Wilms' Tumor in Resource-Challenged Nations

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Sharpening the needlepoint of surgical expertise will, of itself, not compensate for the major infrastructural deficiencies, but must proceed in tandem with resource development and allow health planners to realize that pediatric surgical oncology is a cost-effective service that can uplift regional services.—Hadley et al. (2012) [1].

22.1 Introduction

Wilms' tumor (WT) with a quoted 5-year overall survival (OS), ~90% in high-income countries (HIC) cannot still be considered as conquered because 85% of these tumors occur in low-income countries (LIC) where its management still poses enormous challenges and the OS rates are still in the range of 25–50% [2]. The various contributing reasons that are known to exist may vary from country to country, but broadly include late presentations, cultural issues, lack of education, malnutrition, drug toxicity, and limited resources as regards chemotherapy (ChT) drugs, radiotherapy (XRT), and trained pediatric surgeons. Early abandonment of therapy is common. In many African countries including South Africa, the WT patients have been also afflicted with concomitant tuberculosis and/or human-immunodeficiency virus (HIV). In low-middle-income country (LMIC) such as India, the situation may not be very different because of the rampant disparities between different centers as regards the clientele and the available resources. Even the premier teaching tertiary institutions in the capital of India lack local housing, services of pediatric oncologists and radiologists, and intensive care beds for cancer patients. The focus of local governments is still on primary healthcare, and the high-end care available in corporate hospitals is beyond the reach of common people. This results only a few children with WT in LMIC receiving protocolized curative therapy; in LIC; even palliative care is usually not available [3].

Such prevailing situations had made Hadley et al. from South Africa to suggest in 2001 that in the third world, keeping in mind the limited resources that need to be used cost-effectively, the goal of therapy in the high-risk WT such as diffuse anaplastic WT patients should be palliative, and one may choose not to treat this cohort with an intent to cure [4].

It is then obvious that situations are significantly different between LMIC and HIC, and we need to create regimens in LMIC that we could achieve to cure as many children as possible with the locally available resources [5].

22.2 Challenges to WT Care in LMIC

The poor outcomes of children with WT in LMIC could be attributed to many factors; these could be related to the existing healthcare delivery system,

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Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_22

biological differences in the ethnicities, cultural and socioeconomic factors, and the burden of disease at initial presentation [6, 7]. Late presentation, treatment abandonment, and on-therapy mortality due to gaps in standard of care account for most of the poor outcomes in such settings [7].

22.2.1 Late Presentations

Less than 10% patients of WT are known to be in stage I when they reach the specialized centers in LMIC [8], whereas stage I represented ~40% of WT in HIC even in the 1980s and 1990s [9, 10]. Half to two-thirds of patients of WT reporting to major referral centers in LMIC such as Lebanon and South Africa presented with advanced stage disease [10, 11], whereas most of the patients in North America and Europe would present in stage I or II disease. Not only these advanced stages of WT require more toxic and intensive adjunct therapies associated with their attendant morbidity and mortality, but it is also known that WT that present with advanced stage disease could acquire therapy-resistant biologic features, e.g., *TP53* mutation and *MYCN* alteration [12].

22.2.2 Abandonment of Therapy

Completion of therapy for WT in LMICs remains a significant challenge. An audit of eight referral centers in sub-Saharan Africa revealed treatment abandonment rates as high as 14–48% [13]; Sen et al. reported 23% abandonment rate from Asia [14]. The reasons underlying abandonment of therapy include illiteracy, socioeconomic, and cultural factors, and non-availability of healthcare closeby [15]. In sub-Saharan Africa, ˜20% of children with WT have lost a parent to HIV, thus diminishing the family support; further these children may have concomitant HIV and/or tuberculosis [16].

22.2.3 Malnutrition

Malnutrition is rampant in patients of WT in LMIC. Moreira et al. mentioned that more than one-fifth of patients of WT had clinical nutritional indices less than 2SD; 7% had cachexia defined as clinical nutritional indices less than 3D [17]. Furthermore, 22% presented with anemia (<8 g/L hemoglobin) [17]. Malnutrition is known to affect surgical mortality and morbidity as well as ChT toxicity. The Pediatric Oncology in Developing Countries (PODC) Committee of the International Pediatric Oncology Society (SIOP) suggests administering only two-thirds of the ChT doses to patients with malnutrition [18].

