Kidney Cancer Research Network of Canada (KCRNC) consensus statement on the role of cytoreductive nephrectomy for patients with metastatic renal cell carcinoma

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Introduction

In recent decades, there have been significant advances in the systemic treatment options for patients with metastatic renal cell carcinoma (mRCC) with the introduction of targeted therapies and, more recently, immune checkpoint inhibition. Prior to the introduction of these contemporary therapies for mRCC, two randomized controlled trials identified a survival advantage to performing cytoreductive nephrectomy (CN) followed by interferon alpha-2b vs. interferon alpha-2b alone.[1,2] However, whether CN, defined as nephrectomy in the setting of metastatic disease, provides a similar survival advantage for patients receiving modern systemic therapy has remained controversial, with two recent randomized trials calling into question the value of CN.[3,4] In addition, several important questions remain surrounding the appropriate application of CN, particularly with regards to optimal patient selection and the timing of surgery.

Herein, the Kidney Cancer Research Network of Canada (KCRNC) provides consensus recommendations on the role of CN in patients with mRCC in order to guide clinicians who manage patients with advanced RCC.

Methods

Evidence acquisition

A comprehensive search was conducted to identify studies relevant to the development of this consensus statement. Databases searched included MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SCOPUS. The search strategy was designed and conducted by an experienced librarian with input from the consensus statement authors. The full search strategy can be found in Appendix 1.

Consensus statement development

This consensus document was developed to address six questions related to CN that were judged to be the most relevant to patient care:

1) Should patients with mRCC be offered CN and what is the optimal patient selection and timing?
2) Is there a role for CN in patients with non-clear-cell mRCC?
3) Is there a role for biopsy prior to CN?
4) Is there a role for concomitant regional lymph node dissection (LND) during CN?

5) Is there a preferred surgical approach for CN?

The statements contained herein were developed by consensus of the authors of this document, which include stakeholders across multiple specialties.

Should patients with mRCC be offered CN and what is the optimal patient selection and timing?

1. **Recognizing the complex nature of advanced kidney cancer management, decisions regarding CN should ideally be made in a multidisciplinary setting.**
2. **Patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] ≤1 or Karnofsky performance status (KPS) ≥80%), minimal symptoms related to metastases, a resectable primary tumour, and a limited burden of metastatic disease should be offered upfront CN followed by metastases-directed therapy, a period of surveillance, or systemic therapy.**
3. **Patients with significant systemic symptoms from metastatic disease, active central nervous system metastases, a limited burden of disease within the kidney relative to the cumulative extra-renal volume of metastases, rapidly progressing disease, a poor performance status (ECOG >1 or KPS <80%), and/or limited life expectancy should not undergo CN.**
4. **Patients with mRCC but without characteristics of (2) or (3) should be offered initial treatment with systemic therapy with consideration of CN given to those with a significant clinical response.**

Beyond the clinical trials performed prior to the modern era, several recent studies have investigated the role of CN in patients receiving targeted therapy (Table 1). The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) randomized patients with mRCC to CN followed by sunitinib therapy or sunitinib without CN.[3] Contrary to the clinical trials performed in the pre-targeted therapy era, CARMENA did not identify a survival advantage to undergoing CN prior to systemic therapy. Including 452 patients with a median followup 50.2 months, sunitinib alone was found to be non-inferior to CN followed by sunitinib with regards to overall survival (OS) (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.71–1.10). Furthermore, no significant difference was identified in progression-free survival (PFS) or response to treatment. There are noteworthy limitations to this trial. Most importantly, 44% of patients included in CARMENA had poor-risk disease, as classified by the Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model, and the remaining patients had intermediate-risk disease. This trial was not designed to test whether CN provides a survival advantage among mRCC patients with favourable risk characteristics. CARMENA accrued 21% less patients than initially planned over a long time period (eight years), casting some statistical doubt on the results. Furthermore, systemic therapy in CARMENA consisted of sunitinib, whereas the first-line systemic treatment for mRCC continues to evolve with the use of different targeted therapies and combinations of checkpoint inhibitors proven more active than sunitinib for intermediate- and poor-risk patients.[5] These limitations notwithstanding, CARMENA is the best available data on CN in patients with mRCC, and the findings suggest that CN does not provide a survival advantage in a significant proportion of patients with mRCC.

