Radiotherapy

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20.1 Introduction

As in many pediatric tumors, radiotherapy (XRT) forms an important part of the management of Wilms' Tumor (WT), and its evolution is based on the fact that the tissues have a low threshold for XRT induced long-term sequelae. Over the past half a century, there have been considerable improvements in the management of WT in terms of multimodality treatment. XRT at the site of the primary tumor and local lymph nodes (LNs) enables good local control in terms of relapse and recurrence. Multimodality therapy is associated with risk of significant toxicity in long-term survivors of WT. In particular, studies have shown that treatment including XRT is associated with increased risk of renal failure, intestinal occlusion, scoliosis, ovarian failure, high-risk pregnancies, and diabetes. In addition, studies have shown an increased risk of second malignant neoplasm (SMN) most often occurring within the XRT field [1]. Various cooperative trials done over the years have resulted in a significant decrease in the intensity of chemotherapy (ChT) and XRT.

Broadly, there are two approaches studied by National Wilms Tumour Study group (NWTSG)/ Children's Oncology Group (COG) and Société Internationale d' Oncologie Pédiatrique (SIOP). Both employ risk stratified adjuvant treatment based on initial staging, histopathological subtype, and molecular status, while SIOP also takes into consideration the response to preoperative ChT. Children with metastatic WT are treated with XRT to local as well as metastatic sites. Indian Council of Medical Research (ICMR) has come up with consensus guidelines that are similar to COG/SIOP [2]. Recently, SIOP-Renal Tumor Study Group (RTSG) has formulated the SIOP-RTSG UMBRELLA protocol, taking inputs from all the specialists involved in the diagnosis and treatment [3]. This protocol deviates from the traditional indications of XRT in the management of WT and will be discussed in detail.

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Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_20

20.2 Technical Considerations of Radiotherapy

20.2.1 Pediatric Radiation Oncology

It is essential that XRT where indicated should be administered in a center with experience of pediatric XRT. The staff should be appropriately trained for handling children. The radiation suite must be child friendly, and small points like controlling the ambient temperature goes a long way in gaining confidence of patients and parents both. The support of a pediatric anesthesia team should be in place for easy management of these patients. The parents must be taken into confidence about the short- and long-term complications. There needs to be specific consent and adequate documentation before commencement of therapy.

The support of a pediatric anesthesia team should be in place for easy management of these patients. It is very important that the child does not move during treatment and the patients will be alone for about 10–15 min inside the linear accelerator. In these children, XRT is delivered under sedation and with CCTV monitoring as shown in Fig. 20.1.

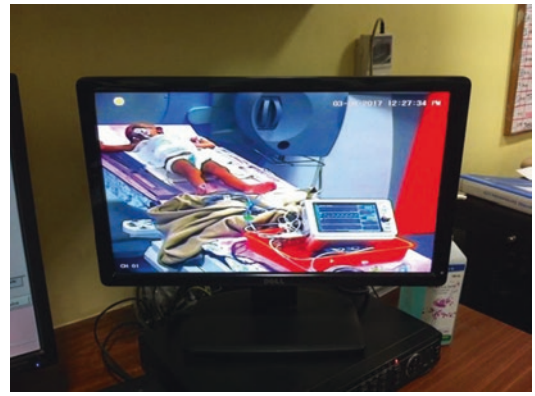

Fig. 20.1 Monitoring of the kid during XRT under sedation

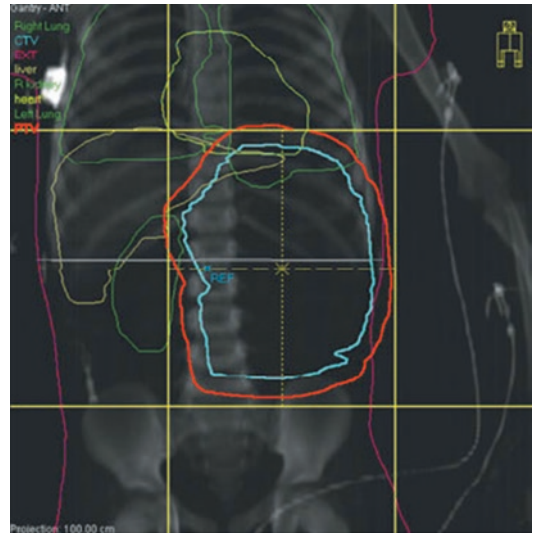

Fig. 20.2 Showing flank irradiation which included the renal bed and the para-aortic nodes