22.2.4 Socioeconomic Factors

Sen et al. emphasized on the socioeconomic factors contributing to late presentation and abandonment of therapy in Asian countries, with many of the patients coming from far-off [14]. Moreira et al. emphasized that the 55% of the children's families had a poor socioeconomic level defined either with an average income below the minimum wage for each household member or, if this was unknown, defined by lack of access to potable water and electricity, in their series; 35% of parents were illiterate [17]. The distance to travel to the center was more than 100 km in half of their patients, and in more than one-third of patients, the travel time was more than 3 h [17].

22.2.5 Cultural Issues

Prevailing cultural issues, poor socioeconomic status of families, illiteracy, and non-availability of primary health services close to home in LMIC help the traditional healers or quacks to flourish. In South Africa, more than three-fourths of WT patients were initially taken to sangoma or nyanga, the traditional healer and a trial of alternative therapy before coming to the hospital [19]. Fear of hospital detention is also known to result in both delayed presentation and abandonment of therapy [20]. These cultural issues need redressal, and society's confidence in modern medicine has to be enhanced before such a situation could be reversed.

22.2.6 Biology

Ethnicity and hereditary predisposition also contributes to a particular outcome. Increased incidence of WT in certain Kenyan tribes pointed towards race disparities in biology. The molecular markers of WT in Kenyan patients when compared to the North American patients (both from black and white populations) pointed to far worse biological behavior and treatment resistance [21, 22].

22.3 SIOP PODC and Adapted Regimens

SIOP PODC have drafted an outline of adapted treatment regimens to manage pediatric cancer including WT in LMIC. The adaptations include focus on preventing treatment abandonment, reduction in doses of ChT drugs to reduce deaths due to drug toxicity, adapting the diagnostic strategy, modification of staging and risk stratification, local control, nutritional assessment, and supportive care [6]. The adapted regimen in LMIC may be of different intensity, than the regimens used in HIC or simply different, e.g., using additional ChT for WT when XRT is not available in a particular center or region. PODC has designed guidelines for at least four malignancies including WT for settings in LIC where only the minimal requirements for treatment with curative intent are available (defined as setting 1) [5–7].

It is not easy to promote the idea of adapted regimens for more than one reason. Above all, there is a general tendency to resist change and preserve the status quo, especially when there is insufficient local data on the follow-ups and outcomes of patients from LMIC. There are also perceived ethical concerns about using modified or totally different regimens. Also, lot of efforts go in formulating the adapted regimens which local LMIC physicians may not be willing to put [5]. So, many continue with the misperception that "more is better" and question why to adapt.

ICMR consensus guidelines published from India in 2017 are not very different from that from SIOP 2001 protocol [23, 24]. There is no denying the fact that there are pediatric cancer units available in India that offer the highest chance of care, but the level of care at various centers is obviously heterogeneous and in the absence of insurance coverage for most, the caretakers have no choice other than to get their wards with WT treated in a sub-optimal center close to their home. We must acknowledge that ChT of solid tumors in majority of the tertiary centers is still being provided by the busy pediatric surgeons for whom pediatric surgical oncology forms less than 3–5% of their total practice, and histopathology reports are often delayed or unreliable as the local pathologists are still not comfortable to report tumors that have undergone ChT-induced changes after administration of neoadjuvant ChT and radiotherapy (XRT) is unavailable, to count a few [25]. We need to wait and see the impact of government schemes in India like Ayushman Bharat—Pradhan Mantri Jan Arogya Yojana (AB-PMJAY) on the heterogenicity of healthcare provided to WT patients.

PODC framework may help selecting an "optimal" adapted regimen that may have the highest probability of cure in the given circumstances. Once put in practice, there should be a willingness for periodic evaluation and constant improvisation, as it is possible that the initially selected regimen may give sub-optimal outcomes. On the other hand, it is possible that the locally available resources get augmented, and even a LMIC center moves on from the best adapted regimen to a situation where a patient with relapsed WT could be treated with the high dose-ChT and autologous transfusion similar to a HIC sitting [5]. This dream could come true when these centers could invest on providing more human resources, better intensive care, better ChT drugs and antibiotics, provision of guest house for patients coming from far, etc.

