunitinib	35/375 (6/375)	IFN	32/360 (3/360)
Blood amylase increase	ROSORC	All tumour types	Sorafenib + IL-2	1/66 (0/66)	Sorafenib	3/62 (0/62)

Increased ALT	SUTENT	CC mRCC	Sunitinib	51/375 (2/375)	IFN	40/360 (2/360)
Increased ALT	Motzer 2013b	CC mRCC	Pazopanib	326/554 (96/554)	Sunitinib	234/558 (21/558)
Increased AST	SUTENT	CC mRCC	Sunitinib	56/375 (2/375)	IFN	38/360 (2/360)
Increased AST	Motzer 2013b	CC mRCC	Pazopanib	333/554 (69/554)	Sunitinib	323/558 (15/558)
Transaminitis	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (0/40)
Transaminase increase	ROSORC	All tumour types	Sorafenib + IL-2	0/66 (0/66)	Sorafenib	3/62 (1/62)
Small bowel obstruction	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Haemorrhoids	ROSORC	All tumour types	Sorafenib + IL-2	1/66 (0/66)	Sorafenib	4/62 (0/62)
Dyspepsia	SUTENT	CC mRCC	Sunitinib	31/375 (2/375)	IFN	5/360 (0/360)
Dyspepsia	Motzer 2013 (b)	CC mRCC	Pazopanib	78/554 (0/554)	Sunitinib	133/558 (3/558)
Flatulence	SUTENT	CC mRCC	Sunitinib	11/375 (0/375)	IFN	2/360 (0/360)
Gastroesophagael reflux disease	SUTENT	CC mRCC	Sunitinib	10/375 (0/375)	IFN	1/360 (0/360)

Table 72 – First-line treatment – Tyrosine Kinase inhibitors: Pain

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Pain	Escudier 2009	CC mRCC	Sorafenib	27/97 (5/97)	IFN	26/90 (4/90)
Back pain	Hutson 2013	CC mRCc	Axitinib	35/189 (8/189)	Sorafenib	21/96 (5/96)
Pain in extremity	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 22% (2%) 16% (0%)	Sorafenib + placebo arm C	 16% (2%)
Pain in extremity	SUTENT	CC mRCC	Sunitinib	18/375 (1/375)	IFN	3/360 (0/360)
Abdominal pain	SUTENT	CC mRCC	Sunitinib	11/375 (2/375)	IFN	3/360 (0/360)
Upper abdominal pain	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 20% (2%) 10% (2%)	Sorafenib + placebo arm C	 4% (0%)
Headache	SUTENT	CC mRCC	Sunitinib	14/375 (1/375)	IFN	16/360 (0/360)
Headache	Mulders 2012	All tumour types	Cediranib	24/53 (2/53)	Placebo	4/18 (0/18)
Oral pain	SUTENT	CC mRCC	Sunitinib	13/375 (1/375)	IFN	1/360 (0/360)

Myalgia	SUTENT	CC mRCC	Sunitinib	8/375 (0/375)	IFN	17/360 (1/360)
Pain in a limb	Motzer 2013b	CC mRCC	Pazopanib	67/554 (2/554)	Sunitinib	91/558 (6/558)

Table 73 – First-line treatment – Tyrosine Kinase inhibitors: Endocrine / metabolic events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hyperuricemia	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (3/40)	Sorafenib	NR (12/40)
Hyperuricemia	ROSORC	All tumour types	Sorafenib + IL-2	4/66 (0/66)	Sorafenib	6/62 (0/62)
Hypothyroidism	Hutson 2013	CC mRCc	Axitinib	39/189 (0/189)	Sorafenib	7/96 (0/96)
Hypothyroidism	SUTENT	CC mRCC	Sunitinib	14/375 (2/375)	IFN	2/360 (0/360)
Hypothyroidism	Motzer 2013b	CC mRCC	Pazopanib	67/554 (0/554)	Sunitinib	133/558 (2/558)

Table 74 – First-line treatment – Tyrosine Kinase inhibitors: Hematologic adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Neutropenia	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (6/40)	Sorafenib	NR (0/40)
Neutropenia	ROSOR	All tumour types	Sorafenib + IL-2	4/66 (1/66)	Sorafenib	0/62 (0/62)
Neutropenia	Motzer 2013b	CC mRCC	Pazopanib	203/554 (25/554)	Sunitinib	370/558 (109/558)
Neutropenia	SUTENT	CC mRCC	Sunitinib	77/375 (18/375)	IFN	50/360 (9/360)
Reversible posterior leuko-encephalopathy	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (0/40)	Sorafenib	NR (1/40)
Anaemia	ROSOR	All tumour types	Sorafenib + IL-2	3/66 (0/66)	Sorafenib	5/62 (0/62)
Anaemia	SUTENT	CC mRCC	Sunitinib	79/375 (8/375)	IFN	70/360 (6/360)
Anaemia	Motzer 2013b	CC mRCC	Pazopanib	171/554 (12/554)	Sunitinib	326/558 (40/558)
Thrombocytopenia	ROSOR	All tumour types	Sorafenib + IL-2	2/66 (0/66)	Sorafenib	4/62 (0/62)
Thrombocytopenia	SUTENT	CC mRCC	Sunitinib	68/375 (9/375)	IFN	26/360 (1/360)
Thrombocytopenia	Motzer 2013b	CC mRCC	Pazopanib	227/554 (20/554)	Sunitinib	421/558 (117/558)
Leukopenia	SUTENT	CC mRCC	Sunitinib	78/375 (8/375)	IFN	57/360 (2/360)
Leukopenia	Motzer 2013b	CC mRCC	Pazopanib	237/554 (8/554)	Sunitinib	423/558 (34/558)
Increased creatinine	SUTENT	CC mRCC	Sunitinib	70/375 (0/375)	IFN	51/360 (0/360)

Increased creatinine	Motzer 2013b	CC mRCC	Pazopanib	177/554 (4/554)	Sunitinib	258/558 (8/558)
Lymphocytopenia	SUTENT	CC mRCC	Sunitinib	68/375 (18/375)	IFN	69/360 (26/360)
Lymphocytopenia	Motzer 2013b	CC mRCC	Pazopanib	208/554 (29/554)	Sunitinib	300/558 (77/558)
Increased alkaline phosphatase	SUTENT	CC mRCC	Sunitinib	46/375 (2/375)	IFN	37/360 (2/360)
Increased alkaline phosphatase	Motzer 2013b	CC mRCC	Pazopanib	154/554 (17/554)	Sunitinib	131/558 (5/558)
Increased bilirubin	SUTENT	CC mRCC	Sunitinib	20/375 (1/375)	IFN	2/360 (0/360)
Increased bilirubin	Motzer 2013b	CC mRCC	Pazopanib	199/554 (18/554)	Sunitinib	144/558 (13/558)
Increased blood LDH	Motzer 2013b	CC mRCC	Pazopanib	39/554 (2/554)	Sunitinib	58/558 (3/558)
Increased blood thyrotropin	Motzer 2013b	CC mRCC	Pazopanib	31/554 (0/554)	Sunitinib	66/558 (2/558)
Hypoalbuminemia	Motzer 2013b	CC mRCC	Pazopanib	179/554 (4/554)	Sunitinib	225/558 (9/558)
Hypoglycaemia	Motzer 2013b	CC mRCC	Pazopanib	83/554 (2/554)	Sunitinib	57/558 (3/558)

Table 75 – First-line treatment – Tyrosine Kinase inhibitors: Musculoskeletal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Arthralgia	ROSORC	All tumour types	Sorafenib + IL-2	5/66 (0/66)	Sorafenib	3/62 (1/62)
Arthralgia	SUTENT	CC mRCC	Sunitinib	11/375 (0/375)	IFN	14/360 (0/360)

Table 76 – First-line treatment – Tyrosine Kinase inhibitors: Dermatological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Alopecia	Escudier 2009	CC mRCC	Sorafenib	40/97 (0/97)	IFN	5/90 (0/90)
Alopecia	ROSOR	All tumour types	Sorafenib + IL-2	4/66 (0/66)	Sorafenib	4/62 (0/62)
Alopecia	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 50% (0%) 45% (0%)	Sorafenib + placebo arm C	 50% (2%)
Alopecia	SUTENT	CC mRCC	Sunitinib	12/375 (0/375)	IFN	9/360 (0/360)
Alopecia	Motzer 2013b	CC mRCC	Pazopanib	75/554 (0/554)	Sunitinib	45/558 (0/558)
Dry skin	Escudier 2009	CC mRCC	Sorafenib	9/97 (0/97)	IFN	9/90 (0/90)
Dry skin	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 24% (0%) 22% (0%)	Sorafenib + placebo arm C	 18% (2%)
Dry skin	SUTENT	CC mRCC	Sunitinib	21/375 (0/375)	IFN	6/360 (0/360)
Hand-foot skin syndrome	Escudier 2009	CC mRCC	Sorafenib	58/97 (11/97)	IFN	4/90 (0/90)
Hand-foot skin syndrome	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (7/40)	Sorafenib	NR (10/40)
Hand-foot skin syndrome	ROSOR	All tumour types	Sorafenib + IL-2	27/66 (8/66)	Sorafenib	32/62 (6/62)
Hand-foot skin syndrome	SUTEN	CC mRCC	Sunitinib	29/375 (9/375)	IFN	3/360 (1/360)
Hand-foot skin syndrome	Motzer 2013b	CC mRCC	Pazopanib	163/554 (32/554)	Sunitinib	275/558 (64/558)
Palmar-plantar erythrodysesthesia	Hutson 2013	CC mRCc	Axitinib	50/189 (14/189)	Sorafenib	37/96 (15/96)
Palmar-plantar erythrodysesthesia	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 52% (12%) 47% (16%)	Sorafenib + placebo arm C	 54% (28%)
Mucositis	Escudier 2009	CC mRCC	Sorafenib	16/97 (0/97)	IFN	3/90 (0/90)
Mucosal inflammation	Motzer 2013b	CC mRCC	Pazopanib	61/554 (3/554)	Sunitinib	141/558 (16/558)

Pruritus	Escudier 2009	CC mRCC	Sorafenib	13/97 (0/97)	IFN	10/90 (0/90)
Pruritus	ROSOR	All tumour types	Sorafenib + IL-2	3/66 (0/66)	Sorafenib	4/62 (0/62)
Pruritus	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 26% (0%) 25% (0%)	Sorafenib + placebo arm C	 24% (2%)
Rash/desquamation	Escudier 2009	CC mRCC	Sorafenib	40/97 (6/97)	IFN	8/90 (0/90)
Rash/desquamation	Jonasch 2010	CC mRCC	Sorafenib + IFN	NR (2/40)	Sorafenib	NR (2/40)
Rash	Hutson 2013	CC mRCc	Axitinib	18/189 (2/189)	Sorafenib	19/96 (1/96)
Rash	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 32% (0%) 31% (6%)	Sorafenib + placebo arm C	 30% (8%)
Rash	SUTENT	CC mRCC	Sunitinib	24/375 (1/375)	IFN	8/360 (0/360)
Rash	Motzer 2013b	CC mRCC	Pazopanib	97/554 (4/554)	Sunitinib	125/558 (4/558)
Stomatitis	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 20% (2%) 12% (0%)	Sorafenib + placebo arm C	 16% (2%)
Stomatitis	SUTENT	CC mRCC	Sunitinib	30/375 (1/375)	IFN	4/360 (0/360)
Stomatitis	Motzer 2013b	CC mRCC	Pazopanib	77/554 (4/554)	Sunitinib	150/558 (8/558)
Stomatitis	Mulders 2012	All tumour types	Cediranib	16/53 (0/53)	Placebo	2/18 (0/18)
Mucosal inflammation	Rini 2012	CC mRCC	Sorafenib + AMG 386 A: 10 mg/kg qw B: 3 mg/kg qw	 26% (2%) 20% (0%)	Sorafenib + placebo arm C	 8% (2%)
Mucosal inflammation	SUTENT	CC mRCC	Sunitinib	26/375 (2/375)	IFN	3/360 (1/360)
Skin decolouration	SUTENT	CC mRCC	Sunitinib	27/375 (0/375)	IFN	1/360 (0/360)
Hair colour change	SUTENT	CC mRCC	Sunitinib	20/375 (0/375)	IFN	1/360 (0/360)
Hair colour change	Motzer 2013b	CC mRCC	Pazopanib	168/554 (0/554)	Sunitinib	58/558 (3/558)
Erythema	SUTENT	CC mRCC	Sunitinib	10/375 (1/375)	IFN	1/360 (0/360)
Yellow skin	Motzer 2013b	CC mRCC	Pazopanib	4/554 (0/554)	Sunitinib	83/558 (0/558)

Table 77 – First-line treatment – Tyrosine Kinase inhibitors: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Glossodynia	SUTENT	CC mRCC	Sunitinib	10/375 (0/375)	IFN	1/360 (0/360)
Dysgeusia	SUTENT	CC mRCC	Sunitinib	46/375 (0/375)	IFN	15/360 (0/360)
Dysgeusia	Motzer 2013b	CC mRCC	Pazopanib	143/554 (1/554)	Sunitinib	198/558 (0/558)

7.3.1.2. Monoclonal antibodies

Table 78 – First-line treatment – Monoclonal antibodies: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fatigue	AVOREN	CC mRCC	Bevacizumab + IFN	110/337 (40/337)	Placebo + IFN	83/304 (25/304)
Fatigue	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	336/362 (135/362)	IFN	312/347 (105/347)
Pyrexia	AVOREN	CC mRCC	Bevacizumab + IFN	152/337 (8/337)	Placebo + IFN	130/304 (2/304)
Weight loss	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	57/362 (15/362)	IFN	42/347 (5/347)

Table 79 – First-line treatment – Monoclonal antibodies: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Asthenia	AVOREN	CC mRCC	Bevacizumab + IFN	109/337 (34/337)	Placebo + IFN	84/304 (20/304)
CNS cebrovascular ischemia	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	5/362 (5/362)	IFN	1/347 (1/347)

Table 80 – First-line treatment – Monoclonal antibodies: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	AVOREN	CC mRCC	Bevacizumab + IFN	88/337 (11/337)	Placebo + IFN	28/304 (2/304)
Hypertension	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	103/362 (39/362)	IFN	13/347 (0/347)
Hypertension	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (14/51)	Bevacizumab + placebo	NR (16/53)
Venous thromboembolic event	AVOREN	CC mRCC	Bevacizumab + IFN	10/337 (6/337)	Placebo + IFN	3/304 (2/304)
Arterial thromboembolic event	AVOREN	CC mRCC	Bevacizumab + IFN	5/337 (4/337)	Placebo + IFN	2/304 (1/304)
Arterial thromboembolic event	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (0/51)	Bevacizumab + placebo	NR (1/53)
Congestive heart failure	AVOREN	CC mRCC	Bevacizumab + IFN	1/337 (1/337)	Placebo + IFN	1/304 (0/304)
Heart failure	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (1/51)	Bevacizumab + placebo	NR (1/53)
Cardiac ischemia/infraction	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	5/362 (5/362)	IFN	0/347 (0/347)
Left ventricular dysfunction	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	2/362 (2/362)	IFN	0/347 (0/347)
Thrombosis / embolism	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	14/362 (6/362)	IFN	6/347 (3/347)

Table 81 – First-line treatment – Monoclonal antibodies: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dyspnoea	AVOREN	CC mRCC	Bevacizumab + IFN	44/337 (2/337)	Placebo + IFN	38/304 (7/304)
Dyspnoea	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	53/362 (23/362)	IFN	32/347 (12/347)

