Metastatic Wilms' Tumor

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30.1 Introduction

The remarkable success story that is the treatment of Wilms' tumor (WT) over the years is in a large measure due to the comprehensive treatment of metastatic disease, to the extent that even widely disseminated WT has a treatment success rate of 70–80%—a feat unmatched in the treatment of any other solid tumor [1, 2]. Fortunately, WT is usually picked up early by the parents, and only about 11–17% of tumors are diagnosed with metastasis at presentation, in contrast to tumors such as neuroblastoma, in which two-thirds of whom may have metastatic disease at presentation [3–5]. Regrettably, the presence of metastases does decrease the overall survival (OS) and increases incidence of relapse, apart from long-term side effects like cardiac dysfunction, musculoskeletal problems, and risk of second malignancy [6, 7]. The current research strongly focuses on ways to treat the metastasis aggressively while at the same time avoiding unnecessary chemotherapy (ChT) or radiation (XRT) so as to decrease the undesirable long-term sequelae. To this end, there has been a constant endeavor to use investigations of increasing sensitivity or find new methods to diagnose and quantify smallest of metastases and tailor treatment intensity according to their biological potential. Over the years, there have been refinements in the investigations, such as adoption of non-contrast computerized tomography (NCCT) chest as the primary investigation for pulmonary metastases, instead of simple chest X-ray (CXR) and attempts to chart the biological characteristics of the tumor to fathom the metastatic and response potential. The research is also aiming to stratify risk groups in metastatic disease based on the biological features of the tumor. Loss of heterozygosity (LOH) at 1p and 16q and gain of chromosome 1q are important targets in this endeavor [8–10].

30.2 Pathophysiology

Metastatic WT, also categorized as stage IV WT, is defined as the presence of hematogenous spread of the tumor to the lungs, liver, brain, bones, or extra-abdominal lymph nodes (LNs). The lung is the most common site of metastases (80%), followed by the liver. Brain and bone metastases are unusual in classical WT and rather indicate an alternative diagnosis like malignant rhabdoid tumor of the kidney (MRTK), with predominantly brain metastasis, or clear cell sarcoma of the kidney (CCSK), with predominantly bone metastasis [4, 11]. Metastasis is independent of the local size and stage of tumors and may be present in local stage I tumors also. Biological factors, which are just being investigated, may have a role in the propensity of a tumor to

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metastasize. Few studies have demonstrated that metastases from WT contained predominantly blastemal component with lesser amount of differentiated elements [12]. It is also proposed that intensive ChT and XRT may initiate differentiation in these metastatic nodules and cause maturation or fibrosis in at least some of the patients, which is the rationale behind requirement of histological confirmation in nodules persisting after chemotherapy and radiation [1, 12]. However, it needs to be noted that this is not a universal phenomenon and may depend on the biological characteristics of the tumor.

30.3 Metastasis to Other Sites

Though this chapter largely describes the management of pulmonary metastasis as the lung is the most common site, the same principles of management apply to the other metastatic sites. It is to be remembered though that metastasis to less common sites such as the brain and bone or rarely the pancreas, spine, gonads, etc. should prompt histological confirmation of the primary tumor.

Unusual sites of metastasis in classical WT have rarely been reported. This includes the spinal canal, pancreas, and gonads [13]. The mechanism of such spread is not clear, but some evidence of it being lympho-vascular and perineural/intraneural (in case of spinal spread) has been reported [14]. Though general principles of management remain the same largely, modifications of investigations and treatment may be required according to the unusual sites. In particular, the metastasis at unusual sites may need a preferential treatment with surgical excision in addition to the adjuvant chemotherapy and radiotherapy. Some symptoms such as spinal compression may need rapid alleviation, and response to chemotherapy may not be predictable [14].

30.4 Diagnosis

Pulmonary metastases, if extensive, can cause cough, tachypnea, and respiratory distress, whereas liver metastasis may cause ascites, anasarca, abdominal pain, prominent abdominal veins, and hepatomegaly or coagulation disorders. Bone pains, seizures, headache, and vomiting are rare occurrences due to metastasis in typical WT. However, usually no specific symptoms are attributable to the metastatic disease, and each child needs to be actively investigated thoroughly to confirm metastasis. Since 80% of metastases are to the lungs, a CT chest is therefore a routine part of work-up of WT. Investigations for metastasis at other sites are guided by the presence of symptoms.

30.4.1 CT Chest

Before the National Wilms Tumor Study (NWTS)-5 and SIOP 2001, CXR was the recommended investigation to look for pulmonary metastasis, and a chest CT was optional. Only the nodules clearly demonstrated on a CXR were treated as metastatic disease. With increasing use of CT by the turn of the century, there arose a distinct cohort of children with small lung nodules <10 mm, demonstrable on a CT, but not visible on plain CXR, and thus arose the dilemma of CT-only nodules. The reason for dilemma regarding the treatment of CT-only nodules arises from the fact that 17–26% of these may actually be benign, incidentally detected lesions such as lung scars or granulomas. Additionally, there is a lot of inter-reader variability among the reporting radiologists regarding these small-sized nodules [15–18].