In addition to this randomized trial, several retrospective observational studies have investigated whether CN provides a survival advantage in patients receiving targeted therapy.[6-18] These observational studies are limited to a varying degree by heterogeneous patient populations, selection bias, and confounding, and as a result, the strength of their evidence and related conclusions regarding the benefits of CN are limited. Despite these limitations, nearly all available observational studies have identified a significant survival advantage in favour of CN for patients treated with targeted therapies.[6-18] For example, in a well-performed analysis from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) (one of only two studies including Canadian patients), a 40% reduction in all-cause mortality was noted among patients receiving CN after controlling for known biases and adjustment for confounders.[13] Similar findings have been noted across many other multi-institutional and population-based studies.[6,7,9-12,14-16,18]

Overall, although CARMENA did not identify an OS advantage to CN, the available evidence suggests that CN may provide a survival advantage in select patients but not in all comers. Risk stratification and patient selection for CN remains difficult. Multiple studies have investigated factors associated with both survival after CN and response to CN,[7,8,11-13,17-32] and a nomogram has been developed and externally validated to aid in the prediction of six-month and one-year survival after CN using preoperative clinical variables.[19,33] However, no validated models exist to predict response to CN. Although the MSKCC[34] and the IMDC[35] prognostic models are widely used to risk-stratify patients with mRCC, and have been incorporated into other professional society recommendations on CN,[36] these models have also not been validated to predict response to CN.

In patients with mRCC who are being considered for CN, the optimal timing relative to the initiation of systemic therapy also remains controversial. Initiating systemic therapy prior to CN may provide symptomatic control and disease stabilization or regression for patients with a large tumour burden. In addition, treating patients with initial systemic therapy may allow the identification of patients not likely to benefit from CN; specifically, patients who progress rapidly on systemic therapy have a poor prognosis and are unlikely to derive a survival advantage by undergoing CN. Approximately 30% of patients who undergo initial targeted

Table 1. Phase 3 randomized trials investigating the role of CN in patients with mRCC in the targeted therapy era

Trial	Patient population	Intervention arm	Control arm	Outcomes	Sample size	Median followup	Results for primary outcome
CARMENA[3]	Clear-cell mRCC, ECOG 0–1, no prior systemic or surgical treatment for RCC	CN followed by sunitinib	Sunitinib alone	– Primary: OS, – Secondary: objective response, PFS, treatment compliance, safety and adverse events	n=452	50.2 months	HR for OS: 0.89 (95% CI 0.7–1.10)
SURTIME[4]	Clear-cell mRCC, ECOG 0–1, no prior systemic or surgical treatment for RCC	Sunitinib followed by CN followed by sunitinib	CN followed by sunitinib	– Primary: disease progression at 28 weeks – Secondary: OS, objective response, safety and adverse events	n=99*	30.9 months	Progression at 28 weeks**: – Upfront CN: 42.0%, – Upfront sunitinib: 42.9% (p>0.99)
TARIBO[48]	Clear-cell mRCC, ECOG 0–1, good- or intermediate-risk disease, no prior systemic or surgical treatment for RCC	CN followed by sunitinib or pazopanib	Sunitinib or pazopanib alone	– Primary: OS – Secondary: objective response, PFS, safety and adverse events, biomarker analysis	n=270 (estimated)	***	***

*Initial accrual target was 458 patients. **Preliminary results presented at the 2017 European Society of Medical Oncology annual meeting. ***Enrollment ongoing. CI: confidence interval; CN: cytoreductive nephrectomy; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; mRCC: metastatic renal cell carcinoma; OS: overall survival; PFS: progression-free survival.