Table 82 – First-line treatment – Monoclonal antibodies: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Proteinuria	AVOREN	CC mRCC	Bevacizumab + IFN	59/337 (22/337)	Placebo + IFN	8/304 (0/304)
Proteinuria	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	257/362 (56/362)	IFN	24/347 (10/347)
Proteinuria	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (3/51)	Bevacizumab + placebo	NR (4/53)
Acute renal failure	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (2/51)	Bevacizumab + placebo	NR (0/53)

Table 83 – First-line treatment – Monoclonal antibodies: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Anorexia	AVOREN	CC mRCC	Bevacizumab + IFN	121/337 (10/337)	Placebo + IFN	92/304 (8/304)
Anorexia	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	258/362 (63/362)	IFN	213/347 (28/347)
Diarrhoea	AVOREN	CC mRCC	Bevacizumab + IFN	69/337 (7/337)	Placebo + IFN	47/304 (3/304)
Diarrhoea	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (16/51)	Bevacizumab + placebo	NR (0/53)
Nausea	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	210/362 (63/362)	IFN	204/347 (17/347)
Gastrointestinal perforation	AVOREN	CC mRCC	Bevacizumab + IFN	5/337 (4/337)	Placebo + IFN	0/304 (0/304)
Gastrointestinal perforation	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	0/362 (0/362)	IFN	0/347 (0/347)

Table 84 – First-line treatment – Monoclonal antibodies: Pain

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Headache	AVOREN	CC mRCC	Bevacizumab + IFN	79/337 (7/337)	Placebo + IFN	49/304 (4/304)

Table 85 – First-line treatment – Monoclonal antibodies: Endocrine / metabolic events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Thyroid dysfunction	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	2/362 (2/362)	IFN	0/347 (0/347)

Table 86 – First-line treatment – Monoclonal antibodies: Hematologic adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Neutropenia	AVOREN	CC mRCC	Bevacizumab + IFN	24/337(15/337)	Placebo + IFN	20/304 (7/304)
Neutropenia	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	158/362 (33/362)	IFN	124/347 (31/347)
Anaemia	AVOREN	CC mRCC	Bevacizumab + IFN	33/337 (9/337)	Placebo + IFN	41/304 (17/304)
Anaemia	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	59/362 (14/362)	IFN	76/347 (13/347)
Thrombocytopenia	AVOREN	CC mRCC	Bevacizumab + IFN	21/337 (7/337)	Placebo + IFN	12/304 (3/304)
Thrombocytopenia	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	38/362 (8/362)	IFN	30/347 (2/347)

Table 87 – First-line treatment – Monoclonal antibodies: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Rash	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (8/51)	Bevacizumab + placebo	NR (0/53)

Table 88 – First-line treatment – Monoclonal antibodies: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Influenza-like illness	AVOREN	CC mRCC	Bevacizumab + IFN	82/337 (10/337)	Placebo + IFN	77/304 (6/304)
Depression	AVOREN	CC mRCC	Bevacizumab + IFN	41/337 (10/337)	Placebo + IFN	31/304 (4/304)
Wound healings complications	AVOREN	CC mRCC	Bevacizumab + IFN	5/337 (2/337)	Placebo + IFN	3/304 (0/304)
Wound healings event /fistula	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (2/51)	Bevacizumab + placebo	NR (0/53)
Bleeding	AVOREN	CC mRCC	Bevacizumab + IFN	112/337 (11/337)	Placebo + IFN	28/304 (1/304)
Haemorrhage, genitourinary	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	3/362 (0/362)	IFN	1/347 (0/347)
Haemorrhage, GI	Rini 2004 Rini 2008, 2010	CC mRCC	Bevacizumab + IFN	18/362 (4/362)	IFN	3/347 (1/347)
Haemorrhage	Bukowski 2007	CC mRCC	Bevacizumab + Erlotinib	NR (2/51)	Bevacizumab + placebo	NR (3/53)

7.3.1.3. mTOR

Table 89 – First-line treatment – mTOR: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fever	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	24/208 (1/208) 60/208 (3/208)	IFN alone	50/200 (4/200)
Pyrexia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	82/393 (4/393)	IFN + Bevacizumab	153/391 (11/391)
Weight loss	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	19/208 (1/208) 32/208 (6/208)	IFN alone	25/200 (2/200)

Weight loss	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	90/393 (7/393)	IFN + Bevacizumab	90/391 (14/391)
Chills	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	19/208 (1/208) 32/208 (6/208)	IFN alone	25/200 (2/200)
Fatigue	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	92/393 (18/393)	IFN + Bevacizumab	123/391 (42/391)
Fatigue, asthenia or malaise	TORAVA	All tumour types	Temsirolimus + Bevacizumab	67/88	Sunitinib or IFN + bevacizumab	34/42 36/40
Decreased appetite	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	104/393 (9/393)	IFN + Bevacizumab	126/391 (13/391)

Table 90 – First-line treatment – mTOR: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Asthenia	Global-ARCC	All tumour type	Temsirolimus Or IFN + Temsirolimus	51/208 (11/208) 62/208 (28/208)	IFN alone	64/200 (26/200)
Asthenia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	96/393 (23/393)	IFN + Bevacizumab	111/391 (39/391)

Table 91 – First-line treatment – mTOR: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	127/393 (44/393)	IFN + Bevacizumab	100/391 (41/391)
Hypertension	TORAVA	All tumour types	Temsirolimus + Bevacizumab	29/88	Sunitinib or IFN + bevacizumab	13/42 17/40
Venous thromboembolism	TORAVA	All tumour types	Temsirolimus + Bevacizumab	1/88	Sunitinib or IFN + bevacizumab	3/42 1/40

Table 92 – First-line treatment – mTOR: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dyspnoea	Global-ARCC	All tumour type	Temsirolimus Or IFN + Temsirolimus	28/208 (9/208) 26/208 (10/208)	IFN alone	24/200 (6/200)
Cough	Global-ARCC	All tumour type	Temsirolimus Or IFN + Temsirolimus	26/208 (1/208) 23/208 (2/208)	IFN alone	14/200 (0/200)
Cough	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	77/393 (2/393)	IFN + Bevacizumab	70/391 (1/391)

Table 93 – First-line treatment – mTOR: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Peripheral oedema	Global-ARCC	All tumour type	Temsirolimus Or IFN + Temsirolimus	27/208 (2/208) 16/208 (0/208)	IFN alone	8/200 (0/200)
Peripheral oedema	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	66/393 (4/393)	IFN + Bevacizumab	30/391 (3/391)
Increased creatinine level	Global-ARCC	All tumour type	Temsirolimus Or IFN + Temsirolimus	14/208 (3/208) 20/208 (3/208)	IFN alone	10/200 (1/200)
Proteinuria	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	141/393 (64/393)	IFN + Bevacizumab	106/391 (52/391)
Proteinuria	TORAVA	All tumour types	Temsirolimus + Bevacizumab	36/88	Sunitinib or IFN + bevacizumab	2/42 10/40

Table 94 – First-line treatment – mTOR: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Nausea	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	37/208 (2/208) 40/208 (3/208)	IFN alone	41/200 (4/200)
Nausea	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	69/393 (3/393)	IFN + Bevacizumab	76/391 (3/391)
Nausea	TORAVA	All tumour types	Temsirolimus + Bevacizumab	27/88	Sunitinib or IFN + bevacizumab	14/42 16/40
Vomiting	TORAVA	All tumour types	Temsirolimus + Bevacizumab	19/88	Sunitinib or IFN + bevacizumab	12/42 9/40
Vomiting	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	19/208 (2/208) 30/208 (2/208)	IFN alone	28/200 (2/200)
Anorexia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	32/208 (3/208) 38/208 (8/208)	IFN alone	44/200 (4/200)
Hyperlipidaemia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	27/208 (3/208) 38/208 (8/208)	IFN alone	14/200 (1/200)
Diarrhoea	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	27/208 (1/208) 27/208 (5/208)	IFN alone	20/200 (2/200)
Diarrhoea	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	127/393 (17/393)	IFN + Bevacizumab	87/391 (8/391)
Diarrhoea	TORAVA	All tumour types	Temsirolimus + Bevacizumab	29/88	Sunitinib or IFN + bevacizumab	25/42 17/40
Constipation	Global-ARCC	All tumour types	Temsirolimus Or	20/208 (0/208)	IFN alone	18/200 (1/200)

			IFN + Temsirolimus	19/208 (0/208)		
Increased aspartate aminotransferase	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	8/208 (1/208) 21/208 (4/208)	IFN alone	14/200 (4/200)
Gastrointestinal perforation	TORAVA	All tumour types	Temsirolimus + Bevacizumab	2/88	Sunitinib or IFN + bevacizumab	0/42 0/40
Oral, anal, or digestive fistula or abscess	TORAVA	All tumour types	Temsirolimus + Bevacizumab	18/88	Sunitinib or IFN + bevacizumab	2/42 5/40

Table 95 – First-line treatment – mTOR: Pain

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Pain	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	8/208 (1/208) 21/208 (4/208)	IFN alone	16/200 (2/200)
Abdominal pain	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	21/208 (4/208) 21/208 (5/208)	IFN alone	17/200 (2/200)
Back pain	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	20/208 (3/208) 15/208 (2/208)	IFN alone	14/200 (4/200)
Headache	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	15/208 (1/208) 22/208 (0/208)	IFN alone	15/200 (0/200)
Myalgia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	18/393 (0/393)	IFN + Bevacizumab	60/391 (11/391)

Table 96 – First-line treatment – mTOR: Hematologic adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Anaemia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	45/208 (20/208) 61/208 (38/208)	IFN alone	42/200 (22/200)
Anaemia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	82/393 (36/393)	IFN + Bevacizumab	65/391 (32/391)
Anaemia	TORAVA	All tumour types	Temsirolimus + Bevacizumab	10/88	Sunitinib or IFN + bevacizumab	8/42 5/40
Thrombocytopenia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	14/208 (1/208) 38/208 (9/208)	IFN alone	8/200 (0/200)
Thrombopenia	TORAVA	All tumour types	Temsirolimus + Bevacizumab	10/88	Sunitinib or IFN + bevacizumab	8/42 5/40
Neutropenia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	14/208 (20/208) 27/208 (15/208)	IFN alone	12/200 (7/200)
Neutropenia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	18/393 (7/393)	IFN + Bevacizumab	65/391 (32/391)
Neutropenia	TORAVA	All tumour types	Temsirolimus + Bevacizumab	4/88	Sunitinib or IFN + bevacizumab	11/42 11/40
Leukopenia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	6/208 (1/208) 31/208 (9/208)	IFN alone	17/200 (5/200)
Hyperglycaemia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	26/208 (11/208) 17/208 (6/208)	IFN alone	11/200 (2/200)

Hypertriglycaemia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab		114/393 (27/393)	IFN + Bevacizumab	81/391 (16/391)
Hyperglycaemia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab		86/393 (25/393)	IFN + Bevacizumab	18/391 (4/391)
Hypercholesterolemia	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus		24/208 (1/208) 26/208 (2/208)	IFN alone	4/200 (0/200)
Hypercholesterolemia	INTORACT	CC mRCC	Temsirolimus + Bevacizumab		125/393 (23/393)	IFN + Bevacizumab	38/391 (5/391)

Table 97 – First-line treatment – mTOR: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Stomatitis	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	20/208 (1/208) 21/208 (5/208)	IFN alone	4/200 (0/200)
Stomatitis	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	102/393 (27/393)	IFN + Bevacizumab	38/391 (6/391)
Mucosal inflammation	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	106/393 (31/393)	IFN + Bevacizumab	39/391 (1/391)
Rash	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	47/208 (4/208) 21/208 (1/208)	IFN alone	6/200 (0/200)
Rash	INTORACT	CC mRCC	Temsirolimus + Bevacizumab	125/393 (13/393)	IFN + Bevacizumab	32/391 (3/391)
Skin disorders	TORAVA	All tumour types	Temsirolimus + Bevacizumab	60/88	Sunitinib or IFN + bevacizumab	27/42 18/40

Table 98 – First-line treatment – mTOR: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Infection	Global-ARCC	All tumour types	Temsirolimus Or IFN + Temsirolimus	27/208 (5/208) 34/208 (11/208)	IFN alone	14/200 (4/200)

7.3.2. Second-line treatment

7.3.2.1. Tyrosine kinase inhibitors

Table 99 – Second-line treatment – Tyrosine kinase inhibitors: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fatigue	Motzer 2013	CC mRCC	Tivozanib	50/259 (14/259)	Sorafenib	41/257 (9/257)
Fatigue	TARGET	CC mRCC	Sorafenib	133/452 (14/452)	Placebo	74/451 (5/451)
Fatigue	AXIS	CC mRCC	Axitinib	133/359 (37/359)	Sorafenib	98/355 (14/355)
Fatigue	Ratain 2006	All tumour types	Sorafenib	147/202 (73/202)	Placebo	NR
Fatigue	VEG105192/107769	CC mRCC	Pazopanib	57/290 (7/290)	Placebo	14/145 (4/145)
Weight loss	Motzer 2013	CC mRCC	Tivozanib	47/259 (7/259)	Sorafenib	53/257 (9/257)
Weight loss	TARGET	CC mRCC	Sorafenib	38/452 (5/452)	Placebo	6/451 (0/451)
Weight loss	AXIS	CC mRCC	Axitinib	70/359 (12/359)	Sorafenib	63/355 (9/355)
Weight loss	Ratain 2006	All tumour types	Sorafenib	66/202 (33/202)	Placebo	NR
Weight loss	VEG105192/107769	CC mRCC	Pazopanib	30/290 (2/290)	Placebo	5/145 (1/145)
Dysphonia	Motzer 2013	CC mRCC	Tivozanib	55/259 (0/259)	Sorafenib	12/257 (0/257)
Dysphonia	AXIS	CC mRCC	Axitinib	102/359 (0/359)	Sorafenib	42/355 (0/355)
Decreased appetite	Motzer 2013	CC mRCC	Tivozanib	27/259 (1/259)	Sorafenib	24/257 (2/257)
Decreased appetite	AXIS	CC mRCC	Axitinib	113/359 (15/359)	Sorafenib	94/355 (7/355)
Fever	Ratain 2006	All tumour types	Sorafenib	24/202 (0/202)	Placebo	NR

Constitutional symptoms, other	Ratain 2006	All tumour types	Sorafenib	45/202 (22/202)	Placebo	NR
Dysphonia	Nosov 2012	Inoperable mRCC	Tivozanib	59/272 (0/272)	Placebo	NR

Table 100 – Second-line treatment – Tyrosine kinase inhibitors: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Asthenia	Motzer 2013	CC mRCC	Tivozanib	40/259 (11/259)	Sorafenib	43/257 (7/257)
Asthenia	AXIS	CC mRCC	Axitinib	66/359 (15/359)	Sorafenib	47/355 (8/355)
Asthenia	VEG105192/107769	CC mRCC	Pazopanib	42/290 (8/290)	Placebo	13/145 (0/145)
Asthenia	Nosov 2012	Inoperable mRCC	Tivozanib	28/272 (7/272)	Placebo	NR
Neurology	Ratain 2006	All tumour types	Sorafenib	97/202 (12/202)	Placebo	NR
Neuropathy, sensory	Ratain 2006	All tumour types	Sorafenib	40/202 (20/202)	Placebo	NR

