Recurrent/Relapsed Wilms' Tumor

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31.1 Introduction

The management of Wilms' tumor (WT) has undergone a sea change with the introduction and refinement of multimodal therapy, which includes surgery, chemotherapy (ChT), and radiotherapy (XRT). With these advancements, children with these tumors can expect an overall survival (OS) rates approaching 90% [1].

However, relapse/recurrence of WT is not uncommon. About 15% of patients with favorable-histology (FH) WT experience a recurrence, whereas half the patients with an anaplastic WT (AWT) have a recurrence [2]. The incidence of recurrences in low and middle income countries (LMIC) have been high, with even the latest rates being reported up to 30% [3]. Most recurrences in WT occur within 2 years from the time of diagnosis. Late recurrences are rare and can occur up to 25 years from the initial diagnosis [4–7]. In a retrospective study in more than 13,000 children across various WT trials, the rate of late recurrence were only 0.5% [8]. Lung and pleura account for 50–60% of recurrences, whereas the abdominal recurrences contribute toward 30% of relapses. Other sites like the brain and bone are involved in 10–15% [9–11].

In contrast to the primary WT, the recurrent Wilms' tumors (RWT) carry poor prognosis, with only 3-year OS of only 24–40%, while a subset of patients with FH have an OS of 77% [3, 12].

The surveillance protocol for a patient treated for WT is discussed in another chapter and is not repeated here.

31.2 Site(s) of Relapse and Presentation

The recurrence can occur in the lungs and abdomen (with or without involvement of the lungs) and rarely in the brain and bones. Most common recurrence is seen within the lungs (58–63%), followed by the abdomen, with or without involvement of other sites (29–49%) [8, 12]. RWT in the brain or bones is a rare event (13%). Abdominal RWT can involve the previous site, liver, and opposite kidney and, sometimes extremely rare, unusual sites like the uterus and cervical lymph nodes (LN) [5, 13]. The distribution of the site of recurrence was similar, irrespective of whether the patients had received XRT or not.

Recurrences, in cases with FH in initial diagnosis, confined to the lungs only tend to have better prognosis compared to abdominal or other site recurrence, with 3-year OS of 44% vs. 28%

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Y. K. Sarin (ed.), *Wilms' Tumor*, https://doi.org/10.1007/978-981-19-3428-5_31

vs. 11% [12]. Unfavorable histology (UH) has poor prognosis irrespective of the site of relapse. Though recurrence in the liver carries poorer prognosis, with 4-year OS of 14%, successful surgical excision of these tumors can have good prognosis.

The RWT may or may not cause symptoms in these patients. The prognosis of patients who present with asymptomatic relapses, which are detected during the surveillance imaging, is better compared to those that present with symptoms (nearly twice the mortality) [14]. Abdominal recurrences may present with lump in the abdomen due to recurrence at previous site or liver or gross distension due to ascites, contralateral kidney mass, or pelvic mass. Pulmonary recurrences manifest as difficulty in breathing due to parenchymal masses or pleural effusion, cough, and very rarely pneumothorax [15]. For those with intracranial recurrences, presentation features include seizures, headache, vomiting, paresis/paralysis, and impaired consciousness [11].

31.3 Time of Recurrence

RWT are more prevalent within 2 years after treatment. Recurrences occurring beyond 5 years of treatment are termed as late recurrences. In the largest study that observed late recurrences, the distribution of recurrences in both alive and dead cases had no correlation with gender (equal incidence in both the genders), initial tumor stage, or type of previous treatment received. However, most of these cases had FH in the previous tumor [8]. Late recurrences can be either true recurrence or a metachronous WT in the contralateral kidney (attributed to persistence of nephrogenic rests). The survival in such case is better (87% vs. 45%) compared to recurrences elsewhere. The exact etiopathogenesis of late recurrences is not known. Quiescent tumor stem cells in such sites might escape the immune vigilance and may get activated by unknown stimuli (e.g., hormones in adolescents).

Grundy et al. measured the time to relapse and divided the period into early (0–5 months), intermediate (6–11 months), and late relapse (12+ months). The early relapse cases were mostly UH types at initial diagnosis and had the poorest 3-year-OS among the above strata (18%) [9].

