Received: 10 July 2020 | Revised: 7 August 2020 | Accepted: 8 August 2020

DOI: 10.1002/pbc.28675

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

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REVIEW

Pediatric and young adult renal cell carcinoma

Satyajit Ray[1] | Robert Jones[2] | Kathy Pritchard-Jones[3] | Kristina Dzhuma[3] | Marry van den Heuvel-Eibrink[4] | Godelieve Tytgat[4] | Justine van der Beek[4] | Grenville Oades[5] | Dermot Murphy[1]

[1] Department of Paediatric Oncology, Royal Hospital for Children, Glasgow, Scotland, UK

[2] Beatson West of Scotland Cancer Centre, Institute of Cancer Sciences, University of Glasgow, Glasgow, Scotland, UK

[3] University College London Institute of Child Health, London, UK

[4] Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[5] Department of Uro-Oncology, Queen Elizabeth University Hospital, Glasgow, Scotland, UK

Correspondence
Satyajit Ray, Department of Paediatric Haematology and Oncology, Royal Hospital for Children, Ward 6A, Glasgow G51 4TF, UK.
Email: buburay@hotmail.com

Abstract

Renal cell carcinoma (RCC) is rare in children but is the most common renal tumor in adults. Pediatric RCC has different clinical characteristics, histopathology, and treatment compared with 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 localized 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. Pediatric 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 pediatric RCC, including the evolving role of precision medicine.

KEYWORDS
pediatrics, renal cell carcinoma, targeted therapy, treatment

1 | INTRODUCTION

In Europe, around 1000 children are diagnosed with a malignant renal tumor annually.[1] Renal cell carcinomas (RCC) make up 1.9% to 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 pediatric RCC is increasing globally, almost doubling, in 0- to 19-year-olds between the 1990s and 2010s (Supporting Information Figure S1). The relative incidence compared with the much commoner Wilms tumor (WT) varies with age, such that over half of all pediatric renal tumors are RCC in 14-year-olds, and RCC remains the predominant renal tumor 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) rate of > 80% in newly diagnosed 13- to 24-year-old RCC patients.[7]

Pediatric 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

Abbreviations: ccRCC, clear-cell renal cell carcinoma; CN, cytoreductive Nephrectomy; COG, Children's Oncology Group; CPI, checkpoint inhibitor; CTLA-4, cytotoxic T-cell lymphocyte-associated antigen 4; EFS, event-free survival; HSCT, Hematopoietic stem cell transplantation; IFN-α, interferon-alpha; IICC-3, International Incidence of Childhood Cancer Volume 3; IL-2, interleukin-2; mTOR, mammalian target of rapamycin; NSS, nephron-sparing surgery; OS, overall survival; PD-1, programmed cell death protein 1; PDGF, platelet-derived growth factor; PD-L1, programmed death ligand 1; PFS, progression-free survival; PN, partial nephrectomy; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma; RCT, randomized controlled trial; RLND, radical lymph node dissection; RN, radical nephrectomy; RTK, receptor tyrosine kinase; SABR, stereotactic ablative radiotherapy; SIOP, The International Society of Paediatric Oncology; TKI, tyrosine kinase inhibitor; TNM, tumor, node, metastasis (staging system); tRCC, translocation renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VHL, Von Hippel-Lindau; WT, Wilms tumor

Health Organization recommends diagnosis by morphological features together with immunocytochemistry or fluorescence in situ hybridization.

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 upregulation of angiogenic growth factors. Vascular endothelial growth factor (VEGF)– and platelet-derived growth factor (PDGF) receptors are involved in tumor angiogenesis and tumor cell growth, allowing for treatment with antiangiogenic 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.

Subclassification of pediatric 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.

Pediatric RCC occurs in equal frequency in males and females before the age of 15 years compared with a male predominance in adults.[2,6,9] Additionally, pediatric 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- to 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 pediatric 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 report on the specific subtypes, treatments, and outcomes of pediatric RCC.

2 | 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).

