37 Post-Therapy Surveillance of Wilms' Tumor Survivors

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37.1 Introduction

Wilms' tumor (WT) which is the most common renal tumor in children has a recurrence rate of 15–20% [1]. The treatment of children with WT does neither end at removal of the tumor nor with chemotherapy (ChT) or radiation therapy (XRT); it is a continuous process that extends beyond his/her adulthood. Children with WT are at increased risk of developing certain late secondary effects and are associated with chronic health disorders. Cardiomyopathy and congestive heart failure due to anthracyclines and XRT have been known since the inception of therapy, but significant morbidity has been reduced due to careful modification in the current regimens [2]. Survivors of WT are at substantially higher risk of mortality between the third and fifth decade from diagnosis. Approximately three-fourths of such deaths are due to either subsequent primary neoplasm or cardiac disease [3]. This makes the need for the long-term follow-up all the more necessary. The development of end-stage renal disease (ESRD) in unilateral disease is very low but slightly increased in the bilateral disease group [4, 5]. Second malignant neoplasm (SMN), although rare, should be a concern, and screening to pick them up should be our priority. Planned surveillance by imaging modality has enabled to identify more than two-thirds of relapses in asymptomatic children with WT [6]. Planned surveillance imaging identified 70% of the relapses with the following distribution of modalities: ultrasonography (USG) (32%), chest X-ray (CXR) (31%), computerized tomography (CT) (33%), and magnetic resonance imaging (MRI) (4%) [6].

37.2 Role of Surveillance and Allied Controversies

The goal of scheduled interval diagnostic imaging is to detect the relapse before the development of any signs and symptoms [7]. Surveillance strategy is based on the assumption that it will help in early detection of recurrence and thus will improve the salvage rate and help in minimizing the intensity of the therapy and its associated adverse effects [7]. However, little information is available regarding the costs, benefits, and risks involved with the different surveillance strategy

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[8]. The surveillance risks include ionizing radiation, need for sedation, intravenous cannulation, and frequent follow-up visits leading to psychological distress for the families and child [9, 10]. The intensive surveillance strategy also puts financial burden on the family and has implications over the education of the child and the job of the parents.

Few studies have also tried to determine the beneficial effect of the routine surveillance imaging on the salvage rate of the relapsed patients. Many such studies did not find any difference in salvage rate between the patients detected by imaging or clinically [8].

Another controversy is regarding the optimal imaging to detect the relapse early. The CT scan does detect the smaller size (1–2 cm) lesions that are not detected by CXR/USG. However, the prognosis gets affected only when the relapsed lesion is more than 2 cm in size [6]. The CXR/USG has been found to have enough sensitivity to detect the lesion before the tumor burden has any adverse impact on the outcome. The advantages offered by CXR/USG over the CT include less ionizing radiation, no need for sedation/intravenous cannulation, less cost, and optimal sensitivity. The high sensitivity of CT may lead to high false positivity that needs to be resolved by further evaluation posing unnecessary risk and burden on child and family [6].

Recommendations for post-therapy imaging surveillance followed worldwide are based on the guidelines proposed by the Children's Oncology Group (COG) and Societe Internationale D'oncologie Pediatrique (SIOP). These guidelines were originally proposed for the research purpose but are widely followed as surveillance protocol [6].

37.2.1 Post-Therapy Follow-Up

The surveillance for relapse detection and toxicity surveillance should start right after nephrectomy as about 15% of the patients with WT relapse after treatment [1]. Most of the relapse occur within 2 years after surgery, and only occasionally relapse occurs 5 years after nephrectomy [1]. Surveillance plays a major role in the management of recurrences and the long-term successful outcome. Surveillance involves history, physical examination, and imaging during the follow-up visits.

Since children with WT have overall survival (OS) rates greater than 90%, follow-up imaging after therapy treatment should be minimally invasive. The OS for patients with recurrent WT (RWT) favorable histology (FH) is around 50%; it is very important to identify and treat them early [7]. In addition, all childhood cancer survivors should undergo annual physical examination incorporating anthropometric measurements, nutritional status, and overall health [11].

The common site of relapse in WT are the lungs, which account for 50–60%, and the abdomen with 30%, while other sites (bone or brain) are involved in approximately 15% of cases [9].

