Paediatric and young adult renal cell carcinoma

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<table>
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<td>Renal cell carcinoma</td>
<td>RCC</td>
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<tr>
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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\textsuperscript{(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.

Subclassification 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\textsuperscript{(2,6,9)}. Additionally, paediatric RCC has been reported in
patients suffering from another underlying disorder\textsuperscript{(3,14)} or having undergone prior
chemotherapy\textsuperscript{(15)}. A specific subgroup exists as a secondary malignancy following
neuroblastoma\textsuperscript{(5,16)} with one reported case of secondary tRCC in a child following
medulloblastoma\textsuperscript{(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\textsuperscript{(6)}. In addition, one
review has reported only 12 cases of allograft RCC in children\textsuperscript{(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\textsuperscript{(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
synthesize 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-\(\alpha\))\(^{(39)}\).

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 therapy⁴¹. 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 base⁴²–⁴⁵. Secondary metastasectomy is recommended if there is detectable remaining disease⁵.

(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 lacking⁴⁶. 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 RCC⁴⁶.

(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 cells⁴⁷,⁴⁸.
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 5\(^{th}\) 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\(^\text{72}\). Gurrera reported a case of collecting duct carcinoma in an 11-year old boy and described only 8 further reported cases in the literature\(^\text{73}\).

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\(^\text{60}\). 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\(^\text{74,75}\) 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\(^\text{44}\). One predominantly adult series with 6 patients with metastatic tRCC reported at least stable disease in 5 and disease progression in 1\(^\text{76}\).
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.

**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**


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.


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