20.2.2 Target Volume Definition

Target volume definition will be performed on a planning CT scan, taking into account the post ChT, pre-surgery magnetic resonance imaging (MRI), or computerised tomography (CT) scans. The surgeon may have placed clips to mark the extent of the tumor or any areas suspicious for residual disease.

The clinical target volume (CTV) is defined as the preoperative extent of disease plus the remaining ipsilateral kidney, as defined on imaging, plus a 1 cm margin. This may be modified by additional information from the operation note, position of clips, and pathology report. The CTV will be extended medially to cover the full width of the vertebral bodies (Fig. 20.2). Any definite residual disease should be volumed as a separate CTV. The remaining kidney and liver should be volumed as organs at risk (OAR). The dose variation within the CTV should not exceed ±5% until ±7–10% of the prescribed dose.

Ideally, XRT should be administered soon after surgery. A delay of XRT beyond 10 days after surgery has shown higher risk of abdominal recurrences, but these studies have a bias of unfavorable histology [4]. The COG protocol recommend starting the XRT for locoregional disease by the 9th postoperative day (POD), if possible and not later than POD 14 [5]. The SIOP Umbrella protocol recommends that abdominal and flank

XRT must commence between 2nd and 4th week after abdominal surgery.

If both abdominal and pulmonary XRT are to be administered in the presence of metastatic disease, they can either be administered simultaneously (Fig. 20.3) or sequentially (Fig. 20.4); both are well tolerated as the dose delivered is very less. In the COG sequential XRT protocol, lungs would be irradiated first, and the abdominal XRT should be delayed and administered after the lung metastatectomy. In cases of high-risk histology (like anaplasia), the abdominal RT should be given as soon as possible, and the lung XRT can be given later.

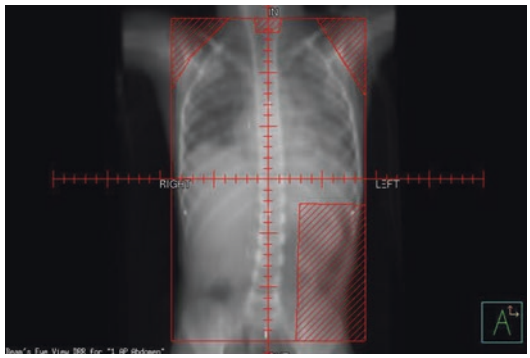

Fig. 20.3 Showing simultaneous thoraco-abdominal irradiation

20.2.3 Equipment and Treatment Techniques

There is continuous evolution of the XRT techniques over the years. Earlier days, XRT used to be delivered with Telecobalt machines using a cobalt source. These machines have been replaced by modern linear accelerator (LA) which is the standard unit used nowadays. It uses an X-ray tube emitting 4–6 MV photons and opposing AP/PA fields. XRT beam, on day-to-day basis, can be verified using on board X-ray or CT scan which is called Image-Guided Radiation therapy (IGRT). Using LA, the XRT beam can be modified to any shape of the tumor using multileaf collimators. This technique is called three-dimensional conformal radiation therapy (3-DCRT).