Table 101 – Second-line treatment – Tyrosine kinase inhibitors: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	Motzer 2013	CC mRCC	Tivozanib	115/259 (70/259)	Sorafenib	88/257 (46/257)
Hypertension	TARGET	CC mRCC	Sorafenib	78/452 (15/452)	Placebo	5/451 (0/451)
Hypertension	AXIS	CC mRCC	Axitinib	145/359 (56/359)	Sorafenib	103/355 (39/355)
Hypertension	Ratain 2006	All tumour types	Sorafenib	62/202 (62/202)	Placebo	NR
Hypertension	VEG105192/107769	CC mRCC	Pazopanib	116/290 (13/290)	Placebo	15/145 (1/145)
Hypertension	Nosov 2012	Inoperable mRCC	Tivozanib	122/272 (32/272)	Placebo	NR
Blood pressure increased	AXIS	CC mRCC	Axitinib	3/359 (1/359)	Sorafenib	3/355 (2/355)
Hypertension crisis	AXIS	CC mRCC	Axitinib	2/359 (2/359)	Sorafenib	0/355 (0/355)
Accelerated hypertension	AXIS	CC mRCC	Axitinib	1/359 (1/359)	Sorafenib	0/355 (0/355)

Table 102 – Second-line treatment – Tyrosine kinase inhibitors: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dyspnoea	Motzer 2013	CC mRCC	Tivozanib	29/259 (4/259)	Sorafenib	22/257 (5/257)
Dyspnoea	Ratain 2006	All tumour types	Sorafenib	77/202 (18/202)	Placebo	NR
Cough	Ratain 2006	All tumour types	Sorafenib	57/202 (0/202)	Placebo	NR
Pulmonary, other	Ratain 2006	All tumour types	Sorafenib	36/202 (7/202)	Placebo	NR

Table 103 – Second-line treatment – Tyrosine kinase inhibitors: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypophosphatemia	Motzer 2013	CC mRCC	Tivozanib	76/259 (11/259)	Sorafenib	182/257 (67/257)
Proteinuria	Motzer 2013	CC mRCC	Tivozanib	186/259 (29/259)	Sorafenib	84/257 (17/257)
Proteinuria	AXIS	CC mRCC	Axitinib	45/359 (11/359)	Sorafenib	27/355 (4/355)
Proteinuria	VEG105192/107769	CC mRCC	Pazopanib	30/290 (7/290)	Placebo	0/145 (0/145)
Oedema	Ratain 2006	All tumour types	Sorafenib	30/202 (0/202)	Placebo	NR
Creatinine	Ratain 2006	All tumour types	Sorafenib	29/202 (0/202)	Placebo	NR

Table 104 – Second-line treatment – Tyrosine kinase inhibitors: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Diarrhoea	Motzer 2013	CC mRCC	Tivozanib	59/259 (29/259)	Sorafenib	84/257 (17/257)
Diarrhoea	TARGET	CC mRCC	Sorafenib	216/452 (14/452)	Placebo	49/451 (4/451)
Diarrhoea	AXIS	CC mRCC	Axitinib	193/359 (40/359)	Sorafenib	185/355 (27/355)
Diarrhoea	Ratain 2006	All tumour types	Sorafenib	117/202 (8/202)	Placebo	NR
Diarrhoea	VEG105192/107769	CC mRCC	Pazopanib	152/290 (13/290)	Placebo	13/145 (1/145)
Diarrhoea	Nosov 2012	Inoperable mRCC	Tivozanib	33/272 (5/272)	Placebo	NR
Increased lipase	Motzer 2013	CC mRCC	Tivozanib	119/259 (29/259)	Sorafenib	164/257 (63/257)

Increased amylase	Motzer 2013	CC mRCC	Tivozanib	104/259 (12/259)	Sorafenib	135/257 (17/257)
Increased ALT	Motzer 2013	CC mRCC	Tivozanib	73/259 (5/259)	Sorafenib	130/257 (10/257)
ALT	Ratain 2006	All tumour types	Sorafenib	22/202 (0/202)	Placebo	NR
Increased AST	Motzer 2013	CC mRCC	Tivozanib	97/259 (12/259)	Sorafenib	135/257 (17/257)
AST	Ratain 2006	All tumour types	Sorafenib	23/202 (0/202)	Placebo	NR
Nausea	TARGET	CC mRCC	Sorafenib	85/452 (1/452)	Placebo	56/451 (1/451)
Nausea	AXIS	CC mRCC	Axitinib	109/359 (6/359)	Sorafenib	67/355 (3/355)
Nausea	Ratain 2006	All tumour types	Sorafenib	61/202 (0/202)	Placebo	NR
Nausea	VEG105192/107769	CC mRCC	Pazopanib	74/290 (2/290)	Placebo	13/145 (0/145)
Vomiting	AXIS	CC mRCC	Axitinib	63/359 (5/359)	Sorafenib	47/355 (0/355)
Vomiting	Ratain 2006	All tumour types	Sorafenib	48/202 (0/202)	Placebo	NR
Vomiting	VEG105192/107769	CC mRCC	Pazopanib	62/290 (8/290)	Placebo	13/145 (3/145)
Anorexia	TARGET	CC mRCC	Sorafenib	63/452 (2/452)	Placebo	31/451 (4/451)
Anorexia	Ratain 2006	All tumour types	Sorafenib	95/202 (6/202)	Placebo	NR
Anorexia	VEG105192/107769	CC mRCC	Pazopanib	70/290 (6/290)	Placebo	17/145 (1/145)
Constipation	TARGET	CC mRCC	Sorafenib	33/452 (0/452)	Placebo	16/451 (0/451)
Constipation	AXIS	CC mRCC	Axitinib	45/359 (1/359)	Sorafenib	47/355 (1/355)
Constipation	Ratain 2006	All tumour types	Sorafenib	65/202 (0/202)	Placebo	NR
Gastrointestinal, other	Ratain 2006	All tumour types	Sorafenib	58/202 (7/202)	Placebo	NR

Table 105 – Second-line treatment – Tyrosine kinase inhibitors: Pain

Adverse events	Study ID	Tumour type	Intervention	All grade (grade 3-4)	Control	All grade (grade 3-4)
Headache	TARGET	CC mRCC	Sorafenib	29/452 (0/452)	Placebo	16/451 (0/451)
Headache	AXIS	CC mRCC	Axitinib	39/359 (3/359)	Sorafenib	25/355 (0/355)
Headache	Ratain 2006	All tumour types	Sorafenib	38/202 (0/202)	Placebo	NR
Headache	VEG105192/107769	CC mRCC	Pazopanib	31/290 (0/290)	Placebo	7/145 (0/145)
Joint pain	TARGET	CC mRCC	Sorafenib	25/452 (1/452)	Placebo	10/451 (0/451)

Abdominal pain	TARGET	CC mRCC	Sorafenib	23/452 (1/452)	Placebo	14/451 (1/451)
Abdominal pain or cramping	Ratain 2006	All tumour types	Sorafenib	39/202 (0/202)	Placebo	NR
Abdominal pain	VEG105192/107769	CC mRCC	Pazopanib	32/290 (7/290)	Placebo	2/145 (0/145)
Muscle pain	TARGET	CC mRCC	Sorafenib	23/452 (0/452)	Placebo	7/451 (0/451)
Pain in extremity	AXIS	CC mRCC	Axitinib	32/359 (1/359)	Sorafenib	36/355 (3/355)
Arthralgia	Ratain 2006	All tumour types	Sorafenib	25/202 (0/202)	Placebo	NR
Myalgia	Ratain 2006	All tumour types	Sorafenib	22/202 (0/202)	Placebo	NR
Pain, other	Ratain 2006	All tumour types	Sorafenib	117/202 (15/202)	Placebo	NR

Table 106 – Second-line treatment – Tyrosine kinase inhibitors: Endocrine / metabolic events

Adverse events	Study ID	Tumour type	Intervention	All grade (grade 3-4)	Control	All grade (grade 3-4)
Hypothyroidism	AXIS	CC mRCC	Axitinib	72/359 (1/359)	Sorafenib	29/355 (0/355)

Table 107 – Second-line treatment – Tyrosine kinase inhibitors: Hematologic adverse events

Adverse events	Study ID	Tumour type	Intervention	All grade (grade 3-4)	Control	All grade (grade 3-4)
Neutropenia	Motzer 2013	CC mRCC	Tivozanib	28/259 (6/259)	Sorafenib	27/257 (5/257)
Neutropenia	VEG105192/107769	CC mRCC	Pazopanib	100/290 (5/290)	Placebo	9/145 (0/145)
Thrombocytopenia	Motzer 2013	CC mRCC	Tivozanib	47/259 (1/259)	Sorafenib	31/257 (0/257)
Thrombocytopenia	VEG105192/107769	CC mRCC	Pazopanib	95/290 (5/290)	Placebo	9/145 (0/145)
Leukopenia	VEG105192/107769	CC mRCC	Pazopanib	106/290 (1/290)	Placebo	10/145 (0/145)
Lymphopaenia	VEG105192/107769	CC mRCC	Pazopanib	96/290 (14/290)	Placebo	35/145 (2/145)
Anaemia	VEG105192/107769	CC mRCC	Pazopanib	73/290 (9/290)	Placebo	45/145 (3/145)
Infection / febrile neutropenia	Ratain 2006	All tumour types	Sorafenib	75/202 (10/202)	Placebo	NR
Infection without neutropenia	Ratain 2006	All tumour types	Sorafenib	73/202 (10/202)	Placebo	NR

Low haemoglobin	Motzer 2013	CC mRCC	Tivozanib	105/259 (9/259)	Sorafenib	125/257 (8/257)
Haemoglobin	Ratain 2006	All tumour types	Sorafenib	54/202 (14/202)	Placebo	NR
Hyperglycaemia	Ratain 2006	All tumour types	Sorafenib	34/202 (6/202)	Placebo	NR
Hyperglycaemia	VEG105192/107769	CC mRCC	Pazopanib	120/290 (2/290)	Placebo	48/145 (2/145)
Hypoglycaemia	VEG105192/107769	CC mRCC	Pazopanib	50/290 (1/290)	Placebo	4/145 (0/145)
Hyperuricemia	Ratain 2006	All tumour types	Sorafenib	26/202 (0/202)	Placebo	NR
Hypophosphatemia	Ratain 2006	All tumour types	Sorafenib	31/202 (14/202)	Placebo	NR
Hypophosphatemia	VEG105192/107769	CC mRCC	Pazopanib	100/290 (15/290)	Placebo	18/145 (2/145)
Blood/marrow	Ratain 2006	All tumour types	Sorafenib	63/202 (16/202)	Placebo	NR
ALT increase	VEG105192/107769	CC mRCC	Pazopanib	153/290 (36/290)	Placebo	33/145 (2/145)
AST increase	VEG105192/107769	CC mRCC	Pazopanib	153/290 (23/290)	Placebo	28/145 (1/145)
Hyperbilirubinaemia	VEG105192/107769	CC mRCC	Pazopanib	103/290 (9/290)	Placebo	16/145 (3/145)
Hypocalcaemia	VEG105192/107769	CC mRCC	Pazopanib	96/290 (8/290)	Placebo	35/145 (3/145)
Hyponatremia	VEG105192/107769	CC mRCC	Pazopanib	92/290 (16/290)	Placebo	35/145 (6/145)
Hypokalaemia	VEG105192/107769	CC mRCC	Pazopanib	28/290 (5/290)	Placebo	3/145 (0/145)

Table 108 – Second-line treatment – Tyrosine kinase inhibitors: Musculoskeletal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grade (grade 3-4)	Control	All grade (grade 3-4)
Skeletal muscle loss	TARGET	CC mRCC	Sorafenib	Result reported in graph for comparison with placebo. In comparison with baseline: At 6 months: 4.9%, p<0.01 at 12 months: -8.0%, p<0.01	Placebo	Result reported in graph
Arthralgia	AXIS	CC mRCC	Axitinib	36/359 (3/359)	Sorafenib	18/355 (1/355)
Musculoskeletal	Ratain 2006	All tumour types	Sorafenib	29/202 (0/202)	Placebo	NR

Table 109 – Second-line treatment – Tyrosine kinase inhibitors: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Alopecia	Motzer 2013	CC mRCC	Tivozanib	6/259 (0/259)	Sorafenib	55/257 (0/257)
Alopecia	TARGET	CC mRCC	Sorafenib	140/452 (0/452)	Placebo	19/451 (0/451)
Alopecia	AXIS	CC mRCC	Axitinib	16/359 (0/359)	Sorafenib	0/355 (0/355)
Alopecia	Ratain 2006	All tumour types	Sorafenib	107/202 (0/202)	Placebo	NR
Palmar-plantar erythrodysesthesia	Motzer 2013	CC mRCC	Tivozanib	36/259 (5/259)	Sorafenib	139/257 (43/257)
Hand-foot skin reaction	TARGET	CC mRCC	Sorafenib	151/452 (29/452)	Placebo	37/451 (2/451)
Hand-food syndrome	AXIS	CC mRCC	Axitinib	100/359 (20/359)	Sorafenib	182/355 (61355)
Hand-foot skin reaction	Ratain 2006	All tumour types	Sorafenib	125/202 (67/202)	Placebo	NR
Stomatitis	Motzer 2013	CC mRCC	Tivozanib	29/259 (1/259)	Sorafenib	23/257 (2/257)
Stomatitis	AXIS	CC mRCC	Axitinib	55/359 (5/359)	Sorafenib	44/355 (1/355)
Stomatitis/ pharyngitis	Ratain 2006	All tumour types	Sorafenib	70/202 (0/202)	Placebo	NR
Dry skin	TARGET	CC mRCC	Sorafenib	58/452 (0/452)	Placebo	12/451 (0/451)
Dry skin	AXIS	CC mRCC	Axitinib	36/359 (0/359)	Sorafenib	36/355 (0/355)
Dry skin	Ratain 2006	All tumour types	Sorafenib	47/202 (0/202)	Placebo	NR
Mucositis (oral)	TARGET	CC mRCC	Sorafenib	23/452 (0/452)	Placebo	8/451 (0/451)
Mucosal inflammation	AXIS	CC mRCC	Axitinib	58/359 (5/359)	Sorafenib	44/355 (3/355)
Rash / desquamation	TARGET	CC mRCC	Sorafenib	187/452 (6/452)	Placebo	59/451 (1/451)
Rash / desquamation	Ratain 2006	All tumour types	Sorafenib	134/202 (5/202)	Placebo	NR
Rash	AXIS	CC mRCC	Axitinib	47/359 (1/359)	Sorafenib	110/355 (13/355)
Pruritus	TARGET	CC mRCC	Sorafenib	77/452 (1/452)	Placebo	20/451 (0/451)
Pruritus	AXIS	CC mRCC	Axitinib	22/359 (0/359)	Sorafenib	46/355 (0/355)
Dermatologic/other	TARGET	CC mRCC	Sorafenib	53/452 (0/452)	Placebo	9/451 (0/451)
Dermatologic/other	Ratain 2006	All tumour types	Sorafenib	87/202 (0/202)	Placebo	NR
Erythema	AXIS	CC mRCC	Axitinib	10/359 (0/359)	Sorafenib	36/355 (1/355)
Flushing	Ratain 2006	All tumour types	Sorafenib	32/202 (0/202)	Placebo	NR

Table 110 – Second-line treatment – Tyrosine kinase inhibitors: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dysgeusia	AXIS	CC mRCC	Axitinib	41/359 (0/359)	Sorafenib	30/355 (0/355)
Allergy/immunology	Ratain 2006	All tumour types	Sorafenib	21/202 (0/202)	Placebo	NR
Haemorrhage	Ratain 2006	All tumour types	Sorafenib	45/202 (8/202)	Placebo	NR
Hepatic	Ratain 2006	All tumour types	Sorafenib	59/202 (10/202)	Placebo	NR