37.2.2 Healthcare Records

Maintaining and organizing the personal record of the child's medical information will be of immense help to the healthcare professional for the long-term follow-up. In the long run when the child enters adulthood, the document about a brief history of the diagnosis, treatments, medications, follow-up, do's and don'ts, any near-death incidents, or complications will be very useful, as a transition back to the family physician or another healthcare professional [12].

37.3 COG Surveillance Protocol

COG recommends chest CT and abdominal CT/MRI for the first 2–3 years, based on disease stage and histology and later chest radiographs and abdominal ultrasonography [13] (Table 37.1). Contrast-enhanced CT and MRI are better than USG in the identification of small tumors (1–2 cm), nephrogenic rests (NR), and nephroblastomatosis (NB) [14].

Table 37.1 COG recommendations for post-therapy CT surveillance imaging in WT [13]

Disease group	Imaging	Frequency
Very low risk stage I	CT chest	End of therapy, then every 2 months × 3, then every 3 months × 4
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy, then every 2 months × 3, then every 3 months × 4, then change to US
Low and standard risk stage I–III	CT chest	End of therapy, then every 6 months to 3 years
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy, then every 6 months to 3 years
Higher risk favorable histology	CT chest	End of therapy then every 3 months × 8
	CT or MRI abdomen/pelvis (use same modality each time)	End of therapy then every 3 months × 8, then change to US

There are studies that have tried to evaluate the need of routine pelvic surveillance imaging and have shown that omitting pelvic CT from the routine off-therapy surveillance imaging can save up to 40% of the effective dose of radiation without having any adverse impact on detection of recurrence [15, 16].

COG provides long-term follow-up guidelines for childhood cancer survivors, and these help prepare survivors who are reaching early adulthood to successfully manage their own healthcare. Third to fifth decade from diagnosis, survivors of WT are at a substantially increased risk of mortality, and 75% of such deaths were attributed to subsequent primary neoplasms and cardiac diseases [3]. Patients who have received XRT are at significantly higher risk [3].

37.3.1 Blood and Other Investigations for Long-Term Follow-Up of Organ-Systems at Risk and Assessment of Overall Well-Being

Following nephrectomy, physical examination including measurement of weight, height, and body mass index (BMI) and testicular examination for hydrocele should be done annually [11]. Blood urea and serum electrolytes should be asked for at the time of entry into the long-term follow-up and should be repeated as clinically indicated. Serum creatinine, estimated glomerular filtration rate (eGFR) calculation, and urinary proteinuria (microalbuminuria) should be tested annually [11].

The National Wilms' Tumor Study (NWTS) report estimated that unilateral WT patients had a 20-year cumulative incidence of ESRD of 1.3%; it was 15% for BWT [17]. However, patients with associated Denys-Drash syndrome (DDS) (75%), WAGR syndrome (36–90%), cryptorchidism, and hypospadias (7%) have significant risk of ESRD [18]. Thus, lifelong nephrological follow-up for renal function must be provided to the patients with high propensity for ESRD (syndromic patients and bilateral tumors) [19].

Renal transplant for children with bilateral WT with ESRD is usually delayed until 1 to 2 years have passed without any evidence of malignancy because majority of tumors recur within 2 years of diagnosis [20]. For children with WT and DDS who proceeded to renal transplantation, the clinical outcomes are comparable to children with other ailments, with no graft failures because of recurrence. Children with WT and DDS have a good outcome following renal transplantation although the numbers of studies are few [20].

37.3.2 Early Screening for Infertility

Puberty, hormonal regulation, fertility, and sexual function are impaired with the use of alkylating ChT and XRT to the central nervous system and ovaries. The long-time female survivors may have an increased risk of miscarriage, premature delivery, small for age infants, and premature menopause [21, 22]. Gonads of postpubertal girls are more sensitive to XRT than prepubertal girls. XRT dose as low as 5 Gy and 10 Gy can affect ovarian function in post- and prepubertal girls, respectively [23]. Infertility causes mental strain impairing quality of life and also can lead to mild post-traumatic stress disorder. All girls with abdominal XRT should be considered at high risk for pregnancy complications and should be managed at appropriate referral for the fertility and obstetric care [24].

37.3.3 Hearing Tests

Hearing tests must be performed for patients who receive carboplatin, and children aged 6 or older should be screened with a pure tone audiogram, but very young kids can be tested using auditory brainstem response (ABR). Those who have hearing impairment are screened yearly till 6 years of age and then every 2 years till 12 years of age, and then frequency can be decreased to once every 5 years [11].