SIOP-RTSG Umbrella protocol propagates the use of intensity-modulated radiation therapy (IMRT) [3]. This technique offers the greater conformality of high dose volume to target

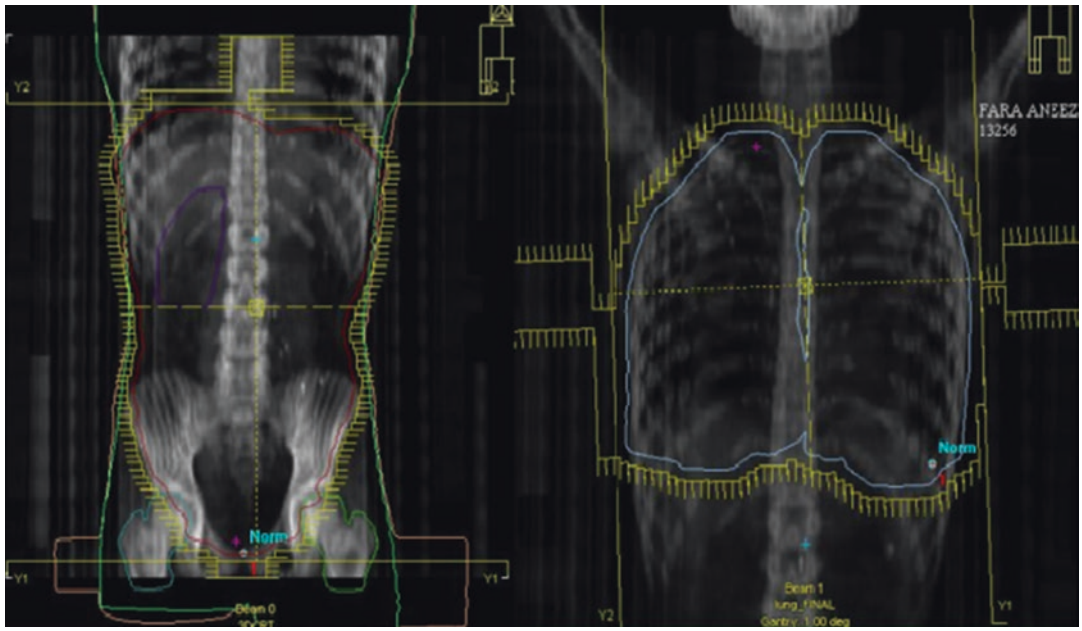

Fig. 20.4 Showing sequential abdominothoracic irradiation

volume thus significantly decreasing the XRT to non-target organs. In view of the low dosage of XRT required in management of WT, the old school of thought wonders if IMRT really matters.

Helical tomotherapy is based on treating the tumor slice-wise, and hence the treatment time is shorter and convenient to the patient.

Intraoperative radiation therapy (IORT) uses 50 kV X-rays to deliver XRT during surgery to a small localized gross disease [6].

The new kid on the block is Proton Beam therapy (PBT). This newer modality has significant advantages in terms improvement in the dosimetric domain as compared to standard beam therapy [7]. It uses pencil beam scanning (PBS) to reduce dose to OAR. PBS plans are more efficient to create than alternative proton modality double-scattered proton therapy (DS-PT) plans [8]. The risk of SMN is also low theoretically; however this needs to be validated by more clinical studies. The major downside of PBT is the escalated costs and unavailability in most parts of the world.

Advanced technologies like IMRT and PBT could be used for recurrent disease, bilateral WT, and WT in horseshoe or ectopic kidney.

20.2.4 Simulation and Shielding

The patient is immobilized using thermoplastic cast in a supine position. This material becomes soft at a temperature of 65 °C and when allowed to cool on the body becomes rigid and takes the shape of the body. The cast is fixed onto the base plate everyday of treatment, and hence the same position is reproduced on all the days of XRT.

CT simulation is done with the cast, and images are imported on to the treatment planning computer system. With the help of preoperative CT scan, the tumor extent is identified in all directions. The same is contoured on every axial CT scan cut as tumor bed and para-aortic LN are also included.

The entire vertebral column is included, and the opposite kidney is completely kept out of XRT portals. Various plans are generated and evaluated, and the best plan which adequately covers the target region and at the same normal structures receive minimal XRT is chosen for execution.