7.3.2.2. Monoclonal antibodies

Table 111 – Second-line treatment – Monoclonal antibodies: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fever without infection	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg Bevacizumab 3 mg/kg	4/39 (0/39) 1/37 (0/37)	Placebo	0/40 (0/40)
Pyrexia	RECORD-1	CC mRCC	Everolimus	20/274 (0/274)	Placebo	9/137 (0/137)
Malaise	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg Bevacizumab 3 mg/kg	13/39 (0/39) 6/37 (0/37)	Placebo	6/40 (0/40)
Fatigue	RECORD-1	CC mRCC	Everolimus	31/274 (5/274)	Placebo	27/137 (3/137)
Infections	RECORD-1	CC mRCC	Everolimus	37/274 (10/274)	Placebo	18/137 (1/137)

Table 112 – Second-line treatment – Monoclonal antibodies: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Asthenia	RECORD-1	CC mRCC	Everolimus	33/274 (3/274)	Placebo	23/137 (4/137)

Table 113 – Second-line treatment – Monoclonal antibodies: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	14/39 (8/39)	Placebo	2/40 (0/40)
			Bevacizumab 3 mg/kg	1/37 (0/37)		

Table 114 – Second-line treatment – Monoclonal antibodies: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dyspnoea	RECORD-1	CC mRCC	Everolimus	24/274 (7/274)	Placebo	15/137 (3/137)
Pneumonitis	RECORD-1	CC mRCC	Everolimus	14/274 (4/274)	Placebo	0/137 (0/137)
Cough	RECORD-1	CC mRCC	Everolimus	30/274 (0/274)	Placebo	16/137 (0/137)

Table 115 – Second-line treatment – Monoclonal antibodies: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Proteinuria	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	25/39 (3/39)	Placebo	15/40 (0/40)
			Bevacizumab 3 mg/kg	15/37 (2/37)		
Peripheral oedema	RECORD-1	CC mRCC	Everolimus	25/274 (0/274)	Placebo	8/137 (0/137)

Table 116 – Second-line treatment – Monoclonal antibodies: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Elevated alanine aminotransferase	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	4/39 (0/39)	Placebo	0/40 (0/40)
			Bevacizumab 3 mg/kg	2/37 (0/37)		
Stomatitis	RECORD-1	CC mRCC	Everolimus	44/274 (4/274)	Placebo	8/137 (0/137)
Diarrhoea	RECORD-1	CC mRCC	Everolimus	30/274 (1/274)	Placebo	7/137 (0/137)
Nausea	RECORD-1	CC mRCC	Everolimus	26/274 (1/274)	Placebo	19/137 (0/137)
Anorexia	RECORD-1	CC mRCC	Everolimus	25/274 (1/274)	Placebo	14/137 (0/137)
Vomiting	RECORD-1	CC mRCC	Everolimus	20/274 (2/274)	Placebo	12/137 (0/137)

Table 117 – Second-line treatment – Monoclonal antibodies: Pain

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Chest pain	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	2/39 (2/39)	Placebo	0/40 (0/40)
			Bevacizumab 3 mg/kg	0/37 (0/37)		
Headache	RECORD-1	CC mRCC	Everolimus	19/274 (0/274)	Placebo	9/137 (0/137)
Pain in extremity	RECORD-1	CC mRCC	Everolimus	10/274 (1/274)	Placebo	7/137 (0/137)

Table 118 – Second-line treatment – Monoclonal antibodies: Hematological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Haematuria	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	5/39 (0/39)	Placebo	0/40 (0/40)
			Bevacizumab 3 mg/kg	1/37 (0/37)		

Hyponatremia	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg Bevacizumab 3 mg/kg	3/39 (0/39) 4/37 (0/37)	Placebo	0/40 (0/40)
Haemoglobin decreased	RECORD-1	CC mRCC	Everolimus	92/274 (13/274)	Placebo	79/137 (5/137)
Lymphocytes decreased	RECORD-1	CC mRCC	Everolimus	51/274 (18/274)	Placebo	28/137 (5/137)
Platelets decreased	RECORD-1	CC mRCC	Everolimus	23/274 (1/274)	Placebo	2/137 (0/137)
Neutrophils decreased	RECORD-1	CC mRCC	Everolimus	14/274 (0/274)	Placebo	4/137 (0/137)
Cholesterol increased	RECORD-1	CC mRCC	Everolimus	77/274 (4/274)	Placebo	35/137 (0/137)
Triglycerides increased	RECORD-1	CC mRCC	Everolimus	73/274 (0/274)	Placebo	34/137 (0/137)
Glucose increased	RECORD-1	CC mRCC	Everolimus	57/274 (15/274)	Placebo	25/137 (1/137)
Creatinine increased	RECORD-1	CC mRCC	Everolimus	50/274 (1/274)	Placebo	34/137 (0/137)
Phosphate decreased	RECORD-1	CC mRCC	Everolimus	37/274 (6/274)	Placebo	8/137 (0/137)
AST increased	RECORD-1	CC mRCC	Everolimus	25/274 (0/274)	Placebo	7/137 (0/137)
ALT increased	RECORD-1	CC mRCC	Everolimus	21/274 (1/274)	Placebo	4/137 (0/137)
Bilirubin increased	RECORD-1	CC mRCC	Everolimus	3/274 (0/274)	Placebo	2/137 (0/137)

Table 119 – Second-line treatment – Monoclonal antibodies: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Rash	RECORD-1	CC mRCC	Everolimus	29/274 (1/274)	Placebo	7/137 (0/137)
Pruritus	RECORD-1	CC mRCC	Everolimus	14/274 (0/274)	Placebo	7/137 (0/137)
Mucosal inflammation	RECORD-1	CC mRCC	Everolimus	19/274 (1/274)	Placebo	1/137 (0/137)
Dry skin	RECORD-1	CC mRCC	Everolimus	13/274 (0/274)	Placebo	5/137 (0/137)

Table 120 – Second-line treatment – Monoclonal antibodies: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Epistaxis	Yang 2003	CC mRCC	Bevacizumab 10 mg/kg	8/39 (0/39)	Placebo	1/40 (0/40)
			Bevacizumab 3 mg/kg	5/37 (0/37)		
Epistaxis	RECORD-1	CC mRCC	Everolimus	18/274 (0/274)	Placebo	0/137 (0/137)
Dysgeusia	RECORD-1	CC mRCC	Everolimus	10/274 (0/274)	Placebo	2/137 (0/137)

7.3.2.3. mTOR

Table 121 – Second-line treatment – mTOR: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fatigue	Hutson 2014	All tumour types	Temsirolimus	100/249 (16/249)	Sorafenib	85/252 (18/252)
Decreased appetite	Hutson 2014	All tumour types	Temsirolimus	77/249 (3/249)	Sorafenib	158/252 (14/252)
Pyrexia	Hutson 2014	All tumour types	Temsirolimus	55/249 (2/249)	Sorafenib	29/252 (1/252)
Weight decreased	Hutson 2014	All tumour types	Temsirolimus	35/249 (2/249)	Sorafenib	51/252 (5/252)

Table 122 – Second-line treatment – mTOR: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Asthenia	Hutson 2014	All tumour types	Temsirolimus	65/249 (10/249)	Sorafenib	65/252 (7/252)

Table 123 – Second-line treatment – mTOR: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Cough	Hutson 2014	All tumour types	Temsirolimus	86/249 (2/249)	Sorafenib	58/252 (1/252)
Dyspnoea	Hutson 2014	All tumour types	Temsirolimus	71/249 (12/249)	Sorafenib	45/252 (11/252)

Table 124 – Second-line treatment – mTOR: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Peripheral oedema	Hutson 2014	All tumour types	Temsirolimus	57/249 (5/249)	Sorafenib	14/252 (0/252)

Table 125 – Second-line treatment – mTOR: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Nausea	Hutson 2014	All tumour types	Temsirolimus	82/249 (4/249)	Sorafenib	71/252 (3/252)
Diarrhoea	Hutson 2014	All tumour types	Temsirolimus	78/249 (6/249)	Sorafenib	158/252 (14/252)
Constipation	Hutson 2014	All tumour types	Temsirolimus	57/249 (0/249)	Sorafenib	57/252 (1/252)
Vomiting	Hutson 2014	All tumour types	Temsirolimus	56/249 (5/249)	Sorafenib	46/252 (7/252)

Table 126 – Second-line treatment – mTOR: Hematological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Anaemia	Hutson 2014	All tumour types	Temsirolimus	84/249 (23/249)	Sorafenib	35/252 (7/252)
Hypertriglyceridemia	Hutson 2014	All tumour types	Temsirolimus	53/249 (8/249)	Sorafenib	18/252 (1/252)
Hypercholesterolemia	Hutson 2014	All tumour types	Temsirolimus	51/249 (6/249)	Sorafenib	16/252 (3/252)

Table 127 – Second-line treatment – mTOR: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Alopecia	Hutson 2014	All tumour types	Temsirolimus	5/249 (0/249)	Sorafenib	78/252 (0/252)
Mucosal inflammation	Hutson 2014	All tumour types	Temsirolimus	74/249 (3/249)	Sorafenib	35/252 (0/252)
Pruritus	Hutson 2014	All tumour types	Temsirolimus	64/249 (2/249)	Sorafenib	65/252 (2/252)
Stomatitis	Hutson 2014	All tumour types	Temsirolimus	54/249 (2/249)	Sorafenib	18/252 (0/252)
Palmar-plantar erythrodysesthesia	Hutson 2014	All tumour types	Temsirolimus	11/249 (0/249)	Sorafenib	131/252 (58/252)
Rash	Hutson 2014	All tumour types	Temsirolimus	104/249 (7/249)	Sorafenib	88/252 (8/252)

Table 128 – Second-line treatment – mTOR: Otorhinolaryngology adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Epistaxis	Hutson 2014	All tumour types	Temsirolimus	51/249 (2/249)	Sorafenib	13/252 (0/252)

7.3.3. Third-line treatment

7.3.3.1. Tyrosine kinase inhibitors

Table 129 – Third-line treatment – Tyrosine kinase inhibitors: Constitutional symptoms

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Fatigue	Motzer 2014	CC mRCC	Dovitinib	115/280 (28/280)	Sorafenib	97/284 (24/284)
Reduced appetite	Motzer 2014	CC mRCC	Dovitinib	92/280 (5/280)	Sorafenib	83/284 (7/284)
Weight decreased	Motzer 2014	CC mRCC	Dovitinib	61/280 (4/280)	Sorafenib	87/284 (1/284)
Pyrexia	Motzer 2014	CC mRCC	Dovitinib	46/280 (2/280)	Sorafenib	42/284 (3/284)
Dysphonia	Motzer 2014	CC mRCC	Dovitinib	22/280 (0/280)	Sorafenib	25/284 (1/284)
General physical health deterioration	Motzer 2014	CC mRCC	Dovitinib	16/280 (10/280)	Sorafenib	17/284 (14/284)
Insomnia	Motzer 2014	CC mRCC	Dovitinib	15/280 (0/280)	Sorafenib	19/284 (0/284)

Table 130 – Third-line treatment – Tyrosine kinase inhibitors: Neurological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dizziness	Motzer 2014	CC mRCC	Dovitinib	28/280 (3/280)	Sorafenib	7/284 (0/284)
Asthenia	Motzer 2014	CC mRCC	Dovitinib	64/280 (13/280)	Sorafenib	47/284 (11/284)

Table 131 – Third-line treatment – Tyrosine kinase inhibitors: Cardiac adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertension	Motzer 2014	CC mRCC	Dovitinib	54/280 (22/280)	Sorafenib	79/284 (47/284)

Table 132 – Third-line treatment – Tyrosine kinase inhibitors: Respiratory adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dyspnoea	Motzer 2014	CC mRCC	Dovitinib	61/280 (16/280)	Sorafenib	57/284 (21/284)
Cough	Motzer 2014	CC mRCC	Dovitinib	50/280 (4/280)	Sorafenib	48/284 (2/284)
Pleural effusion	Motzer 2014	CC mRCC	Dovitinib	17/280 (10/280)	Sorafenib	12/284 (9/284)

Table 133 – Third-line treatment – Tyrosine kinase inhibitors: Renal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Peripheral oedema	Motzer 2014	CC mRCC	Dovitinib	27/280 (1/280)	Sorafenib	17/284 (0/284)

Table 134 – Third-line treatment – Tyrosine kinase inhibitors: Gastrointestinal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Diarrhoea	Motzer 2014	CC mRCC	Dovitinib	189/280 (20/280)	Sorafenib	128/284 (11/284)
Nausea	Motzer 2014	CC mRCC	Dovitinib	147/280 (9/280)	Sorafenib	83/284 (7/284)
Vomiting	Motzer 2014	CC mRCC	Dovitinib	123/280 (10/280)	Sorafenib	46/284 (3/284)
Constipation	Motzer 2014	CC mRCC	Dovitinib	50/280 (0/280)	Sorafenib	69/284 (3/284)
Dyspepsia	Motzer 2014	CC mRCC	Dovitinib	31/280 (0/280)	Sorafenib	14/284 (1/284)
Dry mouth	Motzer 2014	CC mRCC	Dovitinib	23/280 (1/280)	Sorafenib	12/284 (0/284)
Increased in lipase concentration	Motzer 2014	CC mRCC	Dovitinib	16/280 (12/280)	Sorafenib	11/284 (9/284)

Table 135 – Third-line treatment – Tyrosine kinase inhibitors: Pain

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Abdominal pain upper	Motzer 2014	CC mRCC	Dovitinib	30/280 (3/280)	Sorafenib	24/284 (3/284)
Myalgia	Motzer 2014	CC mRCC	Dovitinib	28/280 (3/280)	Sorafenib	17/284 (0/284)
Headache	Motzer 2014	CC mRCC	Dovitinib	26/280 (2/280)	Sorafenib	24/284 (1/284)

Non-cardiac chest pain	Motzer 2014	CC mRCC	Dovitinib	22/280 (5/280)	Sorafenib	18/284 (2/284)
Bone pain	Motzer 2014	CC mRCC	Dovitinib	15/280 (2/280)	Sorafenib	13/284 (4/284)
Back pain	Motzer 2014	CC mRCC	Dovitinib	41/280 (7/280)	Sorafenib	35/284 (8/284)
Abdominal pain	Motzer 2014	CC mRCC	Dovitinib	38/280 (10/280)	Sorafenib	38/284 (4/284)
Pain extremity	Motzer 2014	CC mRCC	Dovitinib	35/280 (5/280)	Sorafenib	29/284 (4/284)

Table 136 – Third-line treatment – Tyrosine kinase inhibitors: Endocrine / metabolic events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hyperthyroidism	Motzer 2014	CC mRCC	Dovitinib	14/280 (0/280)	Sorafenib	8/284 (0/284)