Studies from the National Wilms Tumor Study Group (NWTSG) comparing the outcomes of treatment of patients with CT-only nodules treated as metastatic vs. localized disease found that addition of doxorubicin (DOX) improved the event-free survival (EFS) in the group treated as metastatic disease, but there was no difference in the EFS and OS in those treated with radiotherapy (XRT). This was found to be due to increased events in the form of second malignancies [4, 16]. These studies also found that the patients with CT-only nodules treated as localized disease had a very high incidence of lung recurrence to the tune of 79%, suggesting that the pulmonary metastatic disease was being undertreated. The

second UK Children's Cancer Study Group Wilms' tumor study (UKW2) and SIOP 2001-RTSG analysis also report similar findings. It was seen that stage I patients treated as localized disease only, even in the presence of CT-only nodule(s), had a higher relapse rate [19, 20].

These findings confirmed the hypothesis that even CT-only nodules would have to be treated as metastases, even though there may be a slight chance that these may be some benign lesions such as lung granulomas in a small percentage of cases. Thus, CT chest is now the recommended investigation to look for pulmonary metastasis in all WT treatment protocols.

To decrease the possibility of benign pulmonary lesions being overtreated as metastases, certain radiological criteria have been defined. The COG group considers lung nodules as metastatic disease if they were round, non-calcified, and not in a pulmonary fissure [1]. To improve the accuracy of diagnosis and remove subjectivity, it also recommends all CT scans to be centrally reviewed in the beginning and to assess the response to therapy. Though it has correlated the treatment response rates according to size of nodules also and found best response in nodules <3 mm, however, it does not define size criteria for the pulmonary nodules to be considered metastatic [1]. On the other hand, SIOP-RTSG UMBRELLA protocol considers lung nodules as metastatic disease only if >3 mm in maximum transverse diameter [2]. The UKCCLG group finds CT chest desirable to look for metastases but recommends clinician decision in conjunction with central expert review to confirm the relevance of any positive findings and assess response [21].

30.4.2 CT Chest for Response Assessment

The response of metastatic disease to ChT needs to be carefully assessed as further treatment depends on it. This is done by repeat CT chest at week 6 of ChT.

In the NWTS/COG protocol, those with complete response (CR) of lung nodules at this stage are labeled as *rapid complete responders (RCR)*. They are treated with three-drug ChT; lung XRT can be avoided in these patients, subject to certain biological criteria (no LOH at 1p and 16q and no gain of 1q). Those with slow response or progressive disease (PD) are labeled as *slow incomplete responders (SIR)* and are treated as per Regimen M and whole lung irradiation (WLI) [1].

SIOP also notes disappearance of pulmonary nodules at 6 weeks as an important factor to decide further treatment. However, it stratifies the subsequent treatment further based on histology of primary and metastatic tumors, nodule size, and response to the preoperative ChT or surgery [2].

30.4.3 Volumetric Assessment

The volumetric assessment of residual primary tumor post-ChT by MRI is now an important part of UMBRELLA protocol [2]. There are suggestions that volumetric assessment of pulmonary nodules at the beginning of therapy and post neoadjuvant ChT may also help in a more accurate response assessment [2, 21]. However, more studies are required in this aspect before its usefulness is documented.

30.4.4 CECT Abdomen

This essential investigation for primary tumor assessment also helps in picking up liver metastases that are present in 2% of WT. The number of metastatic nodules, lobes involved, and the remaining healthy liver parenchyma should be noted. Unusual metastases such as pancreatic and gonadal may also be revealed [2, 21].

30.4.5 MRI Head and Spine

MRI head and spine needs to be done in case of suspicion of central nervous system metastases [2, 21].

30.4.6 Bone Scan and Skeletal Survey

Suspected bone metastases should be investigated for site and number by nuclear scans and X-rays. This is required only in patients with clinical symptoms suggestive of bony metastases like bone pains, pathological fractures, etc. Importantly, the primary tumor should be reexamined for alternative pathology like CCSK [2, 21].

30.4.7 Biological Studies

In COG protocol, certain biomarkers, namely, loss of heterozygosity (LOH) at 1p and 16q and chromosome gain at 1q, have a crucial role to decide treatment of metastatic nodules [22]. Even in RCR with CR of nodules at 6 weeks, LOH at 1p and 16q mandates aggressive treatment with Regimen M and WLI. In the AREN0533 study, even after CR and aggressive treatment as detailed above, the 4-year EFS was significantly lower for patients with 1q gain. However, *RCR* with LOH at 1p and 16q, treated aggressively with upgraded Regimen M and XRT, showed similar outcomes to those patients without LOH (Table 30.1) [1].

30.4.8 Biopsy

Histological confirmation of metastatic disease is a controversial issue. On one hand, it is desirable to confirm metastases to prevent overtreatment in incidental lesions such as lung granulomas. On the other hand, it increases morbidity, and if done at the beginning of therapy, it prevents response monitoring and the possibility of omission of lung XRT in cases of CR [11]. Approximately 17–26% of the pulmonary nodules may be proven benign by biopsy [15]. In fact, for this reason, COG recommends full upgradation with three-drug regimen and XRT in patients in whom pulmonary nodules are fully resected at the beginning of therapy and found to be true metastases. These patients may have been *RCR* and could have avoided DOX and WLI but, in the absence of any remaining lesion to monitor response, have to be treated with full metastatic regimen.