37.3.4 Cardiac Function

Anthracycline ChT affects the functioning of the heart if dosage of ≥250 mg/m^2 is administered at the time treatment, echocardiography (ECHO) is recommended every 2-year follow-up, and problems may also result from XRT to the heart or surrounding organs and tissues. If XRT dose is <15 Gy or none, no need for ECHO but if the dose is ≥15–<35 Gy, screening ECHO is required every 5 years. Screening ECHO should be done every 2 years if the radiation dose is >35 Gy [11].

37.3.5 Screening for Colon Cancer

This should start 10 years after XRT or by age 35 (whichever is later). Microscopic examination of stool should be done to look for occult blood [11].

37.3.6 Thyroid Tests

Thyroid testing is required if the patient has received XRT to the head or brain for brain metastasis. In such patients, physical thyroid examination and thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels should be done annually. Female survivors at risk for thyroid problems should be treated for hypothyroidism before becoming pregnant. Thyroid USG should be done every 3 years to screen for thyroid nodules and masses [11].

37.3.7 Breast Screening

Women survivors who have received chest XRT for lung/bone metastasis during childhood have an increased risk of developing breast cancer at a much younger age (usually 30 to 40 years old). Early screening for breast cancer in females should be a part of the follow-up schedule. Monthly breast self-examination is also recommended. Annual physical breast examination by healthcare provider should be done starting at puberty until the age of 25 and then every 6 months thereafter. Mammogram and breast MRI are initiated at age 25 years or 8 years after chest radiation and should be repeated every year [3, 11, 25].

Psychosocial assessment of the cancer survivor is recommended with attention to the education and vocational program. These patients should also be evaluated for social withdrawal annually. Routine discussions should be held to reduce the lifestyle risk factors like obesity, smoking, lack of exercise, etc. [26]

37.4 SIOP Surveillance Protocol

SIOP 2001 and the new SIOP-RTSG (Renal Tumor Study Group) Umbrella protocol recommend chest radiographs and an abdominal ultrasound to detect recurrence (Table 37.2). The Indian Council of Medical Research (ICMR) has adapted the long-term guidelines from the SIOP RTSG 2001 protocol [27].

37.4.1 Surveillance Program of SIOP-RTSG Umbrella Protocol 2016

SIOP-RTSG Umbrella protocol mentions little more elaborate surveillance program for relatively longer periods of follow-up. The off-therapy physical examination (including blood pressure measurements), the diagnostics to detect a relapse, and the toxicity diagnostics and surveillance and their frequencies are mentioned in Table 37.3 [29].

37.5 UKCCLG Surveillance Protocol

The United Kingdom Children's Cancer and Leukemia Group (UKCCLG) guidelines are similar to those of Umbrella protocol [30]. UKCCLG recommends liaison with local pediatric nephrologists at the end of treatment and with the geneticists for the patients with underlying predisposition, malformations, and/or bilateral disease. UKCCLG endorses the recommendations of the International Late Effects of Childhood Cancer Guideline Harmonization Group for the surveillance of breast cancer and cardiac toxicity (Table 37.4) [25, 31].

Table 37.2 Recommendations for long-term follow-up as per SIOP-2001 [28]

	Investigation	Frequency after completing therapy
Patients with nonmetastatic disease at diagnosis	Blood pressure	Every visit
	Serum creatinine	6 months × 8
	Chest X-ray	1st year: Every 3 months Second year: Every 3 months Third year: Every 6 months
	Abdominal USG	End of treatment 1 and 5 years after stopping therapy
	Echocardiography	According to institutional policy
Patients with nephrogenic rest[a]	Abdominal USG	3 months × 8 6 months × 6 Yearly × 5
Metastatic patients in CR after stopping therapy	Chest X-ray	1st year: Every 2 months Second year: Every 2 months Third year: Every 6 months
	Serum creatinine	6 months × 8
Irradiated patients	X-ray bony structures, Spine+/− pelvis	Yearly to full growth and then every 5 years
Bilateral tumors	Chest X-ray and USG abdomen	1st year: Every 2 months Second year: Every 2 months Third year: Every 3 months Fourth year: Every 3 months
	Serum creatinine and proteinuria	5th–tenth year: Every 4 months Every 6 months
Partial nephrectomy	Abdominal USG	3 months × 8 6 months × 6 Yearly × 5