Table 137 – Third-line treatment – Tyrosine kinase inhibitors: Hematological adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Hypertriglyceridemia	Motzer 2014	CC mRCC	Dovitinib	55/280 (38/280)	Sorafenib	2/284 (1/284)
Anaemia	Motzer 2014	CC mRCC	Dovitinib	32/280 (15/280)	Sorafenib	29/284 (17/284)
Increased alkaline phosphatase	Motzer 2014	CC mRCC	Dovitinib	25/280 (6/280)	Sorafenib	5/284 (0/284)
Increased γ-glutamyltransferase	Motzer 2014	CC mRCC	Dovitinib	25/280 (15/280)	Sorafenib	8/284 (2/284)
Hyperkalaemia	Motzer 2014	CC mRCC	Dovitinib	14/280 (4/280)	Sorafenib	10/284 (4/284)
Anaemia	Motzer 2014	CC mRCC	Dovitinib	207/280 (18/280)	Sorafenib	193/284 (16/284)
Lymphopenia	Motzer 2014	CC mRCC	Dovitinib	116/280 (42/280)	Sorafenib	123/284 (40/284)
Leukopenia	Motzer 2014	CC mRCC	Dovitinib	85/280 (6/280)	Sorafenib	28/284 (2/284)
Thrombopenia	Motzer 2014	CC mRCC	Dovitinib	47/280 (6/280)	Sorafenib	30/284 (1/284)
Neutropenia	Motzer 2014	CC mRCC	Dovitinib	45/280 (7/280)	Sorafenib	20/284 (6/284)
Increased AST	Motzer 2014	CC mRCC	Dovitinib	93/280 (4/280)	Sorafenib	63/284 (5/284)
Increased ALT	Motzer 2014	CC mRCC	Dovitinib	81/280 (3/280)	Sorafenib	51/284 (4/284)
Increased total bilirubin	Motzer 2014	CC mRCC	Dovitinib	13/280 (0/280)	Sorafenib	22/284 (3/284)

Table 138 – Third-line treatment – Tyrosine kinase inhibitors: Musculoskeletal adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Arthralgia	Motzer 2014	CC mRCC	Dovitinib	27/280 (5/280)	Sorafenib	26/284 (6/284)
Muscle spasms	Motzer 2014	CC mRCC	Dovitinib	16/280 (1/280)	Sorafenib	24/284 (0/284)
Musculoskeletal weakness	Motzer 2014	CC mRCC	Dovitinib	15/280 (0/280)	Sorafenib	6/284 (1/284)
Musculoskeletal chest pain	Motzer 2014	CC mRCC	Dovitinib	16/280 (1/280)	Sorafenib	13/284 (2/284)

Table 139 – Third-line treatment – Tyrosine kinase inhibitors: Cutaneous adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Rash	Motzer 2014	CC mRCC	Dovitinib	85/280 (4/280)	Sorafenib	66/284 (6/284)
Alopecia	Motzer 2014	CC mRCC	Dovitinib	2/280 (0/280)	Sorafenib	61/284 (1/284)
Palmar-plantar erythrodysaesthesia	Motzer 2014	CC mRCC	Dovitinib	32/280 (3/280)	Sorafenib	115/284 (18/284)
Dry skin	Motzer 2014	CC mRCC	Dovitinib	22/280 (0/280)	Sorafenib	26/284 (0/284)
Pruritus	Motzer 2014	CC mRCC	Dovitinib	15/280 (0/280)	Sorafenib	30/284 (0/284)
Erythema	Motzer 2014	CC mRCC	Dovitinib	1/280 (0/280)	Sorafenib	15/284 (1/284)
Stomatitis	Motzer 2014	CC mRCC	Dovitinib	31/280 (1/280)	Sorafenib	55/284 (6/284)

Table 140 – Third-line treatment – Tyrosine kinase inhibitors: Otorhinolaryngology adverse events and other adverse events

Adverse events	Study ID	Tumour type	Intervention	All grades (grade 3-4)	Control	All grades (grade 3-4)
Dysguesia	Motzer 2014	CC mRCC	Dovitinib	31/280 (0/280)	Sorafenib	8/284 (0/284)
Increased lacrimation	Motzer 2014	CC mRCC	Dovitinib	19/280 (0/280)	Sorafenib	2/284 (0/284)
Conjunctivitis	Motzer 2014	CC mRCC	Dovitinib	14/280 (0/280)	Sorafenib	2/284 (0/284)

7.3.4. Discontinuation rate due to adverse events

Table 141 – Targeted therapies: discontinuation rate due to adverse events

Discontinuation rate for adverse events First-line treatment		
Sorafenib		
Rini 2012°	10%	14%
Escudier 2009	11%	
Jonasch 2010	13%	
ROSORC°°	6%	
Hutson 2013	4%	
Sunitinib		
SUTENT	8%	
Motzer 2013b	20%	
TORAVA	10%	
Pazopanib		
Motzer 2013b	24%	
Axitinib		
Hutson 2013	5%	
Bevacizumab		
TORAVA*	32%	
AVOREN*	26%	
Rini 2004*	23%	
Bukowski 2007***	6%	8%
INTORACT****	20%	17%
Temsirolimus		
Hudes 2007	7%	
TORAVA**	42%	

Discontinuation rate for adverse events Second-line treatment	
Sorafenib	
Ratain 2006	not reported
TARGET	4%
AXIS	6%
Motzer 2013	7%
Hutson 2014	11%
Pazopanib	
Sternberg 2010	14%
Cediranib	
Mulders 2012	11%
Axitinib	
AXIS	9%
Tivozanib	
TIVO-1	7%
Nosov 2012	not reported
Lapatinib	
Ravaud 2008	10%
Bevacizumab	
Yang 2003	not reported
Everolimus	
RECORD-1	10%
Temsirolimus	
Hutson 2014	15%

Discontinuation rate for adverse even Third-line treatment	
Sorafenib	
Motzer 2014	10%
Dovitinib	
Motzer 2014	15%

° combined with AMG 386
°° combined with IL-2
* combined with IFN
** combined with Bevacizumab
***Bevacizumab versus bevacizumab + Erlotinib
****Bevacizumab + temsirolimus versus bevacizumab + IFN

8. EXTERNAL REVIEW

8.1. Evaluation of the recommendations by the Guideline Development Group

8.1.1. GDG meeting 1

Surgery							
KCE recommendation	Score (1 to 5) Agree	NR	NA	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Surgery is recommended to achieve a cure in the management of localized RCC.	1:1 2:0 3:0 4:1 5:3	1	1	a) There is a role for observation in selected patients	Strong: 2 Weak:0 NR: 4 NA: 1		Surgery is recommended to achieve a cure in the management of localized RCC (strong)
2 Nephron-sparing surgery is recommended in patients with T1a renal tumours.	1:1 2:0 3:0 4:2 5:3	0	1	a) I disagree with level of evidence: There is evidence that survival is even prolonged in patients who were operated with partial nephrectomy compared to radical nephrectomy in localised RCC (Weight C et al. J Urol 2010; 183: 1317-23) *Response:* This study has a comparative design (low level of evidence. It is included in the EAU guideline. In the update, there is a meta-analyse including comparative studies (Weight 2010 is in) with high heterogeneity (I^2 very large + one RCT with multiple limitations	Strong: 2 Weak:0 NR: 5 NA:1		Nephron-sparing surgery is recommended in patients with T1a renal tumours (strong)
3 Nephron-sparing surgery should be favored over radical nephrectomy in patients with T1b renal tumour, whenever technically feasible.	1:1 2:0 3:0 4:5 5:0	0	1	a) I disagree with level of evidence: There is evidence that survival is even prolonged in patients who were operated with partial nephrectomy compared to radical nephrectomy in localised RCC (Weight C et al. J Urol 2010; 183: 1317-23) *Response:* This study has a comparative design (low level of evidence. It is included in the EAU guideline. In the update, there is a meta-analyse including comparative studies (Weight 2010 is in) with high heterogeneity (I^2 very large + one RCT with multiple limitations	Strong: 2 Weak:0 NR: 5 NA: 1		Nephron-sparing surgery should be favored over radical nephrectomy in patients with T1b renal tumour, whenever technically feasible (strong)
4 Radical nephrectomy should be limited to patients with T2 tumours and patients with T1 tumours not treatable with less invasive surgery	1:0 2: 1 3: 1 4:1 5: 3	0	1	a) I disagree with level of evidence: There is evidence that survival is even prolonged in patients who were operated with partial nephrectomy compared to radical nephrectomy in localised RCC (Weight C et al. J Urol 2010; 183: 1317-23) *Response:* This study has a comparative design (low level of evidence. It is included in the EAU guideline. In the update, there is a meta-analyse including comparative studies (Weight 2010 is in) with high heterogeneity (I^2 very large + one RCT with multiple limitations	Strong:2 Weak:0 NR: 5 NA: 1		Radical nephrectomy should be limited to patients with T2 tumours and patients with T1 tumours not treatable with less invasive surgery (strong)
5 Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated	1:1 2:1 3:0 4: 1 5: 3	0	1	a) I disagree with level of evidence: There is evidence that survival is even prolonged in patients who were operated with partial nephrectomy compared to radical nephrectomy in localised RCC (Weight C et al. J Urol 2010; 183: 1317-23) *Response:* This study included cT1b tumours b) Very high cost of laparoscopic surgical technique c) What is the frequency of laparoscopic surgery for T1? *Response:* Belgian health insurance data cannot give an answer to this question	Strong:2 Weak:0 NR: 4 NA: 2		New formulation will be discussed during GDG meeting 3

Surgery						
6 Laparoscopic technique is preferred when radical nephrectomy is required	1:0 2:0 3:0 4: 3 5: 1	0	3		Strong: 2 Weak: 0 NR: 4 NA: 2		New formulation will be discussed during GDG meeting 3
7 Retroperitoneal approach may be preferred to transperitoneal laparoscopic radical nephrectomy in order to reduce operative time duration	1:1 2:0 3:0 4: 2 5: 2	0	2	a) not sure if such statement really makes sense, most will use transperitoneal access anyway	Strong: Weak: 2 NR: 4 NA: 1		DELETED
8 Partial nephrectomy can be performed, either with an open or laparoscopic approach, the latter being preferably restricted to centres with laparoscopic expertize.	1:1 2:0 3:0 4: 2 5: 2	0	2	a) This doesn't mean anything. There is no definition of expertise… *Response:* Research agenda: to propose minimal criteria for centres of expertise	Strong: 2 Weak:0 NR: 4 NA: 1		Partial nephrectomy can be performed, either with an open or laparoscopic approach, the latter being preferably performed into centres with laparoscopic expertise (strong)
9 Routine removal of the adrenal gland during tumour (partial or radical) nephrectomy is not recommended when no clinical evidence of invasion of adrenal gland.	1:0 2:0 3: 0 4: 4 5: 2	0	1		Strong: 2 Weak: 0 NR: 4 NA: 1		Routine removal of the adrenal gland during tumour (partial or radical) nephrectomy is not recommended when no clinical evidence of invasion of adrenal gland (strong)
10 Lymph node dissection (lymphadenectomy) should not performed routinely in patients with in localized renal tumour without clinical evidence of lymph node invasion	1:0 2:0 3:1 4: 3 5: 2	0	1		Strong:1 Weak: 1 NR: 4 NA: 1		Lymph node dissection (lymphadenectomy) should not performed routinely in patients with localized renal tumour without clinical evidence of lymph node invasion (strong)
11 It is recommended to limit lymph node dissection to patients with clinically enlarged lymph nodes for staging purposes or local control	1:0 2:0 3:1 4: 3 5: 2	0	1	Reprendre formulation EAU	Strong: Weak:2 NR: 4 NA: 1		In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control (weak)
12 Embolization is not recommended before a routine nephrectomy	1:0 2:0 3: 2 4: 1 5: 3	0	1		Strong:2 Weak: NR: 4 NA: 1		Embolization is not recommended before a routine nephrectomy (strong)

Ablative techniques					
KCE recommendation	Score (1 to 5) Agree NR NA	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
13 Laparoscopic (robot-assisted) partial nephrectomy is preferred to radiofrequency ablation and cryoablation	1:0 0 1 2: 2 3:0 4: 4 5: 1	a) The few study indicate equivalence b) This is too general and certainly not true for all patients. Old and comorbid patients would be put at very high risk should such statement be published.	Strong:1 Weak: 1 NR: 4 NA: 1		Radiofrequency ablation and cryoablation can be a treatment option in a selected group of patients: frail elderly and/or comorbid patients with small renal masses (weak)
Treatment of M+ or local recurrent					
KCE recommendation	Score (1 to 5) Agree NR NA	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
14 Embolization can be considered for palliative approach in inoperable patient or patients with metastatic renal cell carcinoma that suffer from marked local pain or massive haematuria	1:0 0 1 2: 1 3: 3 4: 1 5:0	a) The palliative effect of embolisation on pain has not been demonstrated. b) KCE should consult radiation oncologist about this statement	Strong: Weak:2 NR: 4 NA: 1		New formulation will be discussed during GDG meeting 3

NR :non response
NA: out of my competence

8.1.2. GDG meeting 2

Diagnosis and staging						
KCE recommendation	Level of agrrement Agree Do not agree NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Contrast-enhanced multi-phasic abdominal CT and MRI are recommended for the work-up of patients with RCC and are considered equal both for staging and diagnosis.	4 2 1	- Add comment that MRI is absolutaly recommended in patients with contrast allergy and renal impairment. - it should be ct or mri and not both examinations - The guideline should be "CT OR MRI" (not "CT and MRI"). - It is either one or the other. My preference goes to CT, for three reasons: a. CT has a 4 times higher resolution than MRI (512-matrix instead of 256-matrix), because MRI has to be acquired fast (during a breath-hold). High resolution MRI (512-matrix) takes too long in the upper abdomen. b. MRI is more prone to artifacts (usually breathing artifacts) and therefore frequently inferior to CT. Diagnostic problems therefore occur much more frequently in renal MRI than in renal CT. c. a CT-urography can be obtained easily 6-10 minutes after contrast injection. An MR-urography requires the administration of furosemide. Again, the quality of MR-urography is usually inferior to that of CT-urography.	Strong: 4 Weak: 0	- The diagnosis of renal cancer is mainly based on imaging and an imaging technique with a high diagnostic accuracy is recommended. Therapeutic consequences derived from the findings on imaging are of utmost importance - CT easier and faster to perform compared with MRI. Easier to interpret ('read') by clinicians and very useful in preop planning. Contrast allergy and renal impairment contra-indications for CT and in such cases, MRI is 'second best'. Evidence and guidelines support this. - There is no need to comment. It seems obvious that one of these is required....	Contrast-enhanced multi-phasic abdominal CT is recommended for the diagnosis and characterization of patients with a renal mass. In case of contraindication to Iodine contrast injection, MRI can be used as an alternative.
2 Contrast-enhanced multi-phasic abdominal CT and MRI are the most appropriate imaging modalities for renal tumour characterization and staging prior to surgery.	3 3 1	- Add comment that MRI is absolutaly recommended in patients with contrast allergy and renal impairment. - it should be ct or mri - This is not enough considering the risk of lung and bone metastases and the fact that abdominal CT and MRI do not detect lung metastases appropriately..It should be "CT or MRI", not "CT and MRI".	Strong: 3 Weak:	- see above,CT and MRI provide information about staging and allow pre-treatment planning which are unmatched by any other imaging modality.	Contrast-enhanced multi-phasic abdominal CT or MRI are the most appropriate imaging modalities for renal mass staging prior to surgery.