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

3 | TREATMENTS

3.1 | Nephrectomy

Regardless of subtype, surgery is the cornerstone of therapy for pediatric RCC[1,2] as no literature supports survival benefit from systemic therapy or radiotherapy alone. Localized 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 standardized classification of tumor, lymph node and metastasis (TNM).[20] Comparisons between pediatric and adult patients are hindered by several pediatric 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 tumors ≥7 cm found that although PN preserved renal function, there was a higher surgical complication rate and no difference in cancer-specific survival.[24] A prospective randomized controlled trial (RCT) by the European Organisation for Research and Treatment of Cancer compared RN versus PN in adults with tumors < 5 cm (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 noninferiority for PN versus RN.

Adult data suggest overall noncancer-related survival is directly related to total nephric function, necessitating consideration of PN[26]; however, these data have not been reproduced in pediatrics. Evolving nephron-sparing techniques (robotic surgery, radiofrequency ablation, and cryotherapy) may improve future outcomes.

PN in pediatric 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 pediatric renal tumors including three 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 pediatric 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 pediatric 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 tumor biopsy to prevent over- or undertreatment in these patients. Biopsy was found to be less effective, when compared with central pathology review nephrectomy diagnoses, at identifying

TABLE 1 Pediatric articles reviewed with pediatric renal cell carcinoma patient characteristics

	Author	Year	Country	Total number of patients	Gender		Site			Age range in years (median)	Treatment	Tumor subtype (pRCC, tRCC, ccRCC, chRCC, NOS)	Stage (TNM or modified Robson)				Outcomes
					Male	Female	Left	Right	Bilateral				I	II	III	IV	
1	Jackson TJ et al.	2019	UK	10	N/A	N/A	N/A	N/A	N/A	6 m-≥10 yr	Nephrectomy	N/A	N/A	N/A	N/A	N/A	N/A
2	Geller JI et al.	2015	USA	120	57	63	N/A	N/A	2	1.9-22.1 yr (12.9 yr)	RN x 88, NSS x 18, biopsy x 14	56x tRCC, 20x pRCC, 13x chRCC, 4x oncocytoma, 1x ccRCC. 25x NOS (6 unclassifiable)	35	11	43	25	N/A
3	Barroca H et al.	2014	Portugal	1	1		1			12 yr	PN	RCC NOS	N/A	N/A	N/A	N/A	N/A
4	Gil AT et al.	2013	Portugal	1	1				1	17 yr	Bilateral PN	L biopsy ccRCC, R biopsy chRCC	1				Alive
5	Gilani JA et al.	2011	Pakistan	1	1			1		15 yr	RN	RCC NOS	1				N/A
6	Alrashdi I et al.	2009	UK	1	1			1		11 yr	RN	pRCC	1				Alive
7	Wu A et al.	2008	USA	13	9	4	N/A	N/A	N/A	9-23 yr (17 years)	5x PN, 8x RN, 1x experimental vaccine and autologous BMT, 1x experimental protocol, 1x IL-2 + cisplatin-based CTx + RTx + sunitinib, 1x reresection, 1x PN on contralateral tumor	6x tRCC, 5x ccRCC, 1x pRCC, 1x NOS	7	2	2	2	4 dead, 9 alive
8	Selle B et al.	2006	Germany	49	24	25	25	20	2	1.2-15.9 yr (10.6 yr)	2 of 4 with distant mets had ITx with CTx with surgery. 36x RN, 5x PN, 22/47 (46.8%) adjuvant Tx, 4x RTx (1x adjuvant, 2x with chemo, 1x whole-body hyperthermia). 19 had CTx (11 upfront suspected Wilms). 4x ITx	16x pRCC, 11x tRCC, 12x NOS, 3x ccRCC, 2x pRCC + ccRCC, 2x chRCC, 1x sarcomatoid, 2x post-NBL-RCC.	17	11	4	8	5 dead, 42 alive

(Continues)

TABLE 1 (Continued)

