Paediatric and young adult renal cell carcinoma

Dr. Satyajit Ray[1], Professor Robert Jones[2], Professor Kathy Pritchard-Jones[3], Ms. Kristina Dzhuma[3], Professor Marry van den Heuvel-Eibrink[4], Dr. Godelieve Tytgat[4], Ms. Justine van der Beek[4], Mr. Grenville Oades[5] and Dr. Dermot Murphy[1]

1. Department of Paediatric Oncology, Royal Hospital for Children, Glasgow, Scotland

2. Institute of Cancer Sciences, University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, Scotland

3. University College London Institute of Child Health, London, United Kingdom

4. Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

5. Queen Elizabeth University Hospital, Department of Uro-Oncology, Glasgow, Scotland

Correspondence to:

Dr. Satyajit Ray, MD, Department of Paediatric Haematology and Oncology, Royal Hospital for Children, Ward 6A, Glasgow, G51 4TF, Telephone number: +447528127608 (Fax N/A) Email: buburay@hotmail.com

Text word count 3465;

Abstract word count 130;

Brief running title: A molecular driven review of paediatric renal cancer

Keywords: Paediatrics, renal cell carcinoma, treatment, targeted therapy

20 Tables: 1

21 Figures: 1

22 Supporting Information: 3

23

24

25

26

27

Abbreviations	
Renal cell carcinoma	RCC
Translocation renal cell carcinoma	tRCC
Papillary renal cell carcinoma	pRCC
Clear-cell renal cell carcinoma	ccRCC
International Incidence of Childhood Cancer Volume 3	IICC-3
Von Hippel-Lindau	VHL
Mammalian Target of Rapamycin	mTOR
Receptor Tyrosine Kinase	RTK
Vascular Endothelial Growth Factor	VEGF

Platelet Derived Growth Factor	PDGF
Vascular Endothelial Growth Factor Receptor	VEGFR
Radical Nephrectomy	RN
Partial Nephrectomy	PN
Nephron-Sparing Surgery	NSS
Tumour, Node, Metastasis (staging system)	TNM
Randomised Controlled Trial	RCT
The International Society of Paediatric Oncology	SIOP
Wilms Tumour	WT
Children's Oncology Group	COG
Radical Lymph Node Dissection	RLND
Cytoreductive Nephrectomy	CN
Interferon-alpha	IFN-α
Interleukin-2	IL-2
Stereotactic Ablative Radiotherapy	SABR
Overall Survival	OS
Progression-free Survival	PFS
Event-free Survival	EFS
Haematopoietic Stem Cell Transplantation	HSCT

Tyrosine Kinase Inhibitor	TKI
Checkpoint Inhibitor	CPI
Cytotoxic T-cell Lymphocyte-associated Antigen 4	CTLA-4
Programmed Cell Death Protein 1	PD-1
Programmed Death Ligand 1	PD-L1

Abstract

Renal cell carcinoma (RCC) is rare in children but is the most common renal tumour in adults. Paediatric RCC has different clinical characteristics, histopathology and treatment compared to adult disease. Databases were reviewed from inception to February 2020 identifying 32 publications pertaining to 350 patients under 27 years. Surgery is the cornerstone for cure in localised RCC. Lymph node dissection remains controversial. Conventional radiotherapy has no curative role in RCC; similarly conventional chemotherapy has not proven to be effective in large cohorts. Paediatric metastatic RCC has a poor outlook. There are no published prospective studies demonstrating which adjuvant therapy could improve outcome. Sunitinib, a tyrosine kinase inhibitor, is recommended in this group despite limited evidence. This review provides an overview for paediatric RCC, including the evolving role of precision medicine.

Introduction

In Europe, around 1000 children are diagnosed with a malignant renal tumour annually[1]. Renal cell carcinomas (RCC) make up 1.9-6% of all kidney cancers in children[2–5]. The international incidence of childhood cancer volume 3 (IICC-3) shows that the annual incidence of paediatric RCC is increasing globally, almost doubling, in 0-19 year olds between the 1990s and 2010s (Supporting Information Figure S1). The relative incidence compared to the much commoner Wilms tumour (WT) varies with age, such that over half of all paediatric renal tumours are RCC in 14 year olds and RCC remains the predominant renal tumour type after this age[6].

Despite this global rise, few children die from RCC. In 2013-2015, Public Health England showed an overall survival (OS) of > 80% in newly diagnosed 13-24 year old RCC patients[7].

Paediatric RCCs differ significantly from adult counterparts in morphology, genetics, biology and subtype[3,5,8,9]. The molecular basis of RCC classification in children has recently changed to place more emphasis on the molecular profile. Papillary RCC is rare in adults but the commonest subtype in younger people. Xp11 and t(6;11) translocation RCC (tRCC) (both of which result in overexpression of transcription factor genes: TFE3 and TFEB, respectively) are emerging as a more prevalent subtype in children[3,5,8–10]. Papillary RCC and tRCC subtypes are morphologically distinct. The World Health Organization recommends diagnosis by morphological features together with immunocytochemistry or fluorescence in situ hybridisation.

In contrast, clear cell RCC (ccRCC) in patients with Von Hippel-Lindau (VHL) constitutional gene abnormalities is most common in adults[5,9] and tRCCs represent only 15% of RCCs in patients under 45 years[11]. A Swiss study reported only 15% of all RCCs were ccRCC in a group of 41 patients under 22 years[12]. Adult ccRCCs often show up-regulation of angiogenic growth factors. Vascular endothelial growth factor- (VEGF) and platelet derived growth factor (PDGF) receptors

are involved in tumour angiogenesis and tumour cell growth allowing for treatment with anti-angiogenic drugs([5,13]). All positive phase 3 trials of these drugs have been restricted to ccRCC pathology and current limited evidence suggests these drugs are less active in non-ccRCC.