31.4 Factors Influencing Occurrence of Relapse

Stage and histology are two of the most important factors that dictate the course of the disease. With respect to relapse, though no specific identifiable factors causing relapse are identified, the risk of relapse can be predicted in certain subgroups.

Stage III–IV WT, which have gained access to the lympho-vascular structures, can lead to seeding of tumor cells at local and distant sites, potentially causing more recurrences than the stage I–II tumors. The patients with initial stage I FH WT had better post-relapse survival compared to stage IV FH (57% vs. 17%) [12].

AWT and pretreated tumors with blastemal-type histology, which are considered as high-risk types, are again resistant to treatment and cause early relapses.

Biological markers have been much discussed in recent times. Especially the loss of heterozygosity (LOH) at 1p and 16q, which, in even the FH WT, have caused more relapses [16].

The initial treatment received also holds significance with respect to post-relapse prognosis. Patients who received two-drug therapy, vincristine (VCR) and actinomycin-D (AMD), had better survival rates compared to patients who received three-drug therapy (VCR, AMD, and doxorubicin) (42% vs. 26%), in an analysis done for stage II–III (FH) cases. Perhaps patients who received only two drugs had better sensitivity of RWT for the third drug during post-relapse treatment.

XRT to the abdomen doesn't predict the future risk of relapse. But previously unirradiated abdominal RWT are better salvageable compared to RWT in previously irradiated cases. RWT in the lungs occurred more frequently in unirradiated sites.

Percutaneous biopsy of renal tumor at initial presentation has been considered a risk for

recurrence for a long time. But a study from UK found the initial biopsy increased the risk of local relapse (abdomen, other than liver) while having no effect on distant relapse [17]. But the significance was less when histology and size were considered in the multivariate analysis for local relapse.

Another factor to be considered here is the size of the tumor at initial diagnosis. Tumors >12 cm in size are significantly large and have high risk of rupture. This is more significant for those above 15 cm in size. Rupture of tumor is associated with increased risk of local recurrence [18].

Males fare slightly worse than females [19].

In a multivariate analysis of adverse prognostic factor in children with RWT who had been enrolled under the SIOP-6 or SIOP-9 treatment strategies, SIOP identified various adverse factors for RWT [20]:

1. Stage IV disease.
2. UH.
3. Time to recurrence of 6 months or less after initial diagnosis.
4. Multiple sites of recurrence.
5. Previous history of XRT.

Other studies have analyzed 95 patients and demonstrated an association of LN involvement and anaplasia as an adverse prognostic factor correlated with an increased probability of relapse [21]. A European group analyzed 170 patients with relapse and found the following adverse risk factors for a relapse [22]:

1. Initial stage III or IV.
2. High-risk histology.
3. Time to recurrence of 6 months or less after initial diagnosis.
4. Site of relapse.

The precise effect of site of relapse in a RWT is vitiated by the fact that many abdominal recurrences may occur in irradiated fields and many published reports may include contralateral kidney as a recurrence along with tumor bed, liver, or LN. Similarly, many lung recurrences may occur in previously unirradiated areas but may also include mediastinal recurrences. There is a definite need to further evaluate the site of relapse as a prognostic factor for a recurrence.

31.5 Therapy for RWT

There is a limited experience available for the optimal rescue therapy for RWT. Most patients receive VCR and AMD, with or without doxorubicin (DOX), as part of the initial therapy for the primary lesion. Before the 1990s, the same ChT agents were used for the treatment of both primary and recurrent disease. However, the salvage rates with the same ChT agents in recurrent disease were as low as 25–40% [2]. With the introduction of alternate treatment combinations, the outcomes started improving up to 60% in the last 20 years [23]. As a general principle, it is preferable to avoid the agents that have been previously used as part of the initial therapy and to tailor the therapy using a risk-stratified approach. It is common to use ifosfamide, carboplatin (CARB), and etoposide (ETOP), either as a single agent or in combination (ICE regimen) (Fig. 31.1) [24].