	Author	Year	Country	Total number of patients	Gender		Site			Age range in years (median)	Treatment	Tumor subtype (pRCC, tRCC, ccRCC, chRCC, NOS)	Stage (TNM or modified Robson)				Outcomes
					Male	Female	Left	Right	Bilateral				I	II	III	IV	
9	Indolfi P et al.	2012	Italy	14	7	7	6	6		1.6-16 yr (12.9 yr)	9x RN, 6x CTx, 9x ITx, 2x adjuvant antiangiogenic, 4x RTx.	5x tRCC, 2x pRCC, 5x ccRCC, 2x NOS.				14	14 dead
10	Indolfi P et al.	2008	Italy	16	7	9	11	5		1.8-17.9 yr (10 yr)	RNx 16, 4x pre-op CTx. 9x RLND, 7x limited LND. 3x CTx postop, 2x RTx, 12x ITx	N/A			16		8 alive, 6 dead
11	Winarti NW et al.	2008	Bali, Indonesia	1	1			1		11 yr	Nephroureterectomy	tRCC				1	Alive
12	Menon P et al.	2004	India	1		1		1		8 yr	RN	Cystic RCC	N/A	N/A	N/A	N/A	Alive
13	Grant R et al.	1997	Canada	1	1			1		7 yr	RN, LND, CTx . Left thoracotomy and wedge resection post-CTx, then right thoracotomy and right lower lobe medial basilar segmentectomy	N/A				1	Alive
14	Carcao MD et al.	1998	Canada	16	5	11	N/A	N/A	N/A	3-19 (median 9 yr)	10x RN, 4x simple nephrectomy (+ 1x bilateral simple), 4x RTx, 2x palliative RTx, 4x CTx, 1x thoracotomy, 1x ITx	5x pRCC, 9x ccRCC, 1x chRCC, 1x granular-cell type RCC.	3		7	6	10 alive, 6 dead
15	Hol JA et al.	2019	Netherlands	2		2	1	1		15 yr and 18 yr	RN x 1, PN x 1	N/A	N/A	1	N/A	N/A	2 alive
16	Argani P et al.	2006	USA	5	2	3	5	1		6-22 yr	4x RN, 1x surgical resection ?RN. 1x PN. All received prior CTx. 1x prior RTx	All tRCC.	N/A	N/A	1	1	1 alive, 1 dead
17	Donnelly LF et al.	1996	USA	1	1				1	12 yr	RN + wedge biopsy of opposite kidney	RCC NOS	N/A	N/A	N/A	N/A	Alive

(Continues)

TABLE 1 (Continued)

	Author	Year	Country	Total number of patients	Gender		Site			Age range in years (median)	Treatment	Tumor subtype (pRCC, tRCC, ccRCC, chRCC, NOS)	Stage (TNM or modified Robson)				Outcomes
					Male	Female	Left	Right	Bilateral				I	II	III	IV	
18	Sajid MI et al.	2019	Pakistan	1	1			1		16 yr	RN and adrenalectomy	tRCC	1				N/A
19	Indolfi P et al.	2003	Italy	41	18	23	N/A	N/A	1	1.8-17.9 (10.3 yr)	21x RN with adrenalectomy, 15x RN with RLND, 5x biopsy alone, 24x CTx, 11 x ITx, 7x RTx	7x pRCC, 24x ccRCC, 4x granular-cell RCC, 5x tRCC, 1x chRCC. 1x bilateral	18	1	12	9	24 alive, 15 dead
20	Cook A et al.	2006	Canada	15	N/A	N/A	N/A	N/A	N/A	Mean age 7.9 yr	RNx10, PNx5	8x pRCC, 7x ccRCC	N/A	N/A	N/A	6	14 alive, 1 dead
21	Baek HJ et al.	2012	Korea	1	1			1		2 yr	Preop CTx then RN with RLND. Postop ITx. Conditioning CTx and 2x allogeneic HSCT	pRCC				1	Alive
22	Abdellah A et al.	2015	Morocco	1	1		1			9 yr	RN with RLND	RCC NOS	1				Alive
23	Strouse JJ et al.	2005	USA	2	1	1	1	1		15 yr and 17 yr	2x CTx, 1x RN, 1x palliative RTx	2x RMC				2	2 dead
24	Chowdhury T et al.	2013	UK	1		1	1			11 yr	RN with RLND, sunitinib at relapse, exploratory thoracotomies	tRCC				1	Alive
25	Ambalavanan M et al.	2019	USA	24	13	11	N/A	N/A	N/A	3-27 yr (15 yr)	19x RN, 3x PN, 7x RLND, 11 patients received medicinal anticancer therapies. 10 × antiangiogenic, 8x CTx, 7x mTOR inhibitor, 3x ITx, 4x small-port RTx,	16x tRCC, 6x pRCC, 1x ccRCC, 1x chRCC.	8	2	3	11	12 alive, 11 dead
26	Pressey JG et al.	2010	USA	1	1				1	7 yr	Right RN, sirolimus	chRCC	N/A	N/A	N/A	N/A	Alive