Subclassifcation of paediatric and adolescent renal cancers in population based registries is poor, so distinctions cannot be made at a population level and are only reported in detail in smaller cohorts registered in clinical trials and studies.

Paediatric RCC occurs in equal frequency in males and females before the age of 15 years compared to a male predominance in adults[(2,6,9)]. Additionally, paediatric RCC has been reported in patients suffering from another underlying disorder([3,14]) or having undergone prior chemotherapy([15]). A specific subgroup exists as a secondary malignancy following neuroblastoma([5,16]) with one reported case of secondary tRCC in a child following medulloblastoma([17]). The IICC-3 reports only 34 out of 1011 (3%) 0-19 year old RCC cases as secondary cancer suggesting that this is not as common as previously thought[(6)]. In addition, one review has reported only 12 cases of allograft RCC in children([18]).

Outcomes also appear to differ between children and adults: survival rates in children with regional lymph node disease without distant metastasis is nearly triple that of adult controls[(8)] implying that validated treatment in adults cannot be directly extrapolated to children.

The management of paediatric RCC is still generally based on experience extrapolated from adult RCC despite their differences, due to the limited evidence base in children. This review seeks to synthesise the sparse data in the literature that reports on the specific subtypes, treatments and outcomes of paediatric RCC.

Methods

Databases were reviewed from inception to February 2020 using a Boolean search strategy limited to the English language with full text availability (Supporting Information Table S1).

32 relevant publications pertaining to 350 patients under the age of 27 years were identified (Table 1 and Supporting Figure S2). This was extended with citation tracking and co-author suggestions to include adult data for comparison (Fig. 1).

Treatments

1. Nephrectomy

Regardless of subtype, surgery is the cornerstone of therapy for paediatric RCC[1,2] as no literature supports survival benefit from systemic therapy or radiotherapy alone. Localised disease has an excellent prognosis with surgery alone, whereas metastatic RCC still has poor outcomes, similar to that in adults[3,19]. Completeness of surgical resection and stage of disease are of prognostic significance.

RCC is staged using the standardised classification of tumour, lymph node and metastasis (TNM)[20]. Comparisons between paediatric and adult patients are hindered by several paediatric RCC reviews using modified Robson staging[21].

Nephron-sparing surgery/partial nephrectomy (NSS/PN) is established in adult stage T1 RCC[5,22,23]. A meta-analysis comparing PN with radical nephrectomy (RN) for renal tumours ≥7cm found that although PN preserved renal function, there was a higher surgical complication rate and no difference in cancer-specific survival[24]. A prospective randomised controlled trial (RCT) by the European Organisation for Research and Treatment of Cancer compared RN versus PN in adults with tumours <5cm (and no nodal or metastatic disease). This study showed that NSS was safe with low rates of progression or cancer related death[25]. The study closed early due to poor accrual and had no quality of life or renal function outcomes. There was no evidence of superiority or non-inferiority for PN versus RN.

Adult data suggests overall non-cancer-related survival is directly related to total nephric function necessitating consideration of PN[26], however this data has not been reproduced in paediatrics. Evolving nephron sparing techniques (robotic surgery, radiofrequency ablation and cryotherapy) may improve future outcomes.

PN in paediatric RCC has been reported in small cohorts[5,27]. An adolescent with bilateral RCC treated with PN showed stable disease at follow-up[28]. A retrospective study of paediatric renal tumours including 3 RCC cases showed no significant differences between hospital charges, hospital length of stay and complication rates between PN and RN; however, no data on oncological outcomes were reported[29].

Prospective data and RCTs are not available for PN in paediatric RCC. A single institution study revealed no difference between RN and PN when comparing oncological outcomes[27].

The International Society of Paediatric Oncology (SIOP) has reported recurrence of cancer in the contralateral kidney, particularly in those with underlying conditions, which, in addition to preservation of renal function, may make PN a preferable option[5].

Management of paediatric patients presenting with suspected WT includes neoadjuvant cytotoxic chemotherapy, RN and lymph node sampling and resection[5]. Atypical presentations felt unlikely to be WT are managed differently, generally with national panel discussions. A collaborative study reviewed the diagnostic accuracy of renal tumour biopsy to prevent over- or under-treatment in these patients. Biopsy was found to be less effective, when comparing to central pathology review nephrectomy diagnoses, at identifying non-WTs compared to WTs and rarely changed management in children[30].

In Europe, children ≥7 years of age, or younger children with diagnostic features inconsistent with WT undergo biopsy (infants undergo nephrectomy)[30]. In the USA, the Children's Oncology Group (COG) recommends upfront surgery. Most children with a diagnosis of RCC will therefore be post-nephrectomy[5].

As yet, there is no evidence favouring one approach over the other but the best method could be answered by transatlantic collaboration.

2. Radical Lymph Node Dissection (RLND)

The role of RLND is controversial and there is little evidence regarding efficacy in adult or paediatric RCC[5]. Geller's group reported nearly 90% of patients with tRCC and lymph node

involvement (N+M0) were disease free at a median follow-up of 4.4 years without adjuvant therapy[8,31]. All patients had varying degrees of RLND. European data also suggests improved overall survival with RLND[32,33].

The first national, prospective paediatric RCC study including 120 patients with unilateral RCC showed that lymph node disease was common in patients with small primary tumours and failure to sample lymph nodes resulted in incomplete staging and potential suboptimal disease control[34]. The AREN0321 study included 68 patients with RCC under 30 years. Four-year event-free survival (EFS) and OS for those that had disease clearance at diagnosis was 87.2% and 94.6%, respectively. Within that group, 15 out of 16 patients with nodal-spread only, had complete resection including RLND and their 4-year EFS and OS was 87.5% and 93.8%, respectively. Although non-randomised, this study showed favourable outcomes in completely resected RCC independent of adjuvant therapy, even in cases of locally advanced disease or lymph node involvement[35].