ETOP has demonstrated an efficacy of 42% in clinical trials [25], whereas ifosfamide and CARB have shown a 52% objective response [25, 26]. Recent studies have documented the activity of topotecan in FH RWT but have not demonstrated any efficacy in AWT [27]. The introduction of these drugs led to event-free survival (EFS) rates ranging from 50 to 70% [23]. However, the best combinations, dose intensity, and the duration of

Week	0	3	6	9	12
IFO 1.8 gm/m^2 x 5 days	↓	↓	↓	↓	↓
CARB 400 mg/m^2 **x 2 days**	↓	↓	↓	↓	↓
ETOP 100 mg/m^2 **x 5 days**	↓	↓	↓	↓	↓
IFO ifosfamide, *CARB* carboplatin, *ETOP* etoposide					

Fig. 31.1 ICE regimen *IFO Ifosfamide* [24]

therapy still remain to be fleshed out. Moreover, the prognosis of the patients with RWT depends upon many other factors including the initial tumor stage, histology, previous modalities of therapies, site of relapse, and the time from the initial diagnosis to relapse. It also becomes difficult to standardize the various other modalities for treatment, viz., local surgical excision and XRT, especially for already irradiated relapses. High-dose ChT with stem cell rescue (SCR) is being increasingly utilized for the treatment of RWT with improving survival rates [28].

31.6 Management: Patient Risk Stratification Approach

A number of potential prognostic features influence the outcomes post a relapse. However, it is often difficult to determine the effect of each factor independently, as the numbers are low, and it is difficult to compare the subgroups of these patients. Also, the prognostic factors seem to be changing over time as the understanding and the therapy of primary and RWT evolve [21, 22].

Based on the current state of science, the following risk categories for RWT can be identified (Table 31.1) [29, 30]:

1. Standard risk [30].
   (a) FH RWT with initial therapy with therapy with VCR and/or AMD.
   (b) Account for 30% of all recurrences.
   (c) Event-free survival (EFS) of 70–80%.
2. High risk (HR) [31].
   (a) FH RWT with initial therapy with three or more ChT agents.
   (b) Account for 45–50% of all recurrences.
   (c) EFS of 40–50%.
3. Very high risk (VHR) [32].
   (a) Anaplastic, or blastemal-predominant RWT.
   (b) Account for 10–15% of all recurrences.
   (c) EFS of 10–15% only.

However, it is expected that with changes in treatment and further refinement in treating WT, the factors identified for risk stratification may lose their significance. More aggressive regimens which are more effective in dealing with RWT along with a judicious use of radiotherapy may also affect the significance of factors identified.

31.6.1 Management of Standard Risk RWT

The data on the management of standard risk RWT is limited due to a limited cohort of patients. However, the management of the standard risk RWT has revolved around two main protocols-one from National Wilms Tumor Study (NWTS) Group and the other from United Kingdom's Children's Cancer and Leukaemia Group (UKCCLG):

31.6.1.1 Stratum B of the NWTS-5 Relapse Protocol [33]

NWTS-5 relapse treatment consisted mainly of alternating courses of VCR-DOX- CTX and ETOP, which is similar to the Regimen I used as standard treatment for WT (Fig. 31.2). Surgical excision is employed only in locations which are amenable to surgical excision. XRT may also be used in selected cases. Four-year overall survival (OS) was 81.8% for all patients with a slightly lower EFS rates for children who had lung relapses.

Table 31.1 Risk stratification in RWT

Risk group	Includes	Incidence	EFS	Treatment recommendations
Standard risk	FH, initial therapy VA	30%	70–80%	CTX/DOX-CARB/ETOP
High risk	FH, initial therapy VAD	45–50%	40–50%	I/CARBO/ETOPO—ICE regimen
Very high risk	Diffuse anaplasia WT, blastemal-predominant WT	10–15%	10–15%	ICE regimen with high-dose melphalan

VCR vincristine, *AMD* actinomycin-D, *DOX* doxorubicin, *CTX* cyclophosphamide, *CARB* carboplatin, *ETOP* etoposide, *I* ifosfamide, *VA* VCR/AMD, *VAD* VCR/AMD/DOX

Fig. 31.2 Stratum B of the NWTS-5 Relapse Protocol [33]