Important organs at risk are the opposite kidney in flank XRT, heart and bilateral humerus in whole lung irradiation (WLI), and opposite kidney, small bowel, ovaries and testis, bilateral head of femur, and acetabulum during whole abdominal irradiation (WAI). The dose in organs at risk is calculated and reported for each organ separately. Critical organ dosage should not exceed 10–12 Gy to the remaining kidney and 20 Gy to the liver. The WLI dosage should not be more than 15 Gy in 15 fractions (high-risk patients) with correction for homogeneity. For WLI, the shoulder joints should be shielded and the hips for WAI.

20.2.5 Radiation Dose and Fractionation

The dose of XRT depends on the protocol that is used for the treatment as there are subtle differences in the risk stratification. The COG categorizes each stage as low, intermediate, and high risk based on the pathological subtype, whereas the SIOP protocol takes into account the response to ChT and the relative proportion of the histopathological subtype. The subtle differences in the dose of XRT are highlighted in Tables 20.1 and 20.2.

In the recurrent settings, the same dose of XRT can be repeated, and the decision of sequencing is decided on a case-to-case basis after discussion in multidisciplinary tumor board.

The fraction size should not exceed 1.8 Gy for flank XRT but should be lowered to 1.5 or 1.25 Gy if large volumes are treated, for example, whole lungs or whole abdomen and pelvis and in very young children, for example, less than 2 years old. If there is macroscopic residue, a boost of additional 10.8 Gy 6 fractions may be considered. Earlier a boost for stage III positive LNs was recommended, but there is little

Table 20.1 Dose fractionation schedules for different stages and risk stratification for children with locoregional disease

	SIOP [3]			NWTSG/COG, AREN0321, AREN0532, AREN0533 [14]		
	Intermediate risk	High-risk blastemal	High-risk diffuse anaplasia	Favorable/without LOH1p, 16q	Favorable with LOH1p, 16q	Focal/diffuse anaplasia
Stage I	Nil	Nil	Nil	Nil	Nil	10.8 Gy/6 Fr
Stage II	Nil	Nil	25.2 Gy/14 Fr	Nil	10.8 Gy/6 Fr	10.8 Gy/6 Fr
Stage III	14.4 Gy/8 Fr	25.2 Gy/14 Fr	25.2 Gy/14 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr
Stage IV	15 Gy/10 Fr	19.5 Gy/13 Fr	19.5 Gy/13 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr	10.8 Gy/6 Fr

[a]Additional 10.8 Gray-20 Gy/6–10 Fractions is given to the sites of gross disease identified at the time of radiation on the planning CT scan

Table 20.2 Dose fractionation schedules for different stages and risk stratification for children with metastatic disease

	SIOP [3]			NWTSG/COG [14]
	Low risk	Intermediate risk	High risk	Favorable/unfavorable
Lungs	Nil	12 Gy/8 Fr	15 Gy/10 Fr	10.5 Gy/6 Fr <12 months 12 Gy/8 Fr > 12 months
Liver	Nil	14.4 Gy/8 Fr	19.8 Gy/11 Fr	19.8 Gy/11 Fr
Brain	Nil	15 Gy/10 Fr	25.2 Gy/14 Fr	21.6 Gy/12 Fr < 16 years 30.6 Gy/17 Fr >16 years
Bone	Nil	30.6 Gy/17 Fr	30.6 Gy/17 Fr	25.2 Gy/14 Fr < 16 years 30.6 Gy/15 Fr > 16 years

[a]Additional 10.8 Gray/6 Fractions is given to the sites of gross disease identified at the time of radiation on the planning CT scan

evidence to support this now if the resection is complete.

Once commenced, XRT should be delivered in five daily fractions per week without interruption. If an interruption is inevitable, this should, if possible, be compensated for by hyper-fractionation so that the overall treatment time isn't extended.

For non-metastatic disease, surgery to XRT interval should be started between 9 and 14 days. Delay beyond 14 days is associated with a significant increased risk of death with a hazard ratio of 1.04/day [9]. Hence, it is important that a child with WT needs to be seen by a radiation oncologist before surgery so that planning can be done. Wound healing is not an issue as the dose delivered is so low that it will not hamper the process of postoperative healing.