However, most renal tumours are suspected of being WT which does not involve extensive RLND upfront. In COG and SIOP protocols lymph node sampling is advised in all tumour nephrectomies. There is no strong evidence for the value of secondary lymph node resection based on suspicious lymph nodes on imaging postoperatively. Estrada reported one patient undergoing secondary lymph node dissection based upon residual RCC detected by positron-emission tomography-avid lymphadenopathy and reported no evidence of disease 9 months after nephrectomy[36].

A recent analysis of a large international cohort suggested RLND was not associated with improved oncological outcomes in node positive, metastasis negative adult RCC[37]. European guidelines for

adults state that RLND does not offer survival advantage in lymph node negative disease (cN0) and does not improve oncological outcomes in patients with local, nodal disease (cN1)[38].

In conclusion, there is emerging evidence of the benefit of RLND in paediatric RCC and this should be considered in contrast to the suggested lack of benefit in adult RCC.

Management of Unresectable Tumours and Metastatic RCC

Nephrectomy is the standard of care in low stage tumours and has good outcomes. Advanced stage disease still has poor outcome and this section describes therapeutic options.

(a) Surgery

Although controversial, cytoreductive nephrectomy (CN) to reduce tumour burden may result in a survival benefit regardless of systemic treatment in some adult patients[34]. CN improved outcomes (including OS) in patients with metastatic RCC receiving interferon-alpha (IFN-α)[39].

However, a recent prospective phase 3 RCT compared outcomes between patients with metastatic RCC treated with sunitinib alone or sunitinib and CN. Although not statistically significant, there was a trend towards superior survival in those who did not undergo CN suggesting that CN may not add benefit in all metastatic RCC patients receiving immediate systemic therapy. Results should be interpreted with caution as it was a non-inferiority study, closing early due to non-accrual. Furthermore, it is likely that this study was subject to selection bias, as investigators only included patients in whom the predicted benefit of CN was uncertain[40].

Metastasectomy in the era of targeted therapies still has little data with generally small studies reporting outcomes. A retrospective observational study in adults with predominantly ccRCC showed improved survival with metastasectomy with or without the additional use of targeted therapy[41]. No data on cancer-specific survival was recorded nor was there information on completeness of surgical resection.

In metastatic disease, lymph node sampling but not dissection, is recommended where there are large lymph nodes and adjuvant drug therapy with sunitinib is considered, as this approach has the largest evidence base[42–45]. Secondary metastasectomy is recommended if there is detectable remaining disease[5].

(b) Radiotherapy

RCC is considered to be relatively radioresistant and, conventionally, radiotherapy is limited to the palliative setting. In adults, stereotactic ablative radiotherapy (SABR) may have a role in treatment of the primary renal tumour but prospective data is lacking[46]. SABR may also have a role in the treatment of oligometastatic disease post-nephrectomy. A phase 2 RCT in 99 adults with various cancers showed improved OS for those receiving SABR to limited oligometastatic disease but also a 4.5% treatment related death. It is unclear if any patients had RCC[46].

(c) Immunotherapy

Interleukin-2 (IL-2) and IFN-α were in common use for nearly 3 decades but have now been superseded by targeted therapies to treat metastatic RCC in adults. IL-2 sustains a T-cell response whereas IFN-α activates dendritic cells and possibly has a direct effect on tumour cells[47,48].

There are reports of successful treatment with IL-2 in metastatic paediatric RCC[43,49–51] although numbers are small. Benefit of consolidating surgery with IL-2 has been suggested in highly selected adult populations almost exclusively with ccRCC[52,53]. Recent data in these patients shows median OS with IL-2 alone of 64.5 months in favourable risk patients, 57.6 months in intermediate risk and 14 months in poor risk. Two year survival for the same risk groups was 73.4%, 63.7% and 39.8% respectively[54].

Immune checkpoint inhibitors (CPIs) target cytotoxic T-cell lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1/ligand (PD-1/PD-L1) pathways in immune activation against tumours.

A phase 3 trial in adults with metastatic ccRCC, showed significant improvement in OS and fewer adverse effects with nivolumab (anti-PD-1) compared to everolimus[55].
Nivolumab in combination with ipilimumab (anti-CTLA-4) was approved for adults with advanced RCC after phase 3 trials showed improved OS when compared to TKI monotherapy with sunitinib[56,57].
A phase 3 trial in previously untreated adults with advanced ccRCC demonstrated a median PFS of 15.1 months with pembrolizumab (anti-PD-1) plus axitinib (TKI) compared to a median PFS of 11.1 months with sunitinib alone. OS was also significantly longer in the combination therapy arm independent of disease risk groups and PD-L1 expression[58].
Another phase 3 trial in the same demographic showed avelumab (anti-PD-L1) in combination with axitinib resulted in a significantly longer PFS compared to sunitinib alone, regardless of PD-L1 expression[59].

CPIs in combination with TKIs are now recommended as first-line therapy for adults with metastatic ccRCC[60].

CPIs have been tested in early phase trials in paediatric solid tumours[61–63] showing safety, tolerability and variable clinical efficacy. A single case of a 15 year old with tRCC showed some response to 5th line nivolumab[64]. There is currently a clinical trial recruiting children with tRCC to compare nivolumab alone and nivolumab plus axitinib based on data from the adult population that axitinib alone is not preferred due to more encouraging data regarding PD-1 targeted therapy[65].

Immunotherapy may have a role in paediatric RCC but larger studies with carefully selected patient groups are warranted.

(d) Haematopoietic stem cell transplantation (HSCT)

HSCT is a rescue therapy used to treat various paediatric solid tumours[66,67].