Diagnosis and staging							
3 Ultrasound is not recommended in the diagnostic workup.	3	4	1	- Even though this recommendation is true, many renal tumors are diagnosed by ultrasound. Nevertheless, ultrasound is not recommended for staging and treatment planning. - although it is not the most sensitive imaging technique, there is nothing against the use of ultrasound. In case of any doubt (e.g. angiomyolipoma vs RCC), ultrasound can give additional information - There are cases where absolute diagnostic can be made and contrast-enhanced ultrasound may be used to adjudicate between cancer and benign lesions - Under "diagnostic workup", I understand differential diagnosis of an indeterminate renal mass. Ultrasound can be a powerful tool to differentiate a renal cyst from a renal tumor. If you mean characterization of a known soft-tissue mass, than indeed ultrasound plays no role	Strong: 3 Weak:	- Even though this recommendation is true, many renal tumors are diagnosed by ultrasound. Nevertheless, ultrasound is not recommended for staging and treatment planning. - in accordance with international guidelines	For a tumor ≥ T2 or ≥ N1 or M1 a contrast enhanced CT of the thorax is recommended
4 Bone scan is not routinely recommended.	5	1	1	- The statement should be made more clear: "Bone scan is not routinely recommended IN STAGING OF RENAL CANCER". - only in case of complaints bone and AP rise - I favour the AUA positon	Strong: 5 Weak:	- according to international guidelines - poor cost-benefit balance to perform bone scan in every patient	Bone scan is not routinely recommended in the absence of skeletal symptoms or elevated alkaline phosphatase. *Additional recommendations:* Brain imaging is not routinely recommended in the absence of symptoms. PET/CT is not routinely recommended in the diagnosis and follow up of RCC.
5 Renal tumour biopsy is recommended before ablative therapy and systemic therapy without previous pathology.	6		1	- Many small renal masses are benign, therefore biopsy is mandatory to tailor follow-up schemes post-ablation. For systemic treatment in metastatic cases, the histopathology might guide choice of treatment. - One of the reasons why renal biopsy is not popular is the alleged risk of seeding. I think this should be discussed here.	Strong: 4 Weak: 2	- according to international guidelines,invasive procedure, relative expansive. Poor Quality of evidence - The diagnostic accuracy of biopsy is still a matter of great controversy.	Renal tumour biopsy (preferably with a coaxial technique) is recommended before ablative therapy and systemic therapy without previous pathology.
6 Percutaneous biopsy is recommended in patients in whom active surveillance is pursued.	3	3	1	- If possible depending of tumor localization - I think this is correct only for younger patients with low comorbidities. Old and comorbid patients have competing risks which determine survival in a much more pronounced way than the renal mass. - This should be done in selected cases. The morbidity of biopsy is still high in comparison with the benefit you have in return. - follow up of imaging will in part give an answer to the question if we deal with a renal cancer yes or no	Strong: 1 Weak: 2	- depending on the life expectancy of the patients, the benefit of biopsy may be olimüited,invasive procedure, relative expansive. Poor Quality of evidence	DELETED
7 Percutaneous renal tumor biopsy should be obtained with a coaxial technique.	1		out:4 no opini on: 2		Strong: 1 Weak:		DELETED
8 PET/CT can be considered for restaging after surgery and detection of metastases and recurrence	1	4	1	- No gain over CT or MRI... - The added value is not demonstrated over a standard follow-up with CT. The avidity of RCC for PET-FDG is low. - PET/CT can be used as an adjunct in case CT (or MRI) remain doubtful. As stated in the current recommendation, all patients "could be considered" to get a PET/CT in follow-up, which is not correct. - no evidence	Strong:1 Weak: 1	- no evidence of benefit in relation to diagnosis at symptoms of metastatic disease - evidence based on systematic reviews	DELETED

Prognosis and prediction effectiveness

KCE recommendation	Level of agrement Agree	Do not agree	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Both in metastatic disease and in localized disease, the use of integrated prognostic systems or nomograms can be considered.	3	2	2	- i would agree if it was only for metastatic RCC.,The impact of nomogram on therapy has not been validated.	Strong: 2 Weak:	- some validated nomograms have been developed in patients with metastastic disease	We recommend that prognostic systems are used in the metastatic setting. In localized disease, the use of integrated prognostic systems or nomograms can be considered for prognosis.
2 No molecular prognostic marker is currently recommended t	5		2		Strong: 3 Weak: 2		No molecular prognostic marker is currently recommended for routine clinical use.

Follow-up

KCE recommendation	Level of agrement Agree	Do not agree	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Either nomograms or TNM stage can be used to classify patient in low, intermediate or high risk.	3	2	out: 1 no opini	- I think nomograms are much better at staging compared with TNM stage alone! - TNM classification is standard. The value of nomogram has not been prospectively validated. They have been generated on large dataset that have not been consolidated or monitored, thus suffering from large variations.	Strong: 1 Weak:		Either nomograms or TNM stage can be used to classify patient in low, intermediate or high risk.
2 For low-risk disease after surgery, CT or MRI can be used infrequently.	6		1	- they should only be used if clinically indicated - the recommendation is correct, but nobody known how frequent (or infrequent) MRI of CT should be used in follow-up of these patients. - ultrasonography and clinical follow up seem to be most important here	Strong: 2 Weak: 3	- low level of evidence - rather expert opinion - The recommendation would be strong if it provides a frequency for the use of CT or MRI, but it does not... therefore	For low-risk disease (pT1, N0, Nx, M0; R0.) no routine imaging follow up is recommended.
3 Moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (CT or MRI) every six months for at least three years and annually thereafter to year five.	6		1	- Why not extend follow-up beyond 5 years in high-risk disease?? - No.	Strong: 2 Weak: 3	- no clinical study data - early diagnosis of low-burden metastatic disease might have therapeutic consequences (e.g. metastasectomy of a solitary metastatic lesion)	Moderate to high risk patients undergo baseline chest and abdominal scan (CT or MRI) within three to six months following surgery with continued imaging (CT or MRI) every six months for at least three years and annually thereafter to year five.
4 Patients should undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. Continued imaging (US, CT or MRI) at least annually thereafter is recommended.	6		1	- Although this is based on low evidence, it provides an acceptable framework for the management of these patients.	Strong: 2 Weak: 4	-rather expert opinion - The evidence for active surveillance in RCC is weak - therefore this statement is equally rather weak - Although this is based on low evidence, it provides an acceptable framework for the management of these patients see above.	Patients should undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. Continued imaging (US, CT or MRI) at least annually thereafter is recommended.
5 Patients should undergo cross-sectional scanning (CT or MRI) with and without intravenous contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years.	5		2	- same as active surveillance	Strong: 1 Weak: 4	- The evidence for ablative treatments is weak, therefore this statement is equally rather weak, - Although this is based on low evidence, it provides an acceptable framework for the management of these patients.	Patients should undergo cross-sectional scanning (CT or MRI) with and without intravenous contrast unless otherwise contraindicated at three and six months following ablative therapy to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years.

NR : out of competence

8.1.3. GDG meeting 3

Surgery for non metastatic renal cancer						
KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	4	0	Ooc: 1 Nop: 0 NR: 2		Strong: 2 Weak: 1	a) nephron sparing surgery is oncologically safe and with low morbidity in experienced hands + nephron sparing surgery might reduce the risk on cardiovascular death compared to radical nephrectomy b) no randomized trails available	Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated (strong).
2 Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.	3	0	Ooc: 2 Nop: 0 NR: 2	I suggest to change it into "minimal invasive" in stead of laparoscopic. Retroperitoneoscopic and robot assisted are as safe as laparoscopi	Strong: 2 Weak: 1	a) quicker recovery and reduced hospital stay with minimal invasive surgery, thus reducing the costs of surgery. Early reconvalecence and less incapacity with laparoscopy.	Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery (strong).
3 Laparoscopic technique is preferred when radical nephrectomy is required.	1	1	Ooc: 2 Nop: 1 NR: 2	In case of T3-tumors with V.cava trombus, open nephrectomy is standard ***Response:*** See section in red below	Strong: 1 Weak: 0		Laparoscopic technique is preferred above open surgery, if technically feasible, when radical nephrectomy is required (weak).
Management of RCC with venous thrombus							
KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC			Ooc: Nop :		Strong: Weak:		Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic RCC (strong).
2 To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols			Ooc: Nop		Strong: Weak:		To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols (strong).
Adjuvant treatment							
KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Adjuvant therapy for renal cancer is not recommended outside clinical trials.	5	1	Ooc:1 Nop :0 NR:0	a) urgent need for trial on adjuvant radiotherapy b) This recommendations applies to non-metastatic RCC; however, for metastatic RCC, there is a benefit of cytoreductive nephrectomy and adjuvant systemic treatment c) negative trials so far d) randomized trials running ***Response:*** ***We did not find any RCT showing benefits for adjuvant therapy. Could you send us the trial mentioned above?***	Strong: 3 Weak: 2		Adjuvant therapy for renal cancer is not recommended outside clinical trials (strong).

Active surveillance

KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Active surveillance of small renal mass can be offered in older and/or comorbid patients.	6	0	Ooc: 0 Nop 0 NR: 1		Strong: 4 Weak: 2	a) the level of evidence is still low	Active surveillance of small renal mass can be offered in selected patients with comorbidity (weak).

Surgery for metastatic renal cancer

KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC.	5	0	Ooc: 2 Nop : 0 NR: 0	a) in the era of targeted therapyn, prospective trials are going on studying this topic but no results yet reported b) no information on role in TKI; randomized trials running	Strong: 3 Weak: 2	a) Level 1a evidence of overall survival benefit b) These studies were conducted in the era of immune therapy. Evidence in the ear of targeted therapies is still missing	Cytoreductive nephrectomy is recommended in appropriately selected patients with metastatic RCC (strong).

Systemic treatment

KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1 Chemotherapy, as monotherapy, should not be considered as effective in patients with mRCC.	5	0	Ooc: 1 Nop : 0 NR:1		Strong: 3 Weak: 2 Nop: 1	a) chemotherapy has not proven to be sufficient	Cytotoxic agents are not recommended in patients with clear cell mRCC (strong).
2 Monotherapy with IFN-α or high-dose bolus IL-2 should not routinely be recommended as first-line therapy in mRCC.	5	0	Ooc: 1 Nop : 0 NR:1		Strong: 3 Weak: 1 Nop: 1	a) in fact, those treatments have prolonged live substantially in a subset of patients, but at a high toxicity cost b) results from randomized trails	Monotherapy with IFN-α or high-dose bolus IL-2 should not routinely be recommended as first-line therapy in mRCC but can be used in selected patients (strong).
3 Systemic therapy for mRCC should be based on targeted agents.	5	0	Ooc: 1 Nop : 0 NR:1	a) I agree based on the clinical trial but these patients can be treated with TKIs as well since also bad prgnosis patients were included in the trials with sunitinib/pazopanib	Strong: 4 Weak: Nop: 1	a) randomized trails present	DELETED
4 Sunitinib is recommended as first-line therapy for advanced/metastatic RCC.	5	0	Ooc: 1 Nop : 0 NR:1		Strong: 4 Weak: Nop: 1	a) randomized trails	Sunitinib or Pazopanib is recommended as first-line therapy for metastatic clear cell RCC (strong).
5 Pazopanib can be considered as an alternative of sunitinib in first-line therapy for advanced/metastatic RCC.	4	0	Ooc:1 Nop: 1 NR: 1	a) good toxicity profile b) ESMO guidelines + clinical phase III trial	Strong: 2 Weak: 2	a) randomized trials	DELETED
6 Temsirolimus is recommended as a first-line treatment in poor-risk RCC patients.	5	0	Ooc: 1 Nop: 0 NR: 1	a) I agree based on the clinical trial but these patients can be treated with TKIs as well since also bad prgnosis patients were included in the trials with sunitinib/pazopanib	Strong: 3 Weak: 1 Nop: 1		Bevacizumab + IFN-α is recommended as first-line therapy for metastatic RCC in favourable-risk and intermediate-risk clear-cell RCC. However, three conditions are needed for a reimbursement by health insurance: 1) at least one grade 3 or 4 adverse event due to sunitinib 2) the treatment with sunitinib was stopped for at least 4 weeks 3) patient has no history of arterial thromboembolic disease or uncontrolled hypertension with standard treatment. In addition, the reimbursement role requires that treatment must be stopped in case of tumour progression assessed by CT-Scan or MRI after 8 weeks of treatment (strong).

7	Bevacizumab + IFN-α is recommended as first-line therapy for advanced/metastatic RCC in favourable-risk and intermediate-risk clear-cell RCC.	3	1	Ooc: 1 Nop: 1 NR: 1	a) 2 phase III trials available BUT : reimbursement criteria in Belgium do not make it possible to have it prescribed easily ... as a consequence not used in Belgium in this setting !! b) too toxic treatment; no survival benefit	Strong: 2 Weak: 0 Nop: 1		Temsirolimus is recommended as a first-line treatment only in poor-risk RCC patients (strong).
	Is it still usefull to put forward specific recommendations for patients who got cytokine as first-line?	1 response			a) a small minority of patients still can be treated with cytokines in first line (low burden disease, perfect general condition, clear cell RCC)... however rarely done. specific recommendations not needed in my			
8	Sorafenib can be considered in second-line **after cytokine** treatment in low or intermediate risk mRCC.	4	0	Ooc: 1 Nop: 1 NR: 1		Strong: 4 Weak:0		Sorafenib can be considered as second-line treatment in clear cell mRCC (strong).
9	In mRCC patients previously treated with **cytokines,** Pazopanib can be considered.	4	0	Ooc: 1 Nop: 1 NR: 1		Strong: 2 Weak: 2		Pazopanib, sunitinib or sorafenib can be considered in mRCC patients previously treated with cytokines(strong).
10	In mRCC patients previously treated with **cytokines,** Cediranib can be considered.	1	2	Ooc: 1 Nop: 0 NR: 1	a) not reimbursed, not able to use it in Belgium	Strong:0 Weak: 0		DELETED
11	In mRCC patients previously treated with **cytokines,** Tivozanib can be considered.	1	2	Ooc: 2 Nop: 1 NR: 1	a) not reimbursed, not able to use it in belgium	Strong: 0 Weak:0		DELETED
12	In mRCC patients previously treated with VEGF-pathway targeted therapy or cytokines, Everolimus can be considered.	3	0	Ooc: 1 Nop: 1 NR: 1		Strong: 3 Weak: 0	a) randomized trails	Everolimus can be considered in mRCC patients previously treated with VEGF-pathway targeted therapy or cytokines (strong).
13	In mRCC patients previously treated with targeted therapy, axitinib is recommended.	2	0	Ooc: 1 Nop: 2 NR: 1		Strong: 2 Weak: 0		Axitinib is recommended in mRCC patients previously treated with VEGF-pathway or cytokines. However it is only reimbursed after a failure of first line treatment with TKI or cytokine (strong).
14	In third-line therapy, Everolimus or Dovitinib can be considered.	1	1	Ooc: 1 Nop: 2 NR: 1	a) dovitinib not reimbursed in Belgium b) dovitinib not reimbursed in belgium	Strong: 1 Weak: 0		Everolimus or sorafenib can be considered in third-line therapy (strong).

Palliative Care

	KCE recommendation	Level of agrrement Agree	Do not agre	NR	Comments	Strengh of recommendation	Comments	Final formulation of recommendation
1	Embolization can be considered for palliative approach in inoperable patients or patients with metastatic renal cell carcinoma that suffer from marked local pain or massive haematuria.	6	0	Ooc: 0 Nop: 0 NR: 0		Strong: 2 Weak: 2 Nop: 1 NR: 1		Embolization can be considered for palliative approach in inoperable patients or patients with metastatic renal cell carcinoma that suffer from marked local pain or massive haematuria (strong).