[a]Following CR to treatment, maintenance therapy of vincristine and actinomycin D every 28 days is given for 1 year

Table 37.3 Surveillance program suggested in SIOP-RTSG 2016 Umbrella protocol [29]

	Frequency after completing therapy
Physical examination	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months Fifth year: Every 6 months After 5 years: Once a year
Investigations	
Diagnostics to detect a relapse	
Chest X-ray AP or PA and lateral view	1st year: Every 3 months[a] Second year: Every 3 months[a] Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
Abdominal USG	1st year: Every 3–4 months Second year: Every 3–4 months Third year: Every 4 months Fourth year: Every 6 months Fifth year: Every 6 months After 5 years: Once a year
Toxicity diagnostics and surveillance	
Urine (glucose, albumin, β-microglobulin, calcium, phosphate, magnesium, erythrocyte)	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
24-h urine collection	In case of albuminuria
Blood (full blood count, urea, creatinine, Ca++, PO^{4-}, Mg++, albumin, ALAT, ASAT, bilirubin, TSH)	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Once a year
ECG/echocardiography	After anthracyclines, lung irradiation and in case of high blood pressure
24-h blood pressure	In case of high pressure
Lung function	After lung irradiation once a year
Endocrinology	In case of disorders, contact pediatric endocrinologist
Audiometry	Once after carboplatin, in case of pathological result, refer to ENT specialist
Neuropsychological testing	In case of syndromes with potential retardation (e.g., WAGR)

[a]In case of stage IV disease: X-ray or CT of the lung every 2 months depending on the local standards

37.6 Differences Between Various Collaborative Groups' Post-Therapy Surveillance Protocols

The most important difference between COG and all other guidelines is the imaging method used for the surveillance. The COG group recommends use of chest and abdominal CT to detect any local or distant relapse. In comparison, all other protocols recommend the long-term follow-up using CXR and USG abdomen. The CT scan is a more sensitive screening test than CXR/USG and can detect smaller lesions. However, the need for sedation, intravenous contrast, and exposure to ionizing radiation are well known disadvantages of CT scan. Various studies failed to document any advantage of CT over

Table 37.4 CCLG guidelines for follow-up of renal tumors [30]

	Frequency after completing therapy
Physical examination including BP measurement	1st year: Every 3 months Second year: Every 3 months Third year: Every 4 months Fourth year: Every 6 months After 4 years: Optional
Investigations	
Diagnostics to detect a relapse[a]	
Chest X-ray AP or PA and lateral view	1st year: Every 2–3 months[b] Second year: Every 3 months Third year: Every 3 months
Abdominal USG	1st year: Every 2–3 months[b] Second year: Every 3 months 3rd–seventh year: Every 3 month (or clinical examination in compliant patient) if patient was <12 month at initial diagnosis of Wilms' tumor, nephrogenic rests found in nephrectomy specimen, initial bilateral tumors, partial nephrectomy
Toxicity diagnostics and surveillance	
Urine dipstick	1st year: Every 3 months[b] Second year: Every 3 months[b] Third year: Every 6 months Fourth year: Every 6 months After 4 years: Once a year
GFR and 24-h urine collection	In case of proteinuria, nephrocalcinosis, hypertension, and decreased kidney function[c]
Blood: Full blood count, urea, creatinine, cystatin C, Ca++, phosphate, Mg++, albumin, ALAT/ASAT, bilirubin, and blood gas	1st year: Every 3 months Second year: Every 6 months Third year: Every 6 months Fourth year: Every 6 months Fifth year: Once a year
ECG/echocardiography	Long-term follow-up should be done according to local policy
Lung function	
Endocrinology	
Audiometry	

[a]Relapse surveillance should start right after nephrectomy as a significant proportion of the relapses occur during post-operative treatment
[b]High-risk histology (stage III, IV, and V) and intermediate risk histology (stage IV) have a significantly higher risk of relapse the first year after nephrectomy and should have USS/X-ray every second month
[c]Referral to a local pediatric nephrologist

USG as screening test. In addition, the high sensitivity of CT may lead to high false positivity that needs to be resolved by further evaluation posing unnecessary risk and burden on child and family [6].