In adults, HSCT has been used in metastatic RCC. One study reported 9 out of 19 adults with almost exclusively metastatic ccRCC alive between 287 to 831 days after HSCT[68].
Although a single case reported a 2-year-old with papillary RCC demonstrating PFS of 5.7 years after HSCT[69], there is no strong evidence for HSCT in metastatic paediatric RCC.

(e) Cytotoxic Chemotherapy

RCC has an intrinsic resistance to conventional chemotherapy[19,70]. However, an aggressive subtype, more prevalent in sickle-cell patients, is renal medullary carcinoma. This subtype has been shown to have an excellent short-term response to conventional chemotherapy in adolescents[71].

Collecting duct carcinoma, a subtype reported more frequently in adults shares an overlapping immunohistochemical profile with renal medullary carcinoma. Modest activity has been reported in adults with collecting duct carcinoma[72]. Gurrera reported a case of collecting duct carcinoma in an 11-year old boy and described only 8 further reported cases in the literature[73].

This tumour subtype is so rare that even a transcontinental RCT would be impossible, however a carefully collected international data set may help answer the question of efficacy of conventional chemotherapy in younger patients.

(f) TKIs

Single agent TKIs have now been superseded by combination therapies with CPIs for frontline treatment of metastatic RCC in adults[60]**.** In paediatric RCC, single agent TKIs are used and currently there are no studies published of combined CPI and TKI therapy.

Sunitinib, a multi-targeted TKI which inhibits several growth factor receptors[74,75] is approved for adult RCC.

One report including children and adults with Xp11 tRCC showed improved PFS with sunitinib compared to cytokine therapy alone (8.2 months vs. 2 months). Additionally, 50% of the cohort treated with sunitinib showed partial or complete responses[44]. One predominantly adult series with 6 patients with metastatic tRCC reported at least stable disease in 5 and disease progression in 1[76].

A case report showed stable disease at 2 years in a paediatric patient with relapsed metastatic tRCC after treatment with sunitinib[45].

In adults with metastatic ccRCC, a phase 3 trial of pazopanib, a third generation TKI, showed similar efficacy to sunitinib but with better safety and quality of life outcomes[77].

Axitinib as second line therapy in adult ccRCC showed significantly longer PFS compared to sorafenib (TKI) in a phase 3 RCT[78]. A retrospective analysis of 24 children with RCC who received various systemic agents, 11 of whom had advanced stage disease, demonstrated the mean time to progression was longest with axitinib or sunitinib warranting further study of these two therapies[79].

Prospective data on the best adjuvant therapy in paediatric RCC is lacking. Novel therapies are promising but early phase trials in paediatric patients and appropriately powered phase 3 trials are needed.

(g) mTOR inhibitors: Everolimus

mTOR is involved in the growth and proliferation of malignant cells[80] and inhibitors are used in adult RCC. Argani P. showed increased expression of phosphorylated S6 in Xp11 tRCC and suggested the mammalian target of rapamycin (mTOR) pathway as a possible therapeutic target([81]). A phase 2 RCT in pre-treated adults with advanced stage ccRCC showed a PFS of 14.6 months with everolimus plus lenvatinib (multi-kinase inhibitor) compared to 5.5 months with everolimus alone[82]. Everolimus is now mainly used in licensed combination with lenvatinib in adults.

Prior to this, large trials in pre-treated adults with metastatic ccRCC had shown modest benefit in PFS with everolimus alone[83,84], with a phase 4 trial also demonstrating improved OS[84].

In adults with metastatic non-ccRCC, a phase 2 RCT showed a PFS of 8.3 months with sunitinib versus 5.6 months with everolimus. Treatment effect varied based on histological subtype and there was a trend towards everolimus being specifically active in chromophobe RCC[85].

mTOR inhibitors are approved in some paediatric tumours. Efficacy has been reported in children[86] and adults[87] with RCC although these patients also had tuberous sclerosis, which probably reflects the fact that mTOR is downstream of tuberous sclerosis complex-1 (TSC1).

Data for mTOR inhibition in paediatric RCC is scarce and trials in a similar vein to the adult population could help establish their role.

(h) MET-TKIs

Tivantinib and savolitinib are selective MET inhibitors. A study in tRCC has shown the MET receptor tyrosine kinase gene as being the most up-regulated RTK([5,88]), thereby allowing for potential therapies through MET inhibition. Tivantinib showed limited response in a phase 2 trial and savolitinib has been used against papillary RCC in a phase 2 trial suggesting activity limited to patients with MET aberrations[5,89,90].

Cabozantinib has multiple properties including MET inhibition. Phase 1 trials for cabozantinib have been undertaken[91] with phase II trials underway[92]. Efficacy has been proven in adults with advanced RCC although the precise role of MET in this setting is unknown.

Cabozantinib is approved for second or third line therapy in adult patients and, more recently, as first line treatment for those with intermediate or poor prognosis. A phase 3 trial in adults with advanced ccRCC demonstrated a median PFS more than double with cabozantinib compared to everolimus regardless of prior therapy with tolerable adverse effects[93]. Another study in pre-treated adults with metastatic RCC reported a median PFS of 12.5 months and a 12-month OS of 70.4% in patients subsequently treated with cabozantinib[94]. An Italian study with a similar demographic showed median PFS of 8 months with cabozantinib[95].
A phase 2 trial in previously untreated adults with metastatic ccRCC compared first line systemic therapies. Median PFS was reported as 8.6 months with cabozantinib compared to 5.3 months with sunitinib[96].

The first published data of cabozantinib in paediatric RCC involved 2 patients with recurrent tRCC and both cases expressed MET. Disease control was achieved for over 15 months[97].

Evidence for selective MET-TKIs is lacking and initial studies are disappointing. Newer multi-targeted agents are promising.

Discussion

Advances in the treatment of adult RCC have formed the basis of paediatric studies. An altered approach to initial investigation to include screening for biomarkers could improve diagnosis and management.