22.4 Suggested Management for LMIC

The author had switched from COG to SIOP and then to UKCCLG with its earlier philosophy of performing a retroperitoneal tru-cut biopsy in

every renal tumor. Three strategies have worked to reduce the issue of early abandonment for the author. One, admitting children from remote far-flung areas for the entire duration of their ChT as they were unable to complete therapy on an outpatient basis. Two, administering preoperative ChT to all patients not only created better rapports between the families and the caregivers, but also made the families understand that the treatment of WT is multimodal, and surgery alone may not work. Three, starting a dedicated separate pediatric surgical division within the pediatric surgery ward (along with isolation rooms for the patients suffering from febrile neutropenia) helped families of many patients at different stages of management staying together and sharing a rapport between themselves. The families of the patients who were closer to completion of treatment are source of immense encouragement and hope to those families who have just started their arduous path that would keep them busy for next few weeks.

A thorough search and analysis of literature of management and outcomes of WT in the LMIC (also referred to as third-world countries, developing countries, and even non-developing countries), it is realized that probably a flexible hybrid approach should be recommended in LMIC setups [7, 25–27]. Whatever the approach, it may be imperative to have a tumor board, which is a new, if not a non-existent concept, in majority of LMIC centers. With advancing technology, however, *virtual tumor boards* may be set up at the tertiary well-equipped centers. The multidisciplinary expert panel of these centers could support the peripherally placed pediatric surgeons in management planning of individual cases. One such tumor board is run by the National Cancer Grid and hosted by Tata Memorial Centre, Mumbai, India.

If a child presents with a small operable mass and no metastases, then it would be advisable to do nephrectomy first (Fig. 22.1). The staging and histological classification according to