There are some subtle differences in the recommendations by various groups for the surveillance of other organ-systems at risk also, e.g., breast cancer screening and cardiomyopathy surveillance (Table 37.5) [25, 31].

37.7 Challenges in Resource Challenged Nations

Besides many other challenges, abandonment of adjuvant treatment and lack of post-therapy surveillance are major concerns in resource challenged nations. Infectious complications are a significant contributor to the treatment-related mortality [32]. The early detection of recurrence will help in minimizing adverse sequelae of more

Table 37.5 Breast cancer screening and cardiomyopathy surveillance [25, 31]

		COG	CCLG	Concordance
Breast cancer surveillance	Age of initiating surveillance	25 years	25 years	Yes
	Frequency of surveillance	Every year	Every year	Yes
	When to stop surveillance	No age limit	No age limit	Yes
	Screening test			
	Clinical breast examination, mammography, and breast MRI	Yes	Yes	Yes
	Age at initiation of screening			
	Clinical breast examination	Puberty	Age 25 years and at least 10 years after chest radiation	No
	Mammography	Age 25 years or 8 years after chest radiation	Age 30 years	No
	Breast MRI	Age 25 years or 8 years after chest radiation	Age 25 years	No
	Surveillance frequency			
	Clinical breast examination	Every year from puberty to 25 years of age and then every 6 months	Regularly	No
	Mammography	Every year	Every year (age 30–50 years) and then every 3 years	No
	Breast MRI	Every year	Every year (age 25–29 years) Or age 25–50 years if dense breast tissue	No
Cardiomyopathy surveillance	*Screening test*			
	Echocardiography	Yes	Yes	Yes
	Radionuclide angiography	Yes	No	No
	Surveillance begins at	≥2 years after treatment or ≥5 years after diagnosis (whichever is first)	1–3 months after treatment	No
	Screening frequency	Every 1–5 years	Every 3–5 years	No
	Duration of screening	Lifelong	Not stated	No
	If any abnormality on screening test	Refer to cardiologist	Refer to cardiologist	Yes

intensive adjuvant therapy and decrease cost and resources. The surveillance protocol should be cost-effective and must keep the radiation risk and family inconvenience in account. The expense per test for screening, total number of tests required, population under surveillance, and cost of investigating false positive screening can unnecessarily burden already strained health resources in poor countries. Surveillance imaging regimens that include only CXR and USG cost less than half to the regimens that include CT scans [6]. Mullen et al. have shown that CT has no advantage over USG as a surveillance tool for unilateral favorable histology (FH) WT. Elimination of CT scans from surveillance programs for this cohort of patients is unlikely to

impact survival; in fact, it would result in significant decrease in radiation exposure and expenditure [6]. As most of the recurrences occur within 2 years after treatment, surveillance beyond 2 years is being questioned and needs to be thoroughly evaluated especially in resource challenged nations.

37.8 Palliative and Near End of Life Care

Most of medical schools do not teach about the terminal care and death in pediatric population. This is a very complex issue and involves the caregivers, parents, sibling, society/community, religion, etc.

There are many challenges to providing a decent pediatric palliative care (PPC), including controlling the disease, shifting to end of life care, financial restrictions, and acceptance of death [33]. Symptom control (fever, dyspnea, easy fatigability, anorexia, nausea/vomiting) and the overall well-being of children with advanced disease are a challenge in itself, and the primary objective is to ease their suffering. A multidisciplinary support team should promptly try to communicate between parents and caregivers about the quality of medical care for children who are dying of cancer. The terminal care includes many aspects of symptom management. Adequate pain management is one of the most important aspects, but it must include adequate symptomatic relief to other symptoms like nausea/vomiting, constipation, fever, respiratory distress, etc. Most of the parents in the poor socioeconomic countries are working to earn a living. They would like to take care of their children at home [34]. In such scenario, the primary physician and nearby primary healthcare centers (supported by government) should be communicated and facilitated by educating them about the management of various acute events like acute pain, febrile neutropenia, etc. The availability of oral morphine and other pain medications should be ensured. In addition, it is equally important to identify and arrange the social support (philanthropic) for food, travel, stay, expensive medication, etc. Most of the studies admit the importance of at least one meaningful contact of health providers with the bereaved families. This contact may be in any form such as a call, email, or letter and should comprise of making an effort to remember the child. All grieving families should be provided bereavement support from the psychosocial team, including psychoeducation [33, 34].

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