therapy prior to planned CN have been found ultimately to not receive CN, with the most common reason being disease progression, suggesting that a trial of initial targeted therapy may help select patients for CN.[37-39] The rationale for upfront CN is that it has the potential advantages of palliating symptoms related to the primary tumour, eliminating a source of secondary metastases, and improving host immune dysfunction. Although systemic therapy decreases the size of the primary tumour in a proportion of patients,[37,40-43] the median decrease in size is estimated to be 7–32% and the clinical impact of this is questionable.[37,40-43] Furthermore, if the primary tumour increases in size or complexity during systemic therapy, the feasibility of resection may be decreased.

To investigate the optimal timing of CN relative to initiation of systemic therapy, the Immediate Surgery or Surgery After sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial compared upfront CN vs. sunitinib followed by CN among patients with mRCC with a primary endpoint of disease progression at 28 weeks.[4] Overall, the sequence of upfront CN or sunitinib did not impact disease progression at 28 weeks of followup (42.0% vs. 42.9%, respectively; p>0.99).[4] Although an advantage was seen in OS in the deferred CN group (median OS 32.4 vs. 15 months; p=0.034), it is difficult to interpret this result in light of the underpowered analysis and the discordance with the disease progression results. Indeed, SURTIME was complicated by significant difficulties with accrual, with an initial target of 458 patients and a final accrual of 99 patients. Furthermore, the choice of PFS as an endpoint represents an important flaw in the context of mRCC, where documented OS benefits are ideally needed in testing of alternative treatment strategies. As a result of these factors, the clinical impact of this trial is limited.

Several retrospective observational studies have investigated whether the timing of CN vs. systemic therapy impacts patient outcomes.[9,44,45] Two of these studies found no difference in survival with initial CN vs. initial targeted therapy.[44,45] However, these sample sizes were relatively small (n=35 and n=102), limiting their statistical power. A third, more recent population-based study from the Surveillance, Epidemiology, and End Results Program (SEER) database, found an increased OS among patients receiving initial targeted therapy followed by CN compared with the opposite. Finally, the most recent population-based analysis based on a very large patient sample from the U.S. National Cancer Database found an OS benefit among patients with mRCC treated with CN as the initial treatment modality.[46]

Considering the available evidence, the results from CARMENA and SURTIME show that systemic therapy should be the priority in patients with mRCC, with CN reserved for very select patients. Recognizing the limitations of the existing data on CN in patients with mRCC, we provide the following recommendations, based on expert consensus.

As advanced kidney cancer management is complex and rapidly evolving, decisions regarding the optimal timing of CN should ideally be made after appropriate multidisciplinary discussions and should be followed by a detailed and thorough informed consent process.

In patients with a good performance status (ECOG >1 or KPS <80), no systemic symptoms, a primary tumour that is deemed resectable, and a limited burden of metastatic disease, we recommend offering upfront CN. Following CN, a period of surveillance or metastases-directed therapy may be considered in patients with minimal residual disease.[47] In patients with multiple metastatic deposits remaining, systemic therapy should be initiated after CN.

Conversely, in patients with significant systemic symptoms from metastatic disease, active central nervous system metastases, a limited burden of disease within the kidney relative to the volume of metastases, rapidly progressing disease, a poor performance status (ECOG >1 or KPS <80%), and/or a limited life expectancy, we recommend against performing CN. If a patient's clinical condition improves, the role of CN can be revisited.

For patients with mRCC who do not fall into one of these two groups, we recommend initial treatment with systemic therapy before consideration of CN. For these patients, the duration of therapy before proceeding to CN remains uncertain but CN should ideally be considered in the setting of a complete response or meaningful partial response.