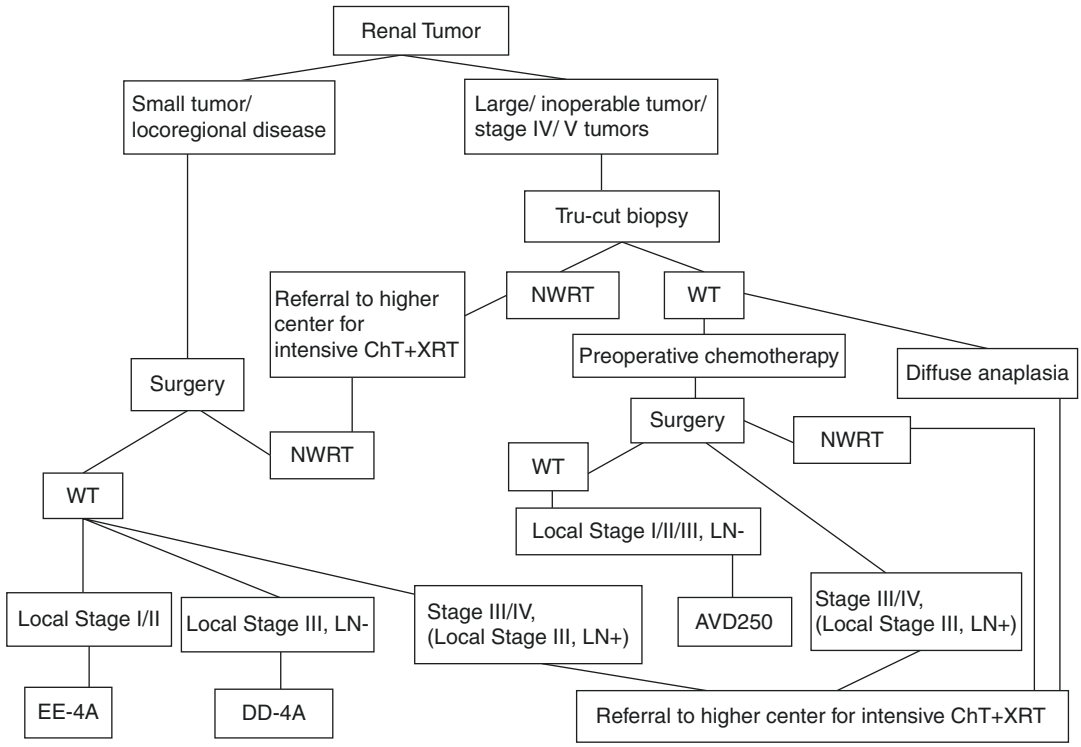

Fig. 22.1 Proposed algorithm for treatment of WT in LMIC

National Wilms Tumor Study Group/Children Oncology Group (NWTSG/COG) criteria are easier for the pathologists than those used in SIOP criteria [27]. It is due to the facts that tumor histology is not altered by preoperative ChT and NWTS criteria for histological subtyping of WT into two broad categories—either non-anaplastic (favorable) or anaplastic (unfavorable)—are simpler. The pathological diagnosis would be easier for the local pathologists and treatment-related errors would be fewer; this is all the more important as rapid central pathology review (CPR) is not feasible in LMIC [27].

Non-anaplastic WTs stage I or II could have the same adjuvant ChT, regimen EE-4A comprising of only two drugs—Actinomycin-D (AMD) and Vincristine (VCR)—administered over 18 weeks, and patients with stage III and IV could be treated with regimen DD-4A comprising of three ChT drugs, AMD, VCR, and Doxorubicin (DOX) [28]. The diffuse anaplasia patients, usually in local stage III at presentation in LMIC, are not going to fare well with regimen DD-4A and would necessitate intensive ChT with its toxic effects, ICU care, and XRT that is definitely not available in LIC. Their treatment with regimen DD-4A alone is not going to be curative; it at best would be palliative.

If a child presents with a large, inoperable WT, or metastatic WT, or bilateral WT, then preoperative treatment for 4–6 weeks of 2- or 3-drug regimen as advised in SIOP should be administered [18]. But in all such patients, a tru-cut biopsy should be considered as considerable data is available from many countries especially India, China, Vietnam, and Japan that the proportion of non-Wilms' renal tumors (NWRT) is higher than as compared to what is reported from Europe [27, 29–31]. In the year 2008, 50% of renal tumors from the principal author's department were reported as NWRT; this prompted him to move from SIOP to UKCCLG approach of doing a mandatory pre-therapy tru-cut biopsy. The Vietnamese study reported WT to represent only 68–76.5% of pediatric renal tumors [27]; this is true for other far-east Asian countries too. An American study showed that the WT comprised of only 73.9% of all renal tumors, and CT studies had diagnostic accuracy of only 82% to pick up the WT [32]. Smets et al. have stated that imaging studies alone cannot distinguish between WT and other non-Wilms' renal tumors (NWRTs) [33]. So, if we give ChT suitable for WT to all patients with renal tumors, a large number of patients with NWRTs would unnecessarily receive non-effective preoperative ChT. Although the UK has subsequently scaled down doing tru-cut biopsy only in few limited situations, the author is not convinced whether any such change of practice is required.

With preoperative ChT, the inoperable WTs would shrink in size and would be less prone to intra-operative tumor spill (IOS). The down-staging effect from preoperative ChT is also expected. This may again curtail the use of XRT postoperatively. The rider is that preoperative ChT would significantly alter the histological types; the excised specimen would show varied extents of ChT-induced changes. It is harder to categorically state the extent of tumor, thus making staging more difficult. It was conceded in SIOP 2011 Congress that there were discrepancies between the institutional pathologists and central pathology review in as many as one-fourth of the patients; 9.5% had diagnostic inaccuracies and 15.5% had staging differences [34]. If these statistics are extrapolated to the local scenarios, many of the WT treated with preoperative ChT would be either under- or overtreated. Some centers have tried taking the benefit of twinning programs and sending the histopathological images of tumors by the Internet for central pathological review in Europe [27], but the specialists could only see limited and selected images. This would be even more difficult for other hospitals in a country that has limited facilities, resources, and international collaborations. But with the advent of 4G and 5G data networks, this situation may change.

So, the institutional policy in all such patients (large, inoperable WT, or metastatic WT or bilateral WT) could be to treat all of them as local stage III and administer 3-drug AVD250 regimen with total cumulative dose of DOX of 250 mg/m^2 (including preoperative ChT).