NR : non response
OoC: Out of my competence
NOp: non opinion
Recommendations discussed during the meeting, not included in the limesurvey

8.2. Evaluation of the recommendations by the stakeholders

Recommendations	SoR	LoE	Score	Comment	Final version of recommendations
Diagnosis and staging					
Constrast-enhanced CT					**Constrast-enhanced CT**
Contrast-enhanced multi-phasic abdominal CT is recommended for the diagnosis and characterization of patients with a renal mass. In case of contraindication to iodine contrast injection, MRI can be used as an alternative			5: 6 4 : 1 NR : 4		Contrast-enhanced multi-phasic abdominal CT is recommended for the diagnosis and characterization of patients with a renal mass. In case of contraindication to iodine contrast injection, MRI can be used as an alternative
Contrast-enhanced multi-phasic abdominal CT or MRI are the most appropriate imaging modalities for renal mass staging prior to surgery.			5: 6 4: 2 NR: 3	(1) CT is preferred over MRI. The statement such as in "5" above (diagnosis and characterization) is better.	Contrast-enhanced multi-phasic abdominal CT or MRI are the most appropriate imaging modalities for renal mass staging prior to surgery.
For a tumour ≥ T2 or ≥ N1 or M1 a contrast-enhanced CT of the thorax is recommended.			5 : 5 4 : 2 3 :1 NR: 3	(1) Chest CT without contrast injection is OK for lung metastases	For a tumour ≥ T2 or ≥ N1 or M1 a contrast-enhanced CT of the thorax is recommended.
Bon scan					**Bon scan**
Bone scan is not routinely recommended in the absence of skeletal symptoms or elevated alkaline phosphatase.			5: 4 4: 4 NR: 3		Bone scan is not routinely recommended in the absence of skeletal symptoms or elevated alkaline phosphatase.
Brain imaging					**Brain imaging**
Brain imaging is not routinely recommended in the absence of symptoms			5: 7 4: 1 NR: 3		Brain imaging is not routinely recommended in the absence of symptoms
PET/CT					**PET/CT**
PET/CT is not routinely recommended in the diagnosis, staging and follow-up of renal cell carcinoma			5: 6 4: 1 3: 1 NR: 3		PET/CT is not routinely recommended in the diagnosis, staging and follow-up of renal cell carcinoma
Biopsy					**Biopsy**
Renal tumour biopsy (preferably with a coaxial technique) is recommended before ablative therapy and systemic therapy in the absence of previous pathology.			5: 5 4: 2 2: 1 NR: 3	(1) disagree with coaxial technique and for systemic therapy	Renal tumour biopsy (preferably with a coaxial technique) is recommended before ablative therapy and systemic therapy in the absence of previous pathology.
Prognosis and prediction of treatment effectiveness					**Prognosis and prediction of treatment effectiveness**
Prognostic systems are recommended in metastatic disease to evaluate survival .			5: 3 4: 2 3: 1 NA: 2 NR: 3		Prognostic systems are recommended in metastatic disease to evaluate survival .
In localized disease, the use of integrated prognostic systems or nomograms can be considered for prognosis as an alternative to TNM.			5: 2 4: 2 3: 2 NA: 2 NR: 3		In localized disease, the use of integrated prognostic systems or nomograms can be considered for prognosis in addition to TNM.
No molecular prognostic marker is currently recommended for routine clinical use.			5: 5 4: 1 NA: 2 NR: 3		No molecular prognostic marker is currently recommended for routine clinical use.

Recommendations	SoR	LoE	Score	Comment	Final version of recommendations
Treatment of localized renal cancer					**Treatment of localized renal cancer**
Surgery					**Surgery**
Surgery with curative intent is recommended in patients with localized renal cell carcinoma.	Strong	Very low	5: 3 4: 2 3: 2 NA: 2 NR: 2	(1) Specify in fit patients, do mention "renal cell carcinoma" only if biopsy was performed. Otherwise, speak about localized renal tumor	Surgery with curative intent is recommended in patients with localized renal cell tumour.
If technically feasible, laparoscopic technique is preferred above open surgery when radical nephrectomy is required.	Weak	Moderate	5: 6 4: 1 NA: 2 NR: 2		If technically feasible, laparoscopic technique is preferred above open surgery when radical nephrectomy is required.
Partial nephrectomy can be performed, either with an open or laparoscopic approach, the latter being preferably performed in centres with laparoscopic expertise.	Strong	Very low	5: 3 4: 2 2: 1 NA: 3 NR: 2		Partial nephrectomy can be performed, either with an open or laparoscopic approach, the latter being preferably performed in centres with laparoscopic expertise.
Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.	Strong	Very low	5: 6 4: 1 3: 1 NA: 1 NR: 2	(1) This sentence is equivocal.	Laparoscopic radical nephrectomy should not be performed in patients with T1 tumours for whom partial nephrectomy is indicated.
Partial nephrectomy is recommended in patients with T1a renal tumours.	Strong	Very low	5: 6 4: 1 3: 1 NA: 1 NR: 2		Partial nephrectomy is recommended in patients with T1a renal tumours.
Partial nephrectomy should be favoured over radical nephrectomy in patients with T1b renal tumour, whenever technically feasible.	Strong	Very low	5: 4 4: 2 3: 2 NA: 1 NR: 2		Partial nephrectomy should be favoured over radical nephrectomy in patients with T1b renal tumour, whenever technically feasible.
When partial nephrectomy is not an option for T1 and T2 renal carcinoma, radical nephrectomy should be performed.	Strong	Low	5: 4 4: 3 3: 1 NA: 1 NR: 2		When partial nephrectomy is not an option for T1 and T2 renal carcinoma, radical nephrectomy should be performed.
Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.	Strong	Low	5: 5 4: 1 3: 1 2: 1 NA: 1 NR: 2	(1) Radical nephrectomy is recommended... Not only laparoscopic radical nephrectomy.	Laparoscopic radical nephrectomy is recommended for patients with T2 tumours and localized renal masses not treatable by nephron-sparing surgery.
Routine removal of the adrenal gland during (partial or radical) nephrectomy is not recommended in the absence of clinical evidence of invasion of adrenal gland.	Strong	Very low	5: 5 4: 1 NA: 3 NR: 2		Routine removal of the adrenal gland during (partial or radical) nephrectomy is not recommended in the absence of clinical evidence of invasion of adrenal gland.

Recommendations	SoR	LoE	Score	Comment	Final version of recommendations
Treatment of localized renal cancer					**Treatment of localized renal cancer**
Surgery					**Surgery**
Lymph node dissection (lymphadenectomy) should not be performed routinely in patients with a localized renal tumour without clinical evidence of lymph node invasion.	Strong	Low	5: 3 4: 4 NA: 2 NR: 2		Lymph node dissection (lymphadenectomy) should not be performed routinely in patients with a localized renal tumour without clinical evidence of lymph node invasion.
In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.	Weak	Low	5: 3 4: 4 NA: 2 NR: 2		In patients with clinically enlarged lymph nodes, lymph node dissection can be performed for staging purposes or local control.
Embolization is not routinely recommended before a nephrectomy.	Strong	Low	5: 6 4: 2 NA: 1 NR: 2		Embolization is not routinely recommended before a nephrectomy.
Management of RCC complicated with caval thrombus					**Management of RCC complicated with caval thrombus**
Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic renal cell carcinoma.	Strong	Very low	5: 6 4: 2 NA: 1 NR: 2		Excision of the kidney tumour and caval thrombus is recommended in patients with non-metastatic renal cell carcinoma.
To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols.	Strong	Very low	5: 7 4: 1 NA: 1 NR: 2	(1) the goverment should encourage centralisation of this pathology and treatment	To ensure optimal care, patients with a supradiaphragmatic tumour thrombus should be treated in a treatment centre with expertise in cardiopulmonary surgical-technical protocols.
Alternative to surgery					**Alternative to surgery**
Active surveillance of small renal masses can be offered in selected groups patients: frail elderly and/or patients with comorbidity	Weak	Low	5: 5 4: 2 3: 1 NA: 1 NR: 2		Active surveillance of small renal masses can be offered in selected groups patients: frail elderly and/or patients with comorbidity
Ablative therapy					**Ablative therapy**
Radiofrequency ablation and cryoablation can be a treatment option in a selected group of patients: frail elderly and/or comorbid patients with small renal masses. For other patients groups, partial nephrectomy is recommended.	Weak	Very low	5: 3 4: 4 3: 2 NR: 2	(1) Results are improving and indications are increasing	Radiofrequency ablation and cryoablation can be a treatment option in a selected group of patients: frail elderly and/or comorbid patients with small renal masses. For other patient groups, partial nephrectomy is recommended.
Adjuvant treatments					**Adjuvant treatments**
Adjuvant therapy is not recommended outside clinical trials.	Strong	Very low	5: 7 4: 1 NA: 1 NR: 2		Adjuvant therapy is not recommended outside clinical trials.

Recommendations	SoR	LoE	Score	Comment	Final version of recommendations
Treatment of local recurrence/metastases					**Treatment of local recurrence/metastases**
Surgery					**Surgery**
Cytoreductive nephrectomy can be considered in patients with metastatic renal cell carcinoma.	Strong	Low	5: 4 4: 3 3: 1 NA: 1 NR: 2		Cytoreductive nephrectomy can be considered in patients with metastatic renal cell carcinoma.
Systemic treatments					**Systemic treatments**
Cytotoxic agents are not recommended in patients with clear cell metastatic renal cell carcinoma.	Strong	High	5: 6 3: 1 NA: 2 NR: 2		Cytotoxic agents are not recommended in patients with clear cell metastatic renal cell carcinoma.
Monotherapy with IFN-α or high-dose bolus IL-2 is not routinely recommended as first-line therapy in metastatic renal cell carcinoma but can be used in selected patients.	Strong	High	5: 2 4: 4 3: 1 NA: 2 NR: 2		Monotherapy with IFN-α or high-dose bolus IL-2 is not routinely recommended as first-line therapy in metastatic renal cell carcinoma but can be used in selected patients.
Sunitinib or Pazopanib is recommended as first-line therapy for clear cell metastatic renal cell carcinoma.	Strong	Low	5: 5 4: 1 3: 1 2: 1 NA: 1 NR: 2	(1) First line therapy is surgery (metastasectomy) in patients with one or few metastases	Sunitinib or Pazopanib is recommended as first-line therapy for clear cell metastatic renal cell carcinoma.
Bevacizumab + IFN-α is recommended as first-line therapy for metastatic renal cell carcinoma in favourable-risk and intermediate-risk clear-cell renal carcinoma.	Strong	Moderate	5: 2 4: 2 3: 1 NA: 4 NR: 2		Bevacizumab + IFN-α is recommended as first-line therapy for metastatic renal cell carcinoma in favourable-risk and intermediate-risk clear-cell renal carcinoma.
Note: the conditions for a reimbursement by the health insurance are: *1) at least one grade 3 or 4 adverse event due to sunitinib;* *2) the treatment with sunitinib was stopped for at least 4 weeks;* *3) patient has no history of arterial thromboembolic disease or uncontrolled hypertension with standard treatment.* *In addition, the reimbursement role requires that treatment must be stopped in case of tumour progression assessed by CT-Scan or MRI after 8 weeks of treatment.*					*Note: the conditions for a reimbursement by the health insurance are:* *1) at least one grade 3 or 4 adverse event due to sunitinib;* *2) the treatment with sunitinib was stopped for at least 4 weeks;* *3) patient has no history of arterial thromboembolic disease or uncontrolled hypertension with standard treatment.* *In addition, the reimbursement role requires that treatment must be stopped in case of tumour progression assessed by CT-Scan or MRI after 8 weeks of treatment.*

Recommendations	SoR	LoE	Score	Comment	Final version of recommendations
Treatment of local recurrence/metastases					**Treatment of local recurrence/metastases**
Systemic treatments					**Systemic treatments**
Temsirolimus is recommended as a first-line treatment in poor-risk renal cell carcinoma patients.	**Strong**	**Moderate**	5: 4 4: 2 3: 1 NA: 2 NR: 2		**Temsirolimus is recommended as a first-line treatment in poor-risk renal cell carcinoma patients.**
Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma.	**Strong**	**High**	5: 4 4: 2 3: 1 NA: 2 NR: 2		**Sorafenib can be considered as second-line treatment in clear cell metastatic renal cell carcinoma.**
Pazopanib, sunitinib or sorafenib can be considered in metastatic renal cell carcinoma patients previously treated with cytokines (*IFN-α, IL-2*).	**Strong**	**Low**	5: 3 4: 2 3: 1 NA: 3 NR: 2		**Pazopanib, sunitinib or sorafenib can be considered in metastatic renal cell carcinoma patients previously treated with cytokines (*IFN-α, IL-2*).**
Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF) -pathway targeted therapy *(i.e. bevacizumab, sunitib, sorafenib,...)* or cytokines (*IFN-α, IL-2*).	**Strong**	**Low**	5: 4 4: 1 3: 1 NA: 3 NR: 2		**Everolimus can be considered in metastatic renal cell carcinoma patients previously treated with Vascular endothelial growth factor (VEGF) -pathway targeted therapy *(i.e. bevacizumab, sunitib, sorafenib,...)* or cytokines (*IFN-α, IL-2*).**
Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines.	**Strong**	**Low**	5: 3 4: 2 3: 1 NA: 3 NR: 2		**Axitinib is recommended in metastatic renal cell carcinoma patients previously treated with VEGF-pathway targeted therapy or cytokines.**
Note: Axitinib is only reimbursed after a failure of first line treatment with TKI or cytokine .					*Note: Axitinib is only reimbursed after a failure of first line treatment with TKI or cytokine .*
Everolimus or sorafenib can be considered in third-line therapy.	**Weak**	**Very low**	5: 2 4: 3 3: 1 NA: 3 NR: 2		**Everolimus or sorafenib can be considered in third-line therapy.**
Palliative care					**Palliative care**
Additional information regarding palliative care for overall cancer population can be found in KCE report 211 (GCP related to cancer pain) and 115 (organisation of care)					*Additional information regarding palliative care for overall cancer population can be found in KCE report 211 (GCP related to cancer pain) and 115 (organisation of care)*
Embolization can be considered for palliative approach in inoperable patients or patients with metastatic renal cell carcinoma who suffer from severe local pain or massive haematuria.	**Strong**	**Low**	5: 4 4: 3 3: 1 NA: 1 NR: 2		**Embolization can be considered for palliative approach in inoperable patients or patients with metastatic renal cell carcinoma who suffer from severe local pain or massive haematuria.**