20.2.6 Sequelae of Radiation

Acute side effects like radiation enteritis are rare as the dose of XRT is very less compared to most other pediatric tumors. Late sequelae include kyphoscoliosis and SMN. To decrease kyphoscoliosis, entire vertebra column is included in the treatment volume, and the dose also is reduced. As regards SMN, the cumulative incidence of SMN was 2.3%, 6.8%, and 12.2% at 30-, 40-, and 50-years post-treatment, respectively, in a population-based cohort study of WT survivors treated over 50 years [10]. There was no difference in the occurrence of SMN between children treated with or without XRT [8]. In addition, the dose is presently reduced to 10.8 Gy, and longer follow-up is required to see further reduction in SMN due to radiation.

20.3 Indications for Radiation

Depending on the tumor stage, histology, resection status, and ChT response about 15–25% patients of WT will have one or another indication for XRT. The broad indications for XRT in WT include:

1. Locoregional disease: To reduce the risk of local recurrence and improve probability of cure.
2. Metastatic disease: Control of lung metastasis with residual disease and rarely distant metastasis (including liver and bones).
3. Recurrent/relapsed disease: As an integral part of multimodality treatment used for salvage therapy.

The three principal fields for XRT include the flank, whole abdomen, and lungs in both major protocols. The NWTSG/COG protocols over the years have helped establish the indications, timings, and dosage of XRT to all the fields.

20.3.1 Locoregional Disease

The NWTS 1 and 2 established that XRT can be avoided in stage I tumors, if they receive vincristine and Actinomycin-D [4]. The NWTS-3 results in addition to the above also reported that favorable histology (FH) stage III tumors could be safely radiated with 10.8 Gy as compared to the previous 20 Gy to the flank (renal bed) and lymph nodal areas.

This significantly decreased the dose of XRT and hence the toxicities [5]. In general, the treatment regimens in the SIOP 2001 protocol for loco regional disease are quite successful, and very few changes have been made in the recent UMBRELLA Protocol [2].

The SIOP and the UKCCSG (now termed as UKCCLG) have over the past 40 years looked at indications and the advantages of XRT in the management of WT. The SIOP 1 randomized patients between preoperative XRT and primary surgery. In patients going upfront tumor resection, there was a significantly higher chance of tumor rupture [6]. SIOP 2 looked at a non-randomized set of patients with either preoperative chemoradiation or surgery alone, and there was significantly less tumor rupture in the first group. The SIOP 5 administered chemoradiation vs ChT alone in a randomized fashion preoperatively. Postoperative XRT was given only to stage II and III and not to stage I. Both arms showed equivalence in terms of rupture and overall survival. An important finding from this study showed that 43% of patients were only stage I and did not receive postoperative XRT. This strategy has been followed in SIOP to further reduce the late effects and toxicities of RT [7]. The SIOP 6 randomized node negative and positive patients to receive or not receive XRT, and the study was abandoned as the unirradiated group had an excess of recurrences [7].

The UK Wilms Tumor Study group had an interesting observation [11]. After neoadjuvant ChT, the number of stage III tumors decreased considerably from 29.8% to 9.8%. This meant that there was a reduction in the requirement of XRT by almost two-thirds.

The preoperative findings are also important for a radiation oncologist, especially when the capsule is ruptured. Prior biopsy and capsule rupture during surgery, even if it is accidental, are all labelled as stage III. As per NWTS-4 subset analysis, the local relapse caused reduced survival at 2 years among those with extensive spillage decreases with event-free survival (EFS) plummeting from 90% to 43% [10]. Extensive spillage associated with higher local relapse with a relative risk of 2.86 requires WAI, whereas accidental rupture in an otherwise intact capsule needs flank XRT only [12]. The patients with ascitic fluid positive for malignant cells and those with peritoneal implants would also need WAI. Entire peritoneal cavity from diaphragm till obturator foramen is included for WAI. Boost dose of XRT is required to control gross disease left behind either in the tumor bed (21Gy) or in the peritoneum (10.5Gy); boost doses mentioned are as per COG protocol.