In addition to these recommendations, we suggest clinicians take into account a patient's age, general health status, and competing health risks when making decisions regarding the role of CN, as these are surrogate markers of OS. Finally, although formal recommendations cannot be made based on the available evidence, the complexity of surgery and the potential for increased morbidity due to anatomic factors (e.g., venous thrombectomy, resection of surrounding organs) should also be considered.

The Consensus Panel also recognized that nephrectomy may provide a purely palliative benefit in select patients with severe symptoms from their primary tumour (e.g., intractable hematuria, paraneoplastic syndromes with majority of tumour burden within the kidney). Decisions regarding surgery in these patients should be individualized, and general recommendations regarding such scenarios cannot be made.

Special considerations

Is there a role for CN in patients with non-clear-cell mRCC?

1. **Patients with non-clear-cell mRCC should be offered CN with similar considerations to those with clear-cell mRCC.**

The majority of available data on CN pertain to patients with clear-cell histology, and thus whether CN provides a survival advantage for appropriately selected patients with non-clear-cell mRCC remains uncertain. Of note, the two aforementioned trials of CN performed in the interferon era did not include information on histological subtypes,[1,2] and all three of the modern tyrosine kinase inhibitor era phase 3 trials investigating CN in mRCC have excluded patients with non-clear-cell mRCC.[3,4,48] Despite this, limited observational data do suggest that CN may provide a survival advantage in patients with non-clear mRCC.[7,13,49-52] In a recent population-based study from the SEER database including 575 patients with non-clear-cell mRCC who underwent CN and 276 who did not, cancer-specific mortality was significantly lower in patients receiving CN after controlling for available confounders (multivariable HR 0.38; 95% CI 0.30–0.47).[49] Furthermore, a subgroup analysis demonstrated that CN was associated with an improvement in survival among all investigated non-clear-cell histological subtypes (chromophobe, papillary, and collecting duct mRCC).[49] In addition, a recent retrospective study from the IMDC including 353 patients with papillary mRCC noted that patients who underwent CN had an improved OS compared to those who did not undergo CN (HR 0.62; 95% CI 0.45–0.85).[53] Three additional observational studies have reported similar findings.[7,13,51] Thus, recognizing very limited data, we suggest that patients with non-clear-cell mRCC may be offered CN with similar indications and contraindications to those with clear-cell mRCC.

Is there a role for biopsy prior to CN?

1. **In patients receiving initial systemic therapy, biopsy of the primary lesion or a metastatic deposit should be performed prior to the initiation of therapy.**
2. **For patients receiving upfront CN, preoperative biopsy of the kidney tumour or metastatic deposit may be performed if the results of the biopsy will influence management.**

In patients proceeding to initial systemic therapy, histological diagnosis is required in order to guide appropriate systemic treatment. Nonetheless, in a patient with clear evidence of mRCC who is proceeding to upfront CN, biopsy is not absolutely indicated. As noted above, CN appears to play a role in treating non-clear-cell mRCC, and appropriately selected patients can thus proceed directly to CN without a biopsy. However, if a non-RCC histology is questioned (e.g., radiographic characteristics suggestive of urothelial carcinoma, lymphoma, etc.), a biopsy prior to CN should be performed, as the results may significantly alter the patient's subsequent management.

Is there a role for concomitant regional LND during CN?

1. **In patients with mRCC undergoing CN who do not have clinical evidence of nodal disease, retroperitoneal LND is not recommended.**
2. **Surgical resection of clinically positive lymph nodes may be considered at the time of CN after weighing the potential for increased surgical morbidity and the uncertain clinical benefit.**

The role of regional LND in patients with RCC continues to be debated, including its role in patients undergoing CN. Neither of the trials performed before the introduction of targeted therapy included standardized LND as part of CN.[1,2] In addition, the modern phase 3 trials have not mandated LND as a component of CN.[3,4,48] Nonetheless, five retrospective,

observational studies and one meta-analysis have investigated whether LND during CN is associated with an improvement in OS among patients with mRCC.[54-59] The common finding between these studies is that LND does not appear to impart a survival advantage in mRCC patients. Similar findings have been noted in patients with and without clinically positive lymph nodes.[54]