Transgenic mice studies suggest microRNA in urinary exosomes have the potential for use as a biomarker in patients with Xp11 tRCC[98]. It is hoped that other tumour subtypes could utilise similar approaches.

Identification of distinct subtypes highlights the importance of a precision medicine approach. Stratified Medicine Paediatrics is a UK research study looking at genetic changes in paediatric tumours allowing for treatment of actionable mutations. Similar initiatives are established in other European countries and North America.

Localised RCC is curable with surgery alone. Advanced RCC still carries a dismal prognosis however this has been improved with adjuvant therapy and this should now be considered as standard.

The efficacy of immunotherapy remains uncertain whilst the efficacy and choice of best second line TKIs are unknown in paediatric RCC. Despite novel targeted therapies in adult RCC, predictive biomarkers of response have not been thoroughly investigated in paediatrics and prospective studies are still lacking.

Although RCC in adults and children are two ends of a disease spectrum, physicians and researchers in both sectors should continue close collaboration to improve outcomes for their patients.

The rarity and complexity of paediatric RCC, the documented rising incidence and poor outlook in advanced disease highlights the need for international collaboration.

Conflict of Interest Statement

There are no conflicts of interest.

References

1. Brok J, Treger TD, Gooskens SL, van den Heuvel-Eibrink MM, Pritchard-Jones K. Biology and treatment of renal tumours in childhood. Eur J Cancer. 2016 Nov;68:179–95.

2. Spreafico F, Collini P, Terenziani M, Marchianò A, Piva L. Renal cell carcinoma in children and adolescents. Expert Rev Anticancer Ther. 2010 Dec;10(12):1967–78.

3. Selle B, Furtwängler R, Graf N, Kaatsch P, Bruder E, Leuschner I. Population-based study of renal cell carcinoma in children in Germany, 1980–2005: More frequently localized tumors and underlying disorders compared with adult counterparts. Cancer. 2006 Dec 15;107(12):2906–14.

4. Pastore G, Znaor A, Spreafico F, Graf N, Pritchard-Jones K, Steliarova-Foucher E. Malignant renal tumours incidence and survival in European children (1978–1997): Report from the

Automated Childhood Cancer Information System project. Eur J Cancer. 2006 Sep;42(13):2103–14.

5. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, van Tinteren H, Furtwängler R, et al. Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP–RTSG 2016 protocol. Nat Rev Urol. 2017 Dec;14(12):743–52.

6. Nakata K, Colombet M, Stiller CA, Pritchard-Jones K, Steliarova-Foucher E, IICC-3 contributors, et al. Incidence of childhood renal tumours: an international population-based study. Int J Cancer. 2020 Jun 16;ijc.33147.

7. Contains public sector information licensed under the Open Government License v3.0. 13-24 year olds with cancer in England: Incidence, mortality and survival. National Cancer Registration and Analysis Service in collaboration with Teenage Cancer Trust.

8. Geller JI, Dome JS. Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer. 2004 Oct 1;101(7):1575–83.

9. Carcao MD, Taylor GP, Greenberg ML, Bernstein ML, Champagne M, Hershon L, et al. Renal-cell carcinoma in children: a different disorder from its adult counterpart? Med Pediatr Oncol. 1998 Sep;31(3):153–8.

10. Abdulfatah E, Kennedy JM, Hafez K, Davenport MS, Xiao H, Weizer AZ, et al. Clinicopathological Characterization of Renal Cell Carcinoma in Young Adults: a contemporary update and review of literature. Histopathology. 2019 Dec 23;his.14051.

11. Komai Y, Fujiwara M, Fujii Y, Mukai H, Yonese J, Kawakami S, et al. Adult Xp11 translocation renal cell carcinoma diagnosed by cytogenetics and immunohistochemistry. Clin Cancer Res Off J Am Assoc Cancer Res. 2009 Feb 15;15(4):1170–6.

12. Bruder E, Passera O, Harms D, Leuschner I, Ladanyi M, Argani P, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol. 2004 Sep;28(9):1117–32.

13. Heng DYC, Bukowski RM. Anti-angiogenic targets in the treatment of advanced renal cell carcinoma. Curr Cancer Drug Targets. 2008 Dec;8(8):676–82.

14. Hol JA, Jongmans MCJ, Littooij AS, de Krijger RR, Kuiper RP, van Harssel JJT, et al. Renal cell carcinoma in young FH mutation carriers: case series and review of the literature. Fam Cancer. 2020 Jan;19(1):55–63.

15. Argani P, Laé M, Ballard ET, Amin M, Manivel C, Hutchinson B, et al. Translocation Carcinomas of the Kidney After Chemotherapy in Childhood. J Clin Oncol. 2006 Apr 1;24(10):1529–34.

16. Donnelly LF, Rencken IO, Shardell K, Matthay KK, Miller CR, Vartanian RK, et al. Renal cell carcinoma after therapy for neuroblastoma. AJR Am J Roentgenol. 1996 Oct;167(4):915–7.

17. Sajid MI, Saleem A, Arshad M, Fadoo Z, Din NU. Metachronous translocation renal cell carcinoma in a child with successfully treated medulloblastoma. Childs Nerv Syst. 2020 Apr;36(4):861–4.

18. Geramizadeh B, Keshavarz P, Kashkooe A, Marzban M. Allograft renal cell carcinoma in pediatrics transplantation: A mini-review. Pediatr Transplant. 2020;24(1):e13614.

19. Indolfi P, Terenziani M, Casale F, Carli M, Bisogno G, Schiavetti A, et al. Renal cell carcinoma in children: a clinicopathologic study. J Clin Oncol Off J Am Soc Clin Oncol. 2003 Feb 1;21(3):530–5.

20. Edge SB, American Joint Committee on Cancer, editors. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. 648 p.

21. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. Trans Am Assoc Genitourin Surg. 1968;60:122–9.

22. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival, tumor recurrence and TNM staging. J Urol. 1999 Dec;162(6):1930–3.

23. Tsui KH, van Ophoven A, Shvarts O, Belldegrun A. Nephron-sparing surgery for renal cell carcinoma. Rev Urol. 1999;1(4):216–25.

24. Deng W, Chen L, Wang Y, Liu X, Wang G, Fu B. Partial nephrectomy versus radical nephrectomy for large (≥ 7 cm) renal tumors: A systematic review and meta-analysis. Urol Oncol. 2019;37(4):263–72.

25. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2011 Apr;59(4):543–52.

26. Sun M, Trinh Q-D, Bianchi M, Hansen J, Hanna N, Abdollah F, et al. A non-cancer-related survival benefit is associated with partial nephrectomy. Eur Urol. 2012 Apr;61(4):725–31.

27. Cook A, Lorenzo AJ, Salle JLP, Bakhshi M, Cartwright LM, Bagi D, et al. Pediatric renal cell carcinoma: single institution 25-year case series and initial experience with partial nephrectomy. J Urol. 2006 Apr;175(4):1456–60; discussion 1460.

28. Gil AT, Brett A, Cordinhã C, Gomes C. Bilateral renal cell carcinoma in a paediatric patient with tuberous sclerosis complex. BMJ Case Rep. 2013 Jul 12;2013.

29. Routh JC, Graham DA, Estrada CR, Nelson CP. Contemporary use of nephron-sparing surgery for children with malignant renal tumors at freestanding children's hospitals. Urology. 2011 Aug;78(2):422–6.

30. Jackson TJ, Williams RD, Brok J, Chowdhury T, Ronghe M, Powis M, et al. The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy: Report of the UK experience in the SIOP UK WT 2001 trial. Pediatr Blood Cancer. 2019;66(6):e27627.

31. Geller JI, Argani P, Adeniran A, Hampton E, De Marzo A, Hicks J, et al. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. Cancer. 2008 Apr 1;112(7):1607–16.

32. Ebert A, Gravou C, Stümpfl M, Rösch WH. [Renal cell carcinoma in childhood. Case report and review]. Urol Ausg A. 2003 Feb;42(2):263–8.

33. Indolfi P, Bisogno G, Cecchetto G, Spreafico F, De Salvo GL, Collini P, et al. Local lymph node involvement in pediatric renal cell carcinoma: a report from the Italian TREP project. Pediatr Blood Cancer. 2008 Oct;51(4):475–8.

34. Massari F, Di Nunno V, Gatto L, Santoni M, Schiavina R, Cosmai L, et al. Should CARMENA Really Change our Attitude Towards Cytoreductive Nephrectomy in Metastatic Renal Cell

Carcinoma? A Systematic Review and Meta-Analysis Evaluating Cytoreductive Nephrectomy in the Era of Targeted Therapy. Target Oncol. 2018;13(6):705–14.

35. Geller JI, Cost NG, Chi Y-Y, Perlman EJ, Kim Y, Cajaiba M, et al. A prospective study of pediatric renal cell carcinoma: A report from the Children's Oncology Group study AREN0321. J Clin Oncol. 2018 May 20;36(15_suppl):10516–10516.

36. Estrada CR, Suthar AM, Eaton SH, Cilento BG. Renal cell carcinoma: Children's Hospital Boston experience. Urology. 2005 Dec;66(6):1296–300.

37. Gershman B, Thompson RH, Boorjian SA, Larcher A, Capitanio U, Montorsi F, et al. Radical Nephrectomy with or without Lymph Node Dissection for High Risk Nonmetastatic Renal Cell Carcinoma: A Multi-Institutional Analysis. J Urol. 2018;199(5):1143–8.

38. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol. 2019;75(5):799–810.

39. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol. 2004 Mar;171(3):1071–6.

40. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval J-B, Bensalah K, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018 Aug 2;379(5):417–27.

41. Sun M, Meyer CP, Karam JA, de Velasco G, Chang SL, Pal SK, et al. Predictors, utilization patterns, and overall survival of patients undergoing metastasectomy for metastatic renal cell

carcinoma in the era of targeted therapy. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2018;44(9):1439–45.

42. Mourad WF, Dutcher J, Ennis RD. State-of-the-art management of renal cell carcinoma. Am J Clin Oncol. 2014 Oct;37(5):498–505.

43. MacArthur CA, Isaacs H, Miller JH, Ozkaynak F. Pediatric renal cell carcinoma: a complete response to recombinant interleukin-2 in a child with metastatic disease at diagnosis. Med Pediatr Oncol. 1994;23(4):365–71.

44. Malouf GG, Camparo P, Oudard S, Schleiermacher G, Theodore C, Rustine A, et al. Targeted agents in metastatic Xp11 translocation/TFE3 gene fusion renal cell carcinoma (RCC): a report from the Juvenile RCC Network. Ann Oncol Off J Eur Soc Med Oncol. 2010 Sep;21(9):1834–8.

45. Chowdhury T, Prichard-Jones K, Sebire NJ, Bier N, Cherian A, Sullivan MO, et al. Persistent complete response after single-agent sunitinib treatment in a case of TFE translocation positive relapsed metastatic pediatric renal cell carcinoma. J Pediatr Hematol Oncol. 2013 Jan;35(1):e1-3.

46. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet Lond Engl. 2019 18;393(10185):2051–8.

47. Choudhry H, Helmi N, Abdulaal WH, Zeyadi M, Zamzami MA, Wu W, et al. Prospects of IL-2 in Cancer Immunotherapy. BioMed Res Int. 2018;2018:9056173.

48. Dutcher JP, Mourad WF, Ennis RD. Integrating innovative therapeutic strategies into the management of renal cell carcinoma. Oncol Williston Park N. 2012 Jun;26(6):526–30, 532, 534.