Whether we use NWTSG/COG or SIOP philosophy, the major ethical dilemma would be

treating patients with local stage III with positive lymph nodes (LN) with ChT alone without any XRT. There is global consensus on the fact that not administering XRT to these patients would mean early local relapses and need of administering intensive and toxic second-line ChT, with consequent secondary malignancies. These patients could be sent for an intensive adjuvant treatment including XRT to an advanced tertiary center. Along with these patients, patients with diffuse anaplasia WT and NWRT such as Clear Cell Sarcoma of Kidney (CCSK), Malignant Rhabdoid Tumor of Kidney (MRTK), etc. could also be sent to advanced tertiary center.

22.5 SIOP PODC Clinical Guidelines for LIC [18]

It would be imperative to mention here the SIOP PODC clinical guidelines for the management of children with WT in LIC that were published in 2013 and later used in many LIC African countries [18]. The minimal requirements suggested by SIOP PODC for treatment with curative intent mentioned were as below [18]:

1. Basic laboratory services: full blood count, thick blood film for malaria parasites, HIV antibody test, stool and urine microscopy.
2. Basic radiology facilities: chest X-ray, ultrasonography.
3. ChT drugs: AMD, VCR, and DOX and their safe administration.
4. Supportive care: safe blood transfusions, intravenous broad-spectrum antibiotics, adequate pain-relief drugs, and reasonable degree of nursing care.
5. A trained (pediatric) surgeon, adequate facilities for surgery and perioperative care.
6. Free medical treatment and social support (meals, money for travel) for poor families so that therapy is not abandoned.

There is no mention of pediatric oncologist in the requirements above as many members of the writing group believed that in Africa, surgeons were inescapably true generalists and, with little training, were capable to administer ChT to WT patients provided ChT regimens are simple and drug toxicity is minimized [35]. Even in some of the good teaching institutions in India, the ChT for most solid tumors is administered by trained pediatric surgeons.

Preoperative ChT in setting 1 is similar to that of SIOP 2001 protocol [18]. It is identical for the patients with localized disease. In metastatic disease, chest X-ray and/or abdominal ultrasound scans is done at week 6 to assess the regression and resectability of metastases (Fig. 22.2). ChT is administered for 3 additional weeks if the metastases are still present. If metastases have not disappeared or not become resectable after 9 weeks, curative treatment is stopped, and the child is sent home with caretakers for palliative care. Treatment flow sheet of metastatic disease is shown below:

The patients with localized disease are operated upon, and the adjuvant ChT is decided as per the histopathology and staging as shown in Table 22.1. If the histopathological staging is unsatisfactory, then it was proposed that the adjuvant ChT can be based on *surgical staging* (staging assigned by the surgeon himself based on the intraoperative findings, IOS, and the extent of resection) [15]. *Surgical stage I* is tumor limited to the kidney and completely

Week	1	2	3	4	5	6*	7	8	9*
AMD 45μg/kg (Day 1 of wk)	↓		↓		↓		↓		↓
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓	↓	↓	↓	↓	↓	↓
DOX 50mg/m^2 (Day 2 of wk)	↓				↓				↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine
*Chest x-ray and US abdomen to assess the regression and resectability of metastases

Fig. 22.2 SIOP PODC treatment schema for metastatic disease

resected; *surgical stage II* is tumor outside kidney, but completely resected; *surgical stage III* is IOS or incomplete resection. This stage also includes assessment of the LNs by the surgeon by gross inspection [15].

It is obvious that intensive ChT regimens and XRT are not used. Neither the tumor volume post ChT is taken into consideration, nor the histological subtypes in a particular risk-stratification category. Further, ChT regimens are simplified [15].

The ChT regimens mentioned in Table 22.1 are further detailed below (Fig. 22.3):

As regards the supportive care, the issue of all prevailing malnutrition in LIC was considered as the preoperative ChT was known to be associated with a higher morbidity and mortality [36]. It was also noted that infectious complications are the most common cause of treatment-related mortality. So, nutritional support and treatment of febrile neutropenia with appropriate antibiotics were given utmost importance [37]. The ChT drugs are administered at two-thirds of the doses to the malnourished children. Three practical recommendations and priorities mentioned in this protocol need to be highlighted—provision of free medical treatment, provision of social support (travel money, free boarding, and lodging), and provision of excellent counselling on diagnosis and need to complete treatment.