(Continues)

TABLE 1 (Continued)

	Author	Year	Country	Total number of patients	Gender		Site			Age range in years (median)	Treatment	Tumor subtype (pRCC, tRCC, ccRCC, chRCC, NOS)	Stage (TNM or modified Robson)				Outcomes
					Male	Female	Left	Right	Bilateral				I	II	III	IV	
27	Wedekind MF et al.	2017	USA	2	1	1	N/A	N/A	N/A	16 yr, 12 yr	16 yr – RN + adjuvant sunitinib, then intratumoral oncolytic virotherapy, zoledronates and ITx. Cabozantinib 12 yr – RN + adjuvant sunitinib, RTx, cabozantinib	tRCC				2	1 alive, 1 dead
28	Unal E et al.	2020	Turkey	3	2	1	N/A	N/A	N/A	6 yr, 11 yr, 13.5 yr	RN x 3	N/A	2			1	3 alive
29	Schultz TD et al.	2011	Canada	1	1		1			9 yr	RN	pRCC	1				Alive
30	Salehipour M et al.	2009	Iran	1		1		1		3 yr	RN with regional lymphadenectomy	Granular RCC	N/A	N/A	N/A	N/A	Alive
31	Reface MA et al.	2007	Canada	1	1		1			17 yr	RN and LN sampling. 2x IL-2 and IFN. 1x irofulven. 2x cyclophosphamide + topotecan. palliative debulking	pRCC Type 2				1	Dead
32	Birken G et al.	1985	USA	1		1		1		15 yr	Radical adrenonephroureterectomy + regional lymphadenectomy. palliative RTx. IFN + cyclic CTx.	Well-differentiated RCC				1	Dead

Abbreviations: BMT, bone marrow transplant; ccRCC, clear-cell renal cell carcinoma; chRCC, chromophobe renal cell carcinoma; CTx, chemotherapy; Dx, diagnosis; HSCT, hematopoietic stem cell transplantation; IFN, interferon; ITx, immunotherapy; N/A, not available; NBL, neuroblastoma; NOS, not otherwise specified; NSS, nephron-sparing surgery; PN, partial nephrectomy; pRCC, papillary renal cell carcinoma; RLND, radical lymph node dissection; RN, radical nephrectomy; RTx, radiotherapy; tRCC, translocation renal cell carcinoma; yr/yrs, years.