49. Bauer M, Reaman GH, Hank JA, Cairo MS, Anderson P, Blazar BR, et al. A phase II trial of human recombinant interleukin-2 administered as a 4-day continuous infusion for children with refractory neuroblastoma, non-Hodgkin's lymphoma, sarcoma, renal cell carcinoma, and malignant melanoma. A Childrens Cancer Group study. Cancer. 1995 Jun 15;75(12):2959–65.

50. Aronson DC, Medary I, Finlay JL, Herr HW, Exelby PR, La Quaglia MP. Renal cell carcinoma in childhood and adolescence: a retrospective survey for prognostic factors in 22 cases. J Pediatr Surg. 1996 Jan;31(1):183–6.

51. Varan A, Akyuz C, Sari N, Buyukpamukçu N, Cağlar M, Buyukpamukçu M. Renal cell carcinoma in children: experience of a single center. Nephron Clin Pract. 2007;105(2):c58-61.

52. Upton MP, Parker RA, Youmans A, McDermott DF, Atkins MB. Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. J Immunother Hagerstown Md 1997. 2005 Oct;28(5):488–95.

53. Achkar T, Arjunan A, Wang H, Saul M, Davar D, Appleman LJ, et al. High-dose interleukin 2 in patients with metastatic renal cell carcinoma with sarcomatoid features. PloS One. 2017;12(12):e0190084.

54. Fishman M, Dutcher JP, Clark JI, Alva A, Miletello GP, Curti B, et al. Overall survival by clinical risk category for high dose interleukin-2 (HD IL-2) treated patients with metastatic renal cell cancer (mRCC): data from the PROCLAIMSM registry. J Immunother Cancer. 2019 27;7(1):84.

55. Escudier B, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, et al. CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma. Eur Urol. 2017;72(6):962–71.

56. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277–90.

57. Dutcher JP. Update on the biology and management of renal cell carcinoma. J Investig Med Off Publ Am Fed Clin Res. 2019;67(1):1–10.

58. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116–27.

59. Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1103–15.

60. Albiges L, Powles T, Staehler M, Bensalah K, Giles RH, Hora M, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. Eur Urol. 2019 Aug;76(2):151–6.

61. Ihara K. Immune checkpoint inhibitor therapy for pediatric cancers: A mini review of endocrine adverse events. Clin Pediatr Endocrinol Case Rep Clin Investig Off J Jpn Soc Pediatr Endocrinol. 2019;28(3):59–68.

62. Lucchesi M, Sardi I, Puppo G, Chella A, Favre C. The dawn of “immune-revolution” in children: early experiences with checkpoint inhibitors in childhood malignancies. Cancer Chemother Pharmacol. 2017 Dec;80(6):1047–53.

63. Davis KL, Fox E, Merchant MS, Reid JM, Kudgus RA, Liu X, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2020;21(4):541–50.

64. Akbaraly T, Saguintaah M, Topart D, Sirvent N. Efficacy and Toxicity of Fifth-line Nivolumab in a 15-Year-Old Girl With Metastatic Juvenile Renal Cell Carcinoma: J Pediatr Hematol Oncol. 2018 Apr;40(3):251–2.

65. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2020 May 15 - . Identifier NCT03595124, A Study to Compare Treatments for a Type of Kidney Cancer Called TFE/Translocation Renal Cell Carcinoma (tRCC) (AREN1721); Available from:https://clinicaltrials.gov/ct2/show/NCT03595124.

66. Matthay KK, Villablanca JG, Seeger RC, Stram DO, Harris RE, Ramsay NK, et al. Treatment of High-Risk Neuroblastoma with Intensive Chemotherapy, Radiotherapy, Autologous Bone Marrow Transplantation, and 13- *cis* -Retinoic Acid. N Engl J Med. 1999 Oct 14;341(16):1165–73.

67. Barrett D, Fish JD, Grupp SA. Autologous and allogeneic cellular therapies for high-risk pediatric solid tumors. Pediatr Clin North Am. 2010 Feb;57(1):47–66.

68. Childs R, Chernoff A, Contentin N, Bahceci E, Schrump D, Leitman S, et al. Regression of Metastatic Renal-Cell Carcinoma after Nonmyeloablative Allogeneic Peripheral-Blood Stem-Cell Transplantation. N Engl J Med. 2000 Sep 14;343(11):750–8.

69. Baek HJ, Han DK, Hwang TJ, Bae SH, Choi YD, Kook H. Long-term graft-versus-tumor effect following reduced intensity hematopoietic stem cell transplantation in a child with metastatic renal cell carcinoma. Pediatr Blood Cancer. 2012 Sep;59(3):583–5.

70. Abdellah A, Selma K, Elamin M, Asmae T, Lamia R, Abderrahmane M, et al. Renal cell carcinoma in children: case report and literature review. Pan Afr Med J. 2015;20:84.

71. Strouse JJ, Spevak M, Mack AK, Arceci RJ, Small D, Loeb DM. Significant responses to platinum-based chemotherapy in renal medullary carcinoma. Pediatr Blood Cancer. 2005 Apr;44(4):407–11.

72. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2017 Nov 6 - . Identifier NCT02363751, Study of Gemcitabine+Platinum Salt+Bevacizumab Combination for Metastatic Collecting Duct Carcinoma (GETUG-AFU 24) (BEVABEL); Available from: https://clinicaltrials.gov/ct2/show/NCT02363751. Available from: https://clinicaltrials.gov/ct2/show/NCT02363751

73. Gurrera A, Amico P, Di Cataldo A, Vasquez E, Magro G. [Carcinoma of the Bellini collecting duct in paediatric patients: a case report and review of the literature]. Pathologica. 2007 Oct;99(5):301–5.

74. Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Feb 10;23(5):1028–43.