The above SIOP PDOC protocol could be easily reproducible even the interiors and most difficult Indian terrains; the only difference the author suggests is that the patients with the metastatic disease who do not show regression of metastases after 9 weeks of ChT could be referred to higher centers rather than their abandonment to respective homes to await their impending death.

There had been many other studies that have adapted changes in regimens. Two of these are worth a mention.

One is GFAOPNEPHRO 01 study (years 2001–2004) using SIOP 2001 protocol approach, comprising of eight African pilot units, namely, Algiers, Casablanca, Rabat, Oran, Tunis, Dakar, Yaounde, and Antananarivo [17]. All patients were treated preoperatively with ChT by the standard SIOP 2001 protocol. Postoperatively, the stage I patients irrespective of histology were treated with two cycles of AMD and VCR with a break in the 5th postoperative week. The stages II–IV patients were treated with AVD regimen

Table 22.1 Risk stratified adjuvant ChT suggested by SIOP PODC

	Treatment		
Disease	Stage I	Stage II	Stage III
Low risk	None	AV X 5 cycles	
Intermediate risk	AV X 1 cycle	AV X 5 cycles	AVD X 5 cycles
High risk	AVD X 5 cycles	AVD X 5 cycles	AVD X 5 cycles

Abbreviations: *A* actinomycin-D, *V* vincristine, *D* doxorubicin

Fig. 22.3 SIOP PODC treatment schemata for adjuvant ChT regimens

Week	1	2	3	4
AMD 45μg/kg	↓			
VCR 1.5mg/kg	↓	↓	↓	↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AMD 45μg/kg (Day 1 of wk)		↓			↓			↓			↓			↓	
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
AMD 45μg/kg (Day 1 of wk)		↓			↓			↓			↓			↓	
VCR 1.5mg/kg (Day 1 of wk)	↓	↓	↓		↓	↓		↓	↓		↓	↓		↓	↓
DOX 50mg/m^2 (Day 2 of wk)		↓			↓			↓			↓			↓	

Abbreviations: AMD; Actinomycin-D; VCR, Vincristine; DOX, Doxorubicin

for 27 weeks. Flank XRT was administered if LN were positive, incomplete resection was done, or there was a localized intraoperative spill. Whole abdominal XRT in case of diffuse intraoperative spill or there was an unresectable tumor. Same group repeated their study (GFAOPNEPHRO 02; years 2005–2011) with minor change in the postoperative management—the stage I tumors were treated with 9 weeks of AV instead of 4 weeks [38].

The other study was by Sen et al. describing the experience from Christian Medical College Hospital, Vellore, India (1985–1995), and from King Faisal Specialist Hospital, Riyadh, Saudi Arabia (1988–1995) [11]. They recommend postoperative XRT for stage I–II disease of favorable histology with features that make relapse likely, such as invasion of the tumor capsule, the presence of an inflammatory pseudocapsule (manifested as tumor adherence to surrounding tissues at surgery), renal-sinus invasion, and tumor in intrarenal vessels [39]. Such a recommendation for large late-presenting tumors in the developing world is unacceptable globally as of today, but is worth a mention nonetheless.

22.6 Post-treatment Surveillance in LMIC

Post-treatment surveillance of children with WT is difficult and has been known as one of the reasons of poor outcomes in LMIC; the referral centers in African countries reported lost-to-follow-up rates of 15–43% in the first year after treatment [40]. Situation is not very different in Indian subcontinent and many other Asian countries. In Malawi, pediatric oncology patients are followed by a field worker using a donated motorcycle. GPS records enable the field worker to trace the patient repeatedly [35]. It is a model worth emulating in other LMIC. In India, Accredited Social Health Activists (popularly now as ASHA workers) that provide primary medical care for minor ailments in the villages and remote communities could be taught clinical features of common childhood cancers; they could help in early diagnosis and referral as well as in post-treatment surveillance.

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