While existing data does not suggest a benefit to LND during CN, several limitations warrant caution before drawing definitive conclusions, most importantly the lack of standardized LND template in all of these studies. Currently, for patients without evidence of clinically positive regional nodes, we do not recommend performing LND. However, observational studies have identified that the degree of tumour debulking at the time of CN may be associated with an improvement in survival.[22,60] The burden of extra-renal metastases should also be taken into account when considering nodal dissection during CN. Thus, recognizing the lack of evidence to guide this decision, we submit that regional LND may be considered at the time of CN for patients with clinically positive nodes, at the discretion of the treating surgeon after considering the potential for increased morbidity associated with LND, along with the uncertain clinical benefit.

Is there a preferred surgical approach for CN?

1. **CN can be performed through both minimally invasive and open surgical approaches at the discretion of the treating surgeon.**

Several observational studies have shown that minimally invasive CN can be safely performed in select patients with the potential for reduced morbidity, decreased blood loss, and shorter length of hospital stay.[61-66] Indeed, there is no reason that CN should be approached differently than radical nephrectomy in patients without metastatic disease. Overall, the surgical approach should be decided taking into consideration patient and tumour characteristics, experience of the surgeon, and the potential need for ancillary procedures (e.g., regional LND, resection of surrounding organs, and/or venous thrombectomy). Adrenal-sparing, when there is no evidence of tumour invasion or metastatic spread and when technically feasible, is appropriate.

Conclusion

CN remains an important component in the multimodal treatment of patients with mRCC. The objective of this consensus statement is to aid Canadian clinicians in the appropriate application of CN, based on currently available evidence, in order to improve the care of patients with mRCC. The management of advanced kidney cancer is rapidly evolving, and it will not be feasible to re-evaluate the role of CN with the introduction of each new incremental improvement in systemic therapy. We provide these recommendations until new, high-quality, and relevant evidence becomes available, at which point this consensus statement will be updated.

Competing interests: Dr. Wood has been an advisory board member (with no compensation) for Astellas, Pfizer, and Novartis; and has participated in clinical trials supported by Aragon, AstraZeneca, BMS, Exelixis, Merck, Pfizer, and Roche. Dr. Kapoor has been an advisory board member for BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche; a speakers bureau member for Eisai, Ipsen, Novartis, and Roche; and has received honoraria from BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche. Dr. Basappa has been an advisory board member for Astellas, AstraZeneca, BI, BMS, Janssen, Novartis, and Pfizer; and has received honoraria from Astellas, BMS, Janssen, Novartis, and Pfizer. Dr. Cagiannos has been an advisory board member for Abbvie and Ferring; and has received honoraria from Abbvie, Acerus, and Ferring. Dr. Jewett has been an advisory board member for Pfizer and Theralase Tech; has received honoraria from Olympus, Pfizer, and Theralase Tech; and holds investments in Theralase Tech. Dr. Kassouf has received honoraria from Astellas, AstraZeneca, Janssen, Merck, and Roche. Dr. Kollmannsberger has been an advisory board member for Astellas, BMS, Novartis, Pfizer, and Sanofi; has received honoraria from BMS, Novartis, and Pfizer; and has participated in clinical trials supported by Astellas, AstraZeneca, BMS, Janssen, Merck, Novartis, Pfizer, and Sanofi. Dr. Lavallée has been an advisory board member for Ferring and Sanofi; and received a grant from Sanofi. Dr. Richard has been an advisory board member for Sanofi; and has received compenstaion from Abbvie, Astellas, and Janssen. Dr. So has been an advisory board member for Abbvie, Amgen, Astellas, Bayer, Ferring, Janssen, and Tersera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. Dr. Tanguay has been an advisory board member for Pfizer; and has received a travel grant from Sanofi. Dr. Rendon has been both an advisory board member and a speakers bureau member for and has received grants/honoraria from Abbvie, Amgen, Astellas, Astra Zeneca, Bayer, Ferring, Jansen and Sanofi Aventis. The remaining authors report no personal or financial conflicts related to this work.