	SoR	LoE	Score	Comment	
Recommendations					Final version of recommendations
Follow-up					**Follow-up**
For low-risk disease (pT1, N0, Nx, M0; R0) no routine imaging follow up is recommended. **Moderate to high-risk patients should undergo baseline chest and abdominal scanning (CT or MRI) within three to six months following surgery with follow-up imaging (CT or MRI) every six months for at least three years and annually thereafter to year five.** **Patients under active surveillance should undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. Follow-up imaging (US, CT or MRI) at least annually thereafter is recommended.** **After ablative therapy, patients should undergo cross-sectional scanning (CT or MRI) with and without intravenous contrast unless contraindicated at three and six months to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years.**			5: 2 4: 2 3: 2 NA: 1 NR: 3 5: 3 4: 4 NA: 1 NR: 3 5: 3 4: 5 NR: 3 5: 3 4: 4 NA: 1 NR: 3	(1) For low risk , CT and MRI should be performed less frequently according to EAU guidelines 2015 and at least for 5 years; Alternance with US could be considered every 6 months the first year and then annually	**For low-risk disease (pT1, N0, Nx, M0; R0) no routine imaging follow up is recommended.** **Moderate to high-risk patients should undergo baseline chest and abdominal scanning (CT or MRI) within three to six months following surgery with follow-up imaging (CT or MRI) every six months for at least three years and annually thereafter to year five.** **Patients under active surveillance should undergo cross-sectional abdominal scanning (CT or MRI) within six months of active surveillance initiation to establish a growth rate. Follow-up imaging (US, CT or MRI) at least annually thereafter is recommended.** **After ablative therapy, patients should undergo cross-sectional scanning (CT or MRI) with and without intravenous contrast unless contraindicated at three and six months to assess treatment success. This should be followed by annual abdominal scans (CT or MRI) thereafter for five years.**
Best practices					Best practices
Diagnosis and staging					**Diagnosis and staging**
Renal cell carcinoma classification					**Renal cell carcinoma classification**
The use of the current TNM classification system is recommended. **The use of grading systems and classification of renal cell carcinoma subtype is recommended.**			5: 8 NR: 3 5: 7 NA: 1 NR: 3		**The use of the current TNM classification system is recommended.** **The use of grading systems and classification of renal cell carcinoma subtype is recommended.**
Patient information					**Patient information**
The patient must be kept fully informed about his condition, the treatment options and consequences. Information should be correct, complete and communicated in a clear and unambiguous way. Patient preferences should be taken into account when deciding on a treatment option.			5: 7 4: 1 NA: 1 NR: 2	(1) psychosocial support should be offered to every patient, before and during diagnosis and during follow up. (2) 1)to support the participation of the patient in the decision making process, supportive tools such as decision aids are useful. 2) can a reference to guidelines about how to communicate, how to break bad news*...be added? 3) keeping patients fully informed is very important for patients who want to be fully informed. But patients may have different information needs, the health care team must take these differences into account when communicating with patients. For patients, there's a right to be fully informed, but there's no duty	**The patient must have the opportunity to be fully informed about his condition, the treatment options, consequences. Information should be correct, communicated in a clear and unambiguous way and adapted to the individual patient. Patient preferences should be taken into account when a decision on treatment is taken. Special attention should be given to breaking bad news and coping with side effects.** **Psychosocial support should be offered to every patient, from diagnosis on.**
Follow-up					**Follow-up**
Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo PROMPT neurologic cross-sectional CT or MRI scanning of the head or spine based on localization of symptomatology.			5: 5 4: 2 NA: 1 NR: 3	(1) Preferrably MRI.	**Patients with a history of a renal neoplasm presenting with acute neurological signs or symptoms must undergo PROMPT (preferrably) MRI or CT scanning of the head or spine based on localization of symptomatology.**

9. TNM CLASSIFICATION

9.1. cTNM Clinical classification

Table 142 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour 7 cm or less in greatest dimension, limited to the kidney T1a Tumour 4 cm or less T1b Tumour more than 4cm but not more than 7 cm
T2	Tumour more than 7 cm in greatest dimension, limited to the kidney T2a Tumour more than 7cm but not more than 10 cm T2b Tumour more than 10 cm, limited to the kidney
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia T3a Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia T3b Tumour grossly extends into vena cava below diaphragm T3c Tumour grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in more than one regional lymph node
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

9.2. pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pM1 Distant metastasis microscopically confirmed

9.3. Stage grouping

Table 143 – Staging kidney cancer[128]

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2, T3	N1	M0
	T3	N0	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

10. REIMBURSEMENT RULE BY HEALTH INSURANCE FOR SYSTEMIC TREATMENT

10.1. Bevacizumab + IFN-α

Chapitre IV, paragraphe 4910200 modifié

La spécialité fait l'objet d'un remboursement si elle est administrée en association à l'interféron alfa-2a pour le traitement de première ligne de patients atteints de cancer du rein avancé et/ou métastatique à la posologie recommandée de 10 mg/kg administrée toutes les deux semaines pour autant que le patient remplisse toutes les conditions suivantes :

1. le patient a présenté au moins un effet indésirable de grade 3 ou 4 au cours des 4 premières semaines de traitement par la spécialité SUTENT dont l'administration a été arrêtée depuis maximum 4 semaines ;

2. le patient ne présente pas d'antécédent thromboembolique artériel (accident cérébro-vasculaire, accident ischémique transitoire, infarctus du myocarde, angine de poitrine, insuffisance artériovasculaire périphérique ou autre événement thromboembolique artériel);

3. le patient ne présente pas d'hypertension non contrôlée par thérapie standard;

Tous les patients doivent être évalués après 8 semaines. Si le CT-Scan ou l'IRM montre une augmentation de la masse tumorale correspondant à la définition de la maladie en progression, le traitement doit être arrêté. A partir de cette évaluation et durant toute la durée du traitement, de nouvelles évaluations par CT-Scan ou IRM seront effectuées toutes les 8 semaines.

Le remboursement est conditionné par la fourniture au pharmacien hospitalier concerné d'un formulaire standardisé, dont le modèle est repris à l'annexe A du présent paragraphe, complété, daté et signé par le médecin responsable

Hoofdstuk IV, paragraaf 4910200 gewijzigd

De specialiteit wordt vergoed als aangetoond wordt dat ze toegediend wordt in combinatie met interferon alfa-2a aan de aanbevolen dosis van 10 mg/kg lichaamsgewicht éénmaal per 2 weken voor de eerstelijnsbehandeling van patiënten met gevorderde en/of gemetastaseerde niercelkanker indien de patiënt aan alle volgende voorwaarden voldoet :

1. de patiënt heeft minstens een graad 3 of 4 ongewenst effect vertoond tijdens de 4 eerste weken van een behandeling met de specialiteit SUTENT waarvan de toediening sinds maximum 4 weken werd stopgezet;

2.de patiënt heeft geen voorgeschiedenis van arteriële thrombo-embolie (cerebrovasculair accident, transiënt ischemisch accident, myocard infarct, angina pectoris, perifere arteriële insufficiëntie of ander arterieel thrombo-embolisch voorval);

3.de patiënt lijdt niet aan hypertensie die niet onder controle is met een standaardbehandeling;

Alle patiënten moeten na 8 weken geëvalueerd worden. Indien de CT-scan of MRI een tumorgroei overeenstemmend met de definitie van een progressieve ziekte vertoont, moet de behandeling stopgezet worden. Vanaf deze evaluatie en zolang de behandeling behouden wordt, zullen er minstens om de 8 weken nieuwe evaluaties met onder andere CT scan of MRI plaatsvinden

De vergoeding is gebaseerd op de aflevering aan de betrokken ziekenhuisapotheker van een gestandaardiseerd formulier waarvan het model is opgenomen in bijlage A van deze paragraaf en ingevuld, gedateerd en ondertekend door de geneesheer verantwoordelijk voor de

du traitement et qui est spécialiste en oncologie médicale ou en urologie et qui possède une compétence particulière en oncologie.

En complétant ainsi ce formulaire aux rubriques ad hoc, le médecin spécialiste susvisé, simultanément:

- mentionne si le patient répond aux critères requis pour l'instauration du traitement (voir ci-dessus) ou s'il s'agit d'une continuation de traitement, les éléments relatifs à l'évolution du patient avec confirmation via CT-scan ou IRM de l'absence de progression ;

- s'engage à tenir à la disposition du médecin-conseil les éléments de preuve confirmant les éléments attestés ;

- atteste disposer du rapport de la consultation oncologique multidisciplinaire (COM) marquant l'accord pour le traitement pour lequel le remboursement est demandé ;

- s'engage à arrêter le traitement AVASTIN en cas de constatation de progression de l'affection.

behandeling en die specialist is in de medische oncologie of in de urologie met een bijzondere bekwaamheid in de oncologie.

Door aldus het formulier volledig in te vullen in de ad hoc rubrieken, vermeldt de geneesheer-specialist van wie hierboven sprake is, gelijktijdig:

- of de patiënt beantwoordt aan de criteria vereist bij het begin van de behandeling (zie hoger) of, wanneer het een voortzetting van de behandeling betreft, de elementen met betrekking tot de evolutie van de patiënt met de bevestiging door middel van een CT-scan of een MRI van het ontbreken van progressie;

- dat hij zich engageert om de bewijsstukken die de geattesteerde gegevens bevestigen, ter beschikking te houden van de adviserend geneesheer~~;~~

- dat hij bevestigt dat hij over het rapport van het multidisciplinair oncologisch consult (MOC) beschikt dat het akkoord voor de behandeling waarvoor terugbetaling wordt aangevraagd vermeldt;

- dat hij zich ertoe verbindt om de behandeling met AVASTIN te stoppen wanneer hij vaststelt dat er progressie van de ziekte is.

10.2. Axitinib

a) La spécialité entre en ligne de compte pour un remboursement si elle est administrée pour le traitement en seconde ligne d'un cancer du rein avancé (stade IV) chez un bénéficiaire chez qui un premier traitement en première ligne avec un inhibiteur de la tyrosine kinase ou une cytokine a échoué.

b) Tous les patients doivent être évalués au cours de la 12ème semaine qui suit le début du traitement ou plus tôt si la situation clinique l'exige. Le traitement doit être arrêté si le CT-scan ou l'IRM met en évidence une croissance tumorale qui répond à la définition de progression de la maladie.

A partir de cette première évaluation et aussi longtemps que le traitement sera maintenu, de nouvelles évaluations, avec notamment la réalisation d'un CT-scan ou d'une IRM, seront effectuées au moins toutes les 12 semaines.

c) Le remboursement est subordonné à la remise au pharmacien hospitalier d'un formulaire de demande, dont le modèle est reproduit à l'annexe A du présent paragraphe, complété et signé par le médecin spécialiste responsable du traitement et qui est agréé en oncologie médicale ou en urologie avec une compétence particulière en oncologie.

En complétant de la sorte les rubriques ad hoc de ce formulaire, le médecin spécialiste dont il est question ci-dessus mentionne également :

- les éléments relatifs à l'état du patient et à la nature du traitement précédemment reçu, les éléments se rapportant à l'évolution du patient et plus particulièrement que l'imagerie médicale réalisée après 12 semaines montre l'absence de progression par rapport à l'évaluation faite au départ du traitement ;

a) De specialiteit komt in aanmerking voor vergoeding indien ze gebruikt wordt voor de 2e lijnsbehandeling van een gevorderd niercelcarcinoom (stadium IV), bij een rechthebbende, bij wie een eerdere eerstelijnstherapie met een tyrosine kinase inhibitor of een cytokine faalde.

b) Alle patiënten moeten in week 12 na het starten van de behandeling of vroeger indien de klinische toestand het vereist geëvalueerd worden. Indien de CT-scan of MRI een tumorgroei overeenstemmend met de definitie van een progressieve ziekte vertoont, moet de behandeling stopgezet worden.

Vanaf deze eerste evaluatie en zolang de behandeling zal behouden worden, zullen er minstens om de 12 weken nieuwe evaluaties met onder andere een CT-scan of een MRI plaats moeten vinden.

c) De vergoeding hangt af van de aflevering aan de betrokken ziekenhuisapotheker van het aanvraagformulier, waarvan het model in bijlage A van de huidige paragraaf is opgenomen, ingevuld en ondertekend door de geneesheer-specialist verantwoordelijk voor de behandeling en die erkend is in de medische oncologie of de urologie met een speciale bekwaamheid in de oncologie.

Door aldus het formulier volledig in te vullen in de ad hoc rubrieken, vermeldt de geneesheer-specialist van wie hierboven sprake is, gelijktijdig:

- de elementen die betrekking hebben op de toestand van de patiënt en op het type behandeling reeds door de patiënt ontvangen, de elementen met betrekking tot de evolutie van de patiënt meer bepaald na week 12 de bevestiging van de medische beeldvorming die het ontbreken van een progressie sinds het begin van de behandeling aantoont;

- qu'il atteste disposer du rapport de la consultation oncologique multidisciplinaire (COM) marquant l'accord du traitement pour le traitement administré ;

- dat hij bevestigt dat hij over het rapport van het multidisciplinair oncologisch consult (MOC) beschikt dat het akkoord voor behandeling geeft voor de behandeling die wordt toegepast;

- qu'il s'engage à tenir à la disposition du médecin conseil les éléments de preuve qui attestent de la situation décrite ;

- dat hij zich engageert de bewijsstukken die de geattesteerde gegevens bevestigen ter beschikking te houden van de adviserend geneesheer;

- qu'il s'engage à effectuer une évaluation avec notamment une imagerie par CT-scan ou par IRM toutes les 12 semaines afin de vérifier l'absence de progression de la maladie ;

- dat hij zich ertoe verbindt om een evaluatie met onder andere een CT-scan of een MRI om de 12 weken te verrichten om de afwezigheid van progressie na te gaan;

- qu'il s'engage à arrêter le traitement lorsqu'il constate que la maladie progresse malgré le traitement.

- dat hij zich ertoe verbindt om de behandeling te stoppen wanneer hij vaststelt dat er progressie is van de aandoening ondanks de lopende behandeling.;

d) Le nombre de conditionnements remboursables tiendra compte d'une dose maximale de 5 mg deux fois par jour.

d) Het aantal vergoedbare verpakkingen zal rekening houden met een maximale dosis van 5 mg twee keer per dag.

Si l'administration une dose supérieure s'avère nécessaire, les coûts liés à la dose au dessus de celle de 5 mg deux fois par jour seront entièrement en charge du titulaire de l'enregistrement. En aucun cas les coûts de cette augmentation de dose ou les couts liés à sa mise en pratique ne peuvent être mise en charge du patient ou de l'Assurance.

Indien de toediening van een hogere dosis aangewezen is, zal de dosis boven 5 mg twee keer per dag volledig ten laste zijn van de titularis van de registratie. Op geen enkele manier mogen de kosten van deze dosisverhoging of de aan de desbetreffende praktische uitwerking verbonden kosten aan patiënt of de Verzekering worden doorgerekend.

e) Le formulaire repris à l'annexe A devra être tenu à la disposition du médecin conseil.

e) Het aanvraagformulier opgenomen in bijlage A moet ter beschikking gehouden worden van de adviserend geneesheer.

f) Mesure transitoire: La spécialité entre également en ligne de compte pour une remboursement si elle est administrée à des patients traités depuis ou moins 12 semaines avec Inlyta dans le cadre d'un Medical Need Program (MNP) au moment de l'entrée en vigueur de cette réglementation, pour le traitement en 2ème ligne du carcinome rénal avancé (stade IV), et chez qui le traitement s'est avéré efficace , qui a été évalués selon les conditions

f) Overgangsmaatregel: De specialiteit is eveneens vergoedbaar indien ze wordt toegediend aan patiënten die minstens sinds 12 weken worden behandeld met Inlyta in het kader van een Medical Need Program (MNP) op het moment van het in werking treden van deze reglementering, voor de 2elijnsbehandeling van een gevorderd niercelcarcinoom (stadium IV), en bij wie de behandeling doeltreffend is gebleken, dienen te worden geëvalueerd volgens de voorwaarden vermeld onder punten a) en b) door de arts-

visées au points a) et b) par le médecin spécialiste en oncologie médicale ou un urologue avec des compétences particulières en oncologie.

Cette procédure permettant de débuter un remboursement après un traitement antérieur dans le cadre d'un Medical Need Program (MNP) est également subordonnée à l'application des dispositions des points c), d) et e) ci-dessus, et ne pourra être appliqué que pendant une période transitoire de 6 mois à partir de l'entrée en vigueur du présent paragraphe.

Le médecin-spécialiste remplit le formulaire dont le modèle figure à l'annexe A.

specialist in de medische oncologie of de uroloog met een bijzondere bekwaamheid in de oncologie.

Deze procedure, die terugbetaling toestaat na een voorafgaandelijke behandeling in het kader van een Medical Need Program (MNP) is eveneens onderworpen aan de bepalingen van punten c), d) en e) hierboven en mag slechts worden toegepast gedurende een overgangsperiode van 6 maanden, vanaf de inwerkingtreding van deze paragraaf.

De arts-specialist vult hiertoe het formulier in, waarvan het model is opgenomen in bijlage A.

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