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	18	21	24
VCR[a] 50 μg/kg or 1.5mg/m^{2bd}		↓	↓		↓	↓	↓	↓	↓		↓	↓	↓[c]	↓[c]		↓[c]		↓[c]
DOX[d] 1.5mg/kg or 45mg/m^2	↓						↓						↓			↓		↓
CTX 14.7mg/kg or 440mg/m^2 **X 5 days**				↓			↓			↓			↓		↓	↓	↓	↓
ETOP 3.3mg/kg or 100mg/m^2 **X 5 days**				↓						↓					↓		↓	
XRT							↓											

[a]Maximum single dose 2mg
[b]for all patients weighing >30kg
[c]67μg/kg or 2mg/m2 for weeks 12, 13, 18, 24
[d]Maximum cumulative dose 250mg/m^2
Dose of DOX at week 6 should be decreased by 50%, if WLI or WAI has been given
Abbreviations: DOX, Doxorubicin; VCR, Vincristine; CTX, Cyclophosphamide; ETOP, Etoposide; XRT, Radiotherapy

Week	0	1	2	3	4	5	6	7	8	9	10	12	13	15	16	18	19	21	22	24	25	27	28	30	31	33	34
AMD 1.5mg/m^2		↓			↓			↓			↓		↓		↓		↓		↓		↓		↓		↓		↓
DOX 30mg/m^2		↓			↓			↓			↓		↓		↓		↓		↓		↓		↓		↓		↓
VCR 1.5mg/m^2	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓		↓		↓		↓		↓		↓		↓		↓		↓	

Cumulative dose of DOX is 360 mg/m^2
If patient is about to receive pulmonary radiation therapy, then DOX should be administered from week 1 to 28.
Cumulative dose is reduced to 300 mg/m^2
Abbreviations: VCR-, Vincristine; AMD, Actinomycin D; DOX, Doxorubicin

Fig. 31.3 UKW-R Protocol [34]

31.6.1.2 UKW-R Protocol of UKCCLG [34]

Here, patients with recurrences were managed by either a pulse intensive regimen of VCR, AMD, and DOX or an alternating course of DOX-CYCLO and CYCLO-ETOPO (Fig. 31.3).

31.6.2 Management of High-Risk RWT

The management of these difficult cases has revolved around either a conventional-dose ChT or a high-dose ChT with an autologous SCR.

31.6.2.1 Conventional-Dose Chemotherapy

A study published on the treatment of 60 children with relapse reported the management of these children by alternate courses of CTX and CARB with CARB and ETOP over a period of 90 weeks as part of the Stratum C of the NWTS relapse protocol [35]. They reported a 4-year EFS and OS of 42.3% and 48%, respectively. Abu-Ghosh et al. reported 63.6% EFS and OS with high-risk (HR) RWT treated with ICE ChT along with other therapies like surgical excision and XRT [36].

31.6.2.2 High-Dose ChT with Autologous SCR

High-dose myeloablative ChT is utilized along with bone marrow transplantation (BMT) and autologous SCR in an effort to treat the HR RWT. However, most of these treatments are outside the realm of controlled clinical trials. The aim is to obtain a better outcome than historical controls and various centers reporting higher 4-year OS rates (60–73%) [36, 37]. The French Society for Paediatric Oncology reported on 28 HR RWT treated with high-dose ChT with SCR and achieved an OS of 60.9% [37]. The regimen used in these studies utilized either a high dose ICE Regimen or a therapy using elphalan, ETOP, and CARB (MEC regimen) [35]. The German Cooperative Wilms Tumor Study Group reported on patients with HR RWT with ChT utilizing alternating regimen of CTX-ETOP with CARB-ETOP. Children who achieved complete response (CR) were continued on the same therapy, whereas who had partial response (PR) or and no response received ablative ChT with autologous SCR [38]. Campbell et al. reported on 13 children with relapsed WT treated with high-dose ChT with SCR and reported a 4-year OS of 73% [39].

Topotecan has been variably incorporated in the treatment of patients with RWT who failed initial treatment with three or more effective drugs. Topotecan is a camptothecin analog that has demonstrated antitumor activity in various childhood cancers including WT. A retrospective review of 16 children who received topotecan as part of their salvage regimens for HR RWT demonstrated no effectiveness in the treatment of HR histology RWT patients. However, its role is still equivocal in standard risk histology [39].