75. Song SH, Jeong IG, You D, Hong JH, Hong B, Song C, et al. VEGF/VEGFR2 and PDGF-B/PDGFR-β expression in non-metastatic renal cell carcinoma: a retrospective study in 1,091 consecutive patients. Int J Clin Exp Pathol. 2014;7(11):7681–9.

76. Al-Daghmin A, Alhamss S, Al-Qasem K, Al-Najjar H, Al-Smadi K, Olaimat A, et al. Patterns of management of translocation renal cell carcinoma. Turk J Urol. 2018 Nov;44(6):467–72.

77. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013 Aug 22;369(8):722–31.

78. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet Lond Engl. 2011 Dec 3;378(9807):1931–9.

79. Ambalavanan M, Geller JI. Treatment of advanced pediatric renal cell carcinoma. Pediatr Blood Cancer. 2019;66(8):e27766.

80. Parikh J, Coleman T, Messias N, Brown J. Temsirolimus in the treatment of renal cell carcinoma associated with Xp11.2 translocation/TFE gene fusion proteins: a case report and review of literature. Rare Tumors. 2009 Dec 28;1(2):e53.

81. Argani P, Hicks J, De Marzo AM, Albadine R, Illei PB, Ladanyi M, et al. Xp11 translocation renal cell carcinoma (RCC): extended immunohistochemical profile emphasizing novel RCC markers. Am J Surg Pathol. 2010 Sep;34(9):1295–303.

82. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015 Nov;16(15):1473–82.

83. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer. 2010 Sep 15;116(18):4256–65.

84. Schostak M, de Geeter P, Decker T, Resch A, Quiering C, Schmitz S. A Phase 4 Study of Everolimus to Evaluate Efficacy and Safety in Patients with Metastatic Renal-Cell Carcinoma after Failure of First-Line Sunitinib or Pazopanib (SUNPAZ). Urol Int. 2019 Nov 14;1–6.

85. Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol. 2016 Mar;17(3):378–88.

86. Pressey JG, Wright JM, Geller JI, Joseph DB, Pressey CS, Kelly DR. Sirolimus therapy for fibromatosis and multifocal renal cell carcinoma in a child with tuberous sclerosis complex. Pediatr Blood Cancer. 2010 Jul 1;54(7):1035–7.

87. Alsidawi S, Kasi PM. Exceptional response to everolimus in a novel tuberous sclerosis complex-2 mutation-associated metastatic renal-cell carcinoma. Cold Spring Harb Mol Case Stud. 2018;4(2).

88. Tsuda M, Davis IJ, Argani P, Shukla N, McGill GG, Nagai M, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res. 2007 Feb 1;67(3):919–29.

89. Wagner AJ, Goldberg JM, Dubois SG, Choy E, Rosen L, Pappo A, et al. Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: results of a multicenter phase 2 trial. Cancer. 2012 Dec 1;118(23):5894–902.

90. Choueiri TK, Plimack E, Arkenau H-T, Jonasch E, Heng DYC, Powles T, et al. Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2017 Sep 10;35(26):2993–3001.

91. Chuk MK, Widemann BC, Minard CG, Liu X, Kim A, Bernhardt MB, et al. A phase 1 study of cabozantinib in children and adolescents with recurrent or refractory solid tumors, including CNS tumors: Trial ADVL1211, a report from the Children's Oncology Group. Pediatr Blood Cancer. 2018 Aug;65(8):e27077.

92. ClinicalTrials.gov [Internet]. National Library of Medicine (US). 2020 May 18 - . Identifier NCT02867592, Cabozantinib-S-Malate in Treating Younger Patients With Recurrent, Refractory, or Newly Diagnosed Sarcomas, Wilms Tumor, or Other Rare Tumors (ADVL 1622); Available from:https://clinicaltrials.gov/ct2/show/NCT02867592.

93. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016 Jul;17(7):917–27.

94. Bodnar L, Kopczyńska A, Żołnierek J, Wieczorek-Rutkowska M, Chrom P, Tomczak P. Real-world Experience of Cabozantinib as Second- or Subsequent Line Treatment in Patients With Metastatic Renal Cell Carcinoma: Data From the Polish Managed Access Program. Clin Genitourin Cancer. 2019;17(3):e556–64.

95. Procopio G, Prisciandaro M, Iacovelli R, Cortesi E, Fornarini G, Facchini G, et al. Safety and Efficacy of Cabozantinib in Metastatic Renal-Cell Carcinoma: Real-World Data From an Italian Managed Access Program. Clin Genitourin Cancer. 2018;16(4):e945–51.

96. Choueiri TK, Hessel C, Halabi S, Sanford B, Michaelson MD, Hahn O, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. Eur J Cancer Oxf Engl 1990. 2018;94:115–25.

97. Wedekind MF, Ranalli M, Shah N. Clinical efficacy of cabozantinib in two pediatric patients with recurrent renal cell carcinoma. Pediatr Blood Cancer. 2017 Nov;64(11).

98. Kurahashi R, Kadmoatsu T, Baba M, Hara C, Itoh H, Miyata K, et al. MicroRNA-204-5p: A novel candidate urinary biomarker of Xp11.2 translocation renal cell carcinoma. Cancer Sci. 2019 Jun:110(6): 1897-908

Figure Legends

Figure 1. Methodology flow chart.

Table Legends

Table 1. Paediatric renal cell carcinoma patient characteristics

Supporting Information Legends

Supporting Information Figure S1 - Age-standardised rate per million of renal tumours from 1996 to 2010. Adapted from Nakata K and IICC-3 Contributors (2020). Incidence of childhood renal tumours: an international population-based study. Int J Cancer. DOI://doi.org/10/1002/ijc.33147

Supporting Information Table S1 – Search strategies on all databases

Supporting Information S2 – Supplement to table 1 for details regarding patient characteristics