Within a given stage, children with diffuse anaplasia (DA) histology WTs fare badly, and hence they require aggressive ChT as well as locoregional XRT. Daw et al. [13] studied all patients of NWTS I to IV and AREN0321 with anaplastic WT and observed a reduction of local recurrence from 6.2% to 4% with addition of flank XRT for focal as well as diffuse anaplasia; recurrences in this series occurred only in cases of DA. Hence, adjuvant XRT was recommended for all the patients with DA. Both COG and Indian Council of Medical Research (ICMR) recommend flank XRT even for stage I anaplastic WT, though it is not advised in SIOP protocol.

20.3.2 Metastatic Disease

Patients with metastatic disease having local stage I and II do not need adjuvant flank XRT. The local radiation for metastatic patients is considered if surgico-pathological features under stage III are present, and it could be either flank or WAI.

Presently in COG as well SIOP protocol, patients with initial chest X-ray negative CT scan positive lung metastases, who achieve complete radiological response after 6 weeks of ChT, are considered to have lesser tumor burden in the lungs; these patients do not need WLI. In COG protocol, these patients are referred to as "Rapid Complete Responders" [5]. The "Slow Incomplete Responders" however would complete their ChT and then receive WLI (Fig. 20.5). However, all patients with loss of heterozygosity (LOH) at 1p and 16q, irrespective of local extent of disease and response to ChT, would receive WLI [14]. ICMR recommends WLI irrespective of response to ChT [2].

Metastatic sites in the liver, brain, and bone are addressed after ChT. Whole organ is treated if the lesions are diffuse, while discrete ones are treated with localized XRT.

The radiotherapy protocol in UMBRELLA SIOP-RTSG 2016 study is in broad accordance with the COG protocol. In SIOP-2001, the WLI dose was 15 Gy, which was decreased to 12 Gy.

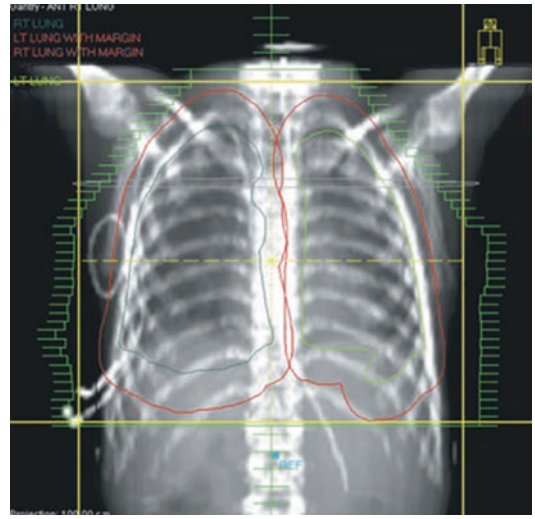

Fig. 20.5 Showing WLI which includes the entire pleural cavity

20.3.3 Recurrent Disease

XRT is used along with ChT with or without surgery in selected recurrent patients. The lesion should be small and could be either locoregional or metastatic; the dose and technique depend on the previous treatment and duration since radiation. In Umbrella protocol, in patients with recurrent disease with lung metastasis without prior lung irradiation, WLI should be administered in all histology types.

20.4 Comparison of Radiotherapy Schedules in COG and SIOP-RTSG (Umbrella Protocol)

There are subtle differences about the XRT protocols that have been highlighted in tabulated form (Tables 20.1 and 20.2). It is obvious that the doses used in COG are marginally less.

20.5 Conclusions

All WT patients should be seen by a radiation oncologist before surgery as it is very important to start adjuvant radiation between 9th and 14th

POD. XRT for WT plays a vital role in preventing local recurrence and thus improving the EFS. It is safe in carefully selected children based on the staging and risk stratification. It has a useful role in recurrent settings too.

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