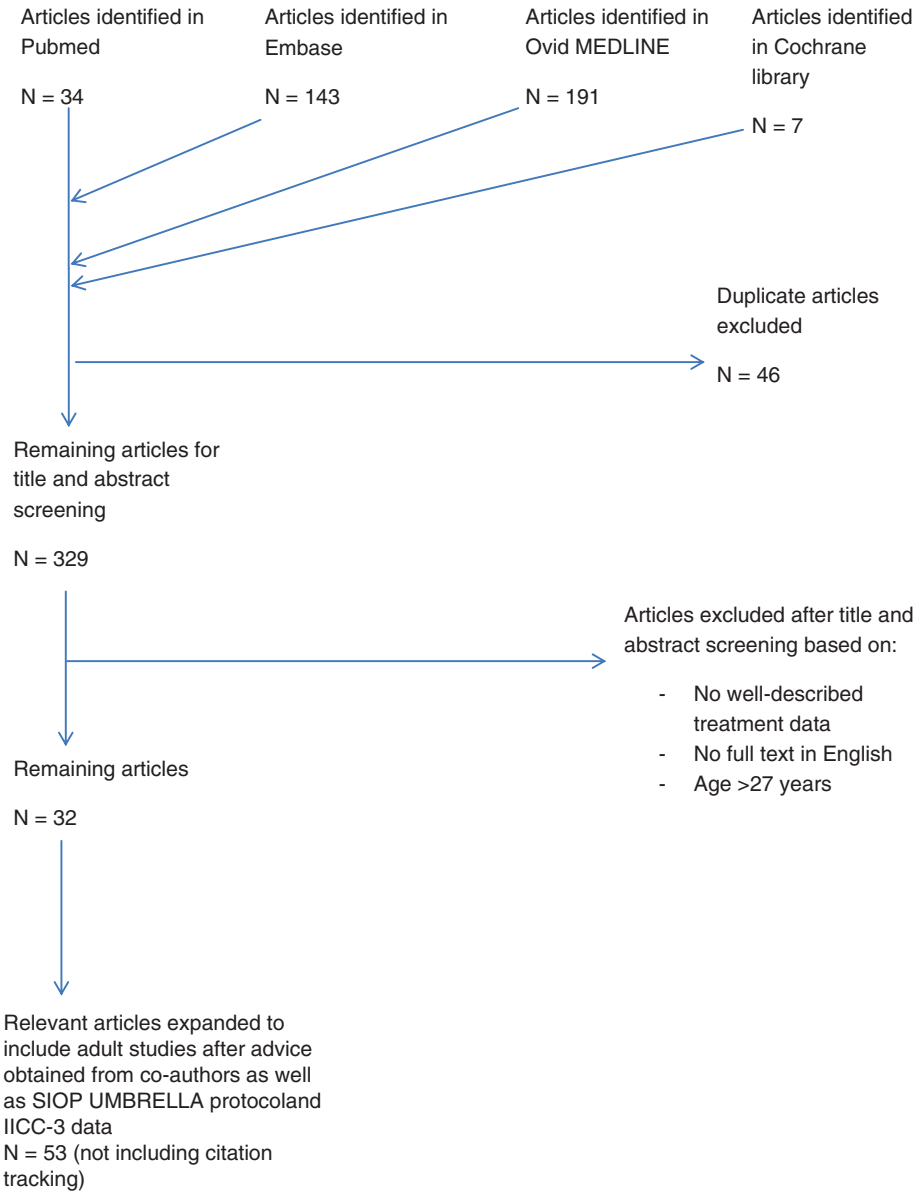

FIGURE 1 Methodology flow chart

non-WTs compared with 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 favoring one approach over the other, but the best method could be answered by transatlantic collaboration.

3.2 | Radical lymph node dissection

The role of radical lymph node dissection (RLND) is controversial, and there is little evidence regarding efficacy in adult or pediatric 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 suggest improved OS with RLND.[32,33]

The first national, prospective pediatric RCC study including 120 patients with unilateral RCC showed that lymph node disease was common in patients with small primary tumors, 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 were 87.2% and 94.6%, respectively. Within that group, 15 of 16 patients with nodal-spread only had complete resection including RLND, and their four-year EFS and OS were 87.5% and 93.8%,

respectively. Although nonrandomized, this study showed favorable outcomes in completely resected RCC independent of adjuvant therapy, even in cases of locally advanced disease or lymph node involvement.[35]

However, most renal tumors are suspected of being WT which does not involve extensive RLND upfront. In COG and SIOP protocols, lymph node sampling is advised in all tumor 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 nine 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 pediatric RCC, and this should be considered in contrast to the suggested lack of benefit in adult RCC.