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Appendix 1. Search strategy – OVID

#	Searches	Results
1	exp Carcinoma, Renal Cell/sc	5615
2	((("renal cell" or "collecting duct") adj3 cancer*) or ((renal or kidney or hypernephroid or "hyper-nephroid" or "Collecting Duct*" or nephroid*) adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or hypernephroma or "hyper-nephroma*" or pyelocarcinoma or "pyelo-carcinoma*")) or "grawitz tumor*" or "grawitz tumour*" or hypernephroma*).ti,ab,hw,kw.	202004
3	exp Neoplasm Metastasis/	688965
4	((secondary adj3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or hypernephroma or "hyper-nephroma*" or pyelocarcinoma or "pyelo-carcinoma*" or "grawitz tumor*" or "grawitz tumour*" or hypernephroma*)) or metastas* or metastatic* or micrometastas* or micrometastatic*).ti,ab,hw,kw.	1243561
5	1 or (2 and (3 or 4))	65767
6	Cytoreduction Surgical Procedures/	12762
7	((cytoreduc* or debulk* or radical*) adj3 (nephrectom* or surg* or resect* or operat*)).ti,ab,hw,kw.	104554
8	6 or 7	104554
9	5 and 8	7262
10	exp survival/	911936
11	exp death/	732815
12	exp mortality/	1233613
13	mortality.fs.	561511
14	exp survival analysis/	305801
15	(surviv* or death* or mortalit* or fatalit*).mp.	5568550
16	or/10-15	5896880
17	9 and 16	3998
18	limit 17 to english language [Limit not valid in CDSR; records were retained]	3472
19	limit 18 to yr="2004 -Current"	2852

Appendix 1 (cont'd). Search strategy – OVID		
#	Searches	Results
20	limit 19 to (letter or conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	871
21	19 not 20	1981
22	(exp animals/ or exp nonhuman/) not exp humans/	9466935
23	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans or patient or patients)).ti,ab,hw,kw.	8138953
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27	remove duplicates from 26	1051

Database(s): Embase 1988 to 2018 Week 01, EBM Reviews - Cochrane Central Register of Controlled Trials November 2017, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 28, 2017, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.

Search strategy – SCOPUS	
1	TITLE-ABS-KEY((("renal cell" or "collecting duct") W/3 cancer*) or ((renal or kidney or hypernephroid or "hyper-nephroid" or "Collecting Duct*" or nephroid*) W/3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or hypernephroma or "hyper-nephroma*" or pyelocarcinoma or "pyelo-carcinoma*")) or "grawitz tumor*" or "grawitz tumour*" or hypernephroma*)
2	TITLE-ABS-KEY((secondary W/3 (cancer* or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or hypernephroma or "hyper-nephroma*" or pyelocarcinoma or "pyelo-carcinoma*" or "grawitz tumor*" or "grawitz tumour*" or hypernephroma*)) OR metastas* OR metastatic* OR micrometastas* OR micrometastatic*)
3	TITLE-ABS-KEY(((cytoreduc* or debulk* or radical*) W/3 (nephrectom* or surg* or resect* or operat*)))
4	TITLE-ABS-KEY(surviv* or death* or mortalit* or fatalit*)
5	PUBYEAR AFT 2003 AND LANGUAGE(english)
6	1 and 2 and 3 and 4 and 5
7	TITLE-ABS-KEY((case W/3 report))
8	6 and not 7

Appendix 1 (cont'd). Search strategy – SCOPUS	
9	TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans or patient or patients))
10	8 and not 9
11	DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ab)
12	10 and not 11
13	PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
14	12 and not