Thus, the current state of literature suggests that high-dose ChT with SCR might be an effective treatment for patients with HR RWT.

31.6.3 Management of Very-High-Risk RWT

Patients with AWT or advanced tumors on initial therapy who present with a recurrence have generally demonstrated abysmal survival rates to the currently employed treatment strategies [23, 40, 41]. Overall, in these patients, a very poor response to any drug combination due to intrinsic drug resistance has been reported and only a handful of survivors. Other ChT agents and novel strategies may be required to improve the outcomes in this group of patients.

31.7 Other Strategies

Most patients with RWT can be rescued with salvage therapy especially in the standard risk group. However, the HR and the VHR groups demonstrate poorer survival rates with almost very poor survival rates in the VHR. There is a need to identify newer novel agent and targeted therapies for the treatment of these children. A systematic review of literature for published phase I and II clinical trials that registered patients with WT had identified 62 trials. Fifty of these were phase I and 12 were phase II trials, and these enrolled a total of 214 patients with RWT [42]. Overall, only 33 WTs demonstrated any degree of tumor control with these strategies with only 5 patients (2%) demonstrating CR and only 15 patients (7%) demonstrating a PR. This highlights the currently dismal outlook with newer strategies. Various agents that have been attempted in the management have been oxaliplatin, thiotepa, VEGF, bevacizumab, and all-trans-retinoic acid among other agents [43].

31.8 Role of Surgery and XRT in the Management of RWT

Logically, surgical removal of operable tumors should be helpful, but the evidence for the same is lacking in literature. The NWTS group suggests that a surgical removal of all pulmonary metastasis is unlikely to improve survival rate when compared to ChT [43]. Fuchs et al. reported on children with liver metastasis and the outcome of surgical excision in those group [44]. They reported that the patients who could be managed

by a complete surgical excision survived. Similarly, an excision of solitary lung metastasis might avoid the toxicity of lung XRT. There have been no clear guidelines for administering XRT in this select group of patients. However, reports of administration of whole abdominal irradiation (WAI) for abdominal or hepatic recurrence and whole lung irradiation (WLI) for pulmonary recurrence(s) do exist [43].

31.9 Treatment of RWT in SIOP-RTSG Umbrella protocol

In the UMBRELLA protocol, patients with relapsed tumours are classified into three groups AA, group BB, and group CC, based on these factors [45]. Treatment of group AA relapsed WT, defined as patients with initial stage I–II low-risk or intermediate-risk tumours, who received only VCR and/or AMD (no XRT) in their first-line treatment, will include four drugs (combinations of DOX and/or CTX and CARB and/or ETOP). The combination of these drugs are same used in NWTS-5 relapse protocol and UKW-R protocol and the, but drug combinations and doses vary. Treatment of group BB relapsed WT without initial diffuse anaplasia or blastemal-type histology, who have already received DOX in their initial treatment receive an intensive reinduction drug regimen (including the combination of ETOP and CARB with either IFO or CTX), followed by either high-dose melphalan and autologous stem cell rescue (ASCR) or two further reinduction courses [29]. Relapsed group CC includes patients with initial diffuse anaplasia or blastemal-type tumours. For patients in this category, and for the other relapsing patients showing no response to salvage treatment, the UMBRELLA protocol advises trying camptothecins (irinotecan or topotecan) or novel compounds, as these patients will have already received most conventional active agents in their first-line therapy and are likely to develop ChT-resistant disease [46]. UMBRELLA protocol also provides structured guide-lines for administering XRT and surgery at relapse [45].

31.10 Surveillance Schedule After a Complete Response (CR) Following Relapse

There is scarce evidence about optimal surveillance schedules and methods for detection of tumor relapse after a CR following a relapse. Since there are no optimal guidelines for surveillance schedules available in literature, a surveillance schedule detailed for WT with high risk of recurrence might be suitable. In view of the late effects of highly intensive and toxic ChT and XRT, a long-term surveillance protocol may be required to capture recurrent relapse, second malignancies, and/or other effects [43].

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