3.2.1 | Management of unresectable tumors and metastatic RCC

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

Surgery

Although controversial, cytoreductive nephrectomy (CN) to reduce tumor 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 toward 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 noninferiority study, closing early due to nonaccrual. 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 were 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]

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 tumor but prospective data are 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]

Immunotherapy

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

There are reports of successful treatment with IL-2 in metastatic pediatric 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 show median OS with IL-2 alone of 64.5 months in favorable-risk patients, 57.6 months in intermediate-risk, and 14 months in poor-risk patients. Two-year survival rates for the same risk groups were 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 tumors.

A phase 3 trial in adults with metastatic ccRCC showed significant improvement in OS and fewer adverse effects with nivolumab (anti-PD-1) compared with 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 with 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 with 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 with 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 pediatric 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 fifth-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 pediatric RCC, but larger studies with carefully selected patient groups are warranted.

Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation (HSCT) is a rescue therapy used to treat various pediatric solid tumors.[66,67]

In adults, HSCT has been used in metastatic RCC. One study reported nine of 19 adults with almost exclusively metastatic ccRCC alive between 287 and 831 days after HSCT.[68]

Although a single case reported a two-year-old with papillary RCC demonstrating PFS of 5.7 years after HSCT,[69] there is no strong evidence for HSCT in metastatic pediatric RCC.

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 eight further reported cases in the literature.[73]

This tumor 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.

TKIs

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

Sunitinib, a multitargeted TKI that 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 with 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 six patients with metastatic tRCC reported at least stable disease in five and disease progression in one.[76] A case report showed stable disease at two years in a pediatric 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 with 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 pediatric RCC are lacking. Novel therapies are promising but early-phase trials in pediatric patients and appropriately powered phase 3 trials are needed.

mTOR inhibitors: Everolimus

The mammalian target of rapamycin (mTOR) is involved in the growth and proliferation of malignant cells,[80] and inhibitors are used in adult RCC. Argani showed increased expression of phosphorylated S6 in Xp11 tRCC and suggested the mTOR pathway as a possible therapeutic target.[81] A phase 2 RCT in pretreated adults with advanced-stage ccRCC showed a PFS of 14.6 months with everolimus plus lenvatinib (multikinase inhibitor) compared with 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 pretreated 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 toward everolimus being specifically active in chromophobe RCC.[85]

mTOR inhibitors are approved in some pediatric tumors. 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 pediatric RCC are scarce, and trials in a similar vein to the adult population could help establish their role.

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 upregulated 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 with everolimus regardless of prior therapy with tolerable adverse effects.[93] Another study in pretreated 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 eight 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 with 5.3 months with sunitinib.[96]

The first published data of cabozantinib in pediatric RCC involved two 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 multitargeted agents are promising.

4 | DISCUSSION

Advances in the treatment of adult RCC have formed the basis of pediatric 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 tumor subtypes could utilize 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 pediatric tumors allowing for treatment of actionable mutations. Similar initiatives are established in other European countries and North America.

Localized 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 while the efficacy and choice of best second-line TKIs are unknown in pediatric RCC. Despite novel targeted therapies in adult RCC, predictive biomarkers of response have not been thoroughly investigated in pediatrics, 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 pediatric RCC, the documented rising incidence, and poor outlook in advanced disease highlight the need for international collaboration.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ORCID

Satyajit Ray https://orcid.org/0000-0003-0581-5420
Kathy Pritchard-Jones https://orcid.org/0000-0002-2384-9475
Kristina Dzhuma https://orcid.org/0000-0003-4559-3252

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Ray S, Jones R, Pritchard-Jones K, et al. Pediatric and young adult renal cell carcinoma. *Pediatr Blood Cancer*. 2020;67:e28675. https://doi.org/10.1002/pbc.28675