The histological confirmation of persistent pulmonary lesions after 6 weeks of ChT is deemed desirable, but not mandatory, by the COG. In the AREN0533 study, 16 out of 175 patients with persistent lung nodules on CT underwent lung nodule biopsy and were classified as having CR on the basis of the biopsy results [1].

On the other hand, the UMBRELLA protocol recommends mandatory resection of any persistent pulmonary nodules to be done at week 10 of ChT. In fact, this is recommended not just for histological confirmation, but the intent is to achieve complete clearance of the pulmonary metastatic disease. WLI is then given only in stage II–IV, high-risk tumors or in those where complete surgical resection was not possible [2]. UKCCLG has similar recommendations [21].

In all the protocols, any pulmonary nodules that persist after completion of all ChT and XRT need surgical removal.

Unusual metastatic sites like the pancreas may require a biopsy to confirm the metastasis.

Table 30.1 Outcomes according to 1q gain status [1]

Group	No. (%)	4-year EFS % (95% CI)	*P*	4-year OS % (95% CI)	*P*
Incomplete lung nodule response					
1q gain+	42 (36.2)	86 (72.2 to 99.3)	0.15	93 (83.1 to 100)	0.45
1q gain−	74 (63.8)	92 (84.4 to 99.8)		96 (90.4 to 100)	
Complete lung nodule response					
1q gain+	21 (21.9)	57 (73.4 to 100)	0.001	89 (73.4 to 100)	0.16
1q gain−	75 (78.1)	86 (73.4 to 100)		97 (73.4 to 100)	

30.4.9 18F-Flourodeoxyglucose (18F-FDG) Positron Emission Tomography (PET)-CT

Though FDG-PET is not currently the standard of care for WT, it has potential to be a very useful noninvasive investigation, especially in metastatic disease. WT is 18F-FDG avid, and it can be a useful adjunct to conventional imaging in monitoring response to preoperative ChT. It is possible that *SIR* with doubtful remaining lesions where biopsy is recommended currently to confirm the metastatic activity may be able to avoid surgical biopsy depending on the 18F-FDG avidity, which corresponds to histologically confirmed active disease [23].

30.5 Management

The entire focus of metastatic WT management is to attempt regime intensification while minimizing secondary and long-term effects of the treatment. The analysis of patients with metastatic disease in NWTS-4 and NWTS-5 and SIOP 2001 revealed that though intensification of ChT and XRT increased cure rates, it did not lead to better OS or EFS in all patients due to increased toxic late effects [6, 7]. Thus, the AREN0533 protocol by COG and UMBRELLA protocol were specifically designed to take into account the stratification of treatment based on the biological behavior of the metastatic disease. Rather than just the presence of metastatic disease, the response of the metastasis to preoperative ChT guides the intensity of the treatment and also the outcomes. Timely monitoring of response thus becomes imperative.

The following section describes the treatment of the lung metastases, but the same principles apply to metastases elsewhere too.

30.5.1 COG Protocol

The AREN0533 study outlines the COG principles of metastatic disease treatment. The study design was inspired mainly by the analysis of patients with CT-only nodules in NWTS-4 and NWTS-5 studies, where a better outcome was achieved with a three-drug treatment, but more late effects toxicity was seen with addition of XRT. This study then sought to provide differential treatment to patients with metastatic disease depending on their response to initial ChT, thus decreasing toxicity in a large proportion of cases.

After confirmation of metastatic disease, all patients are started on three-drug regimen with vincristine (VCR), actinomycin-D (AMD), and DOX (preop cumulative dose of 45 mg/m^2) over 6 weeks [1].

The *RCR* are further treated according to the biomarker status. Those without LOH at 1p/16q continue receiving 3 drugs for 19 more weeks (total 25 weeks) with a cumulative DOX dose for the entire therapy of 150 mg/m^2. The *SIR* and the patients with radiological CR but positive for LOH1p/16q receive the upgraded Regimen M—four doses of cyclophosphamide (CTX) and etoposide (ETOP) in addition to VCR, AMD, and DOX; total ChT is of 31 weeks in addition to WLI. Reassessing the lung nodules and withholding XRT in the *RCR* avoid lung XRT in around 40% of patients [1]. Biopsy of lung lesions in *SIR* is strongly recommended. Any residual metastatic lesion after completion of ChT and XRT needs to be surgically removed. Abdominal XRT is administered if the tumor is local stage III. When both WLI and whole abdomen irradiation (WAI) are given, the radiation fields overlap at the margins to prevent inadequate dosing at the junction.

The recommendations for XRT according to the COG AREN0533 (NCT00379340) study are as in Table 30.2. XRT should be started preferably within 14 days of nephrectomy, and AMD and DOX should be withheld during the duration of XRT.

The treatment protocol for metastasis at any other site remains same as for lung nodules. Pulmonary metastases as also the metastases at any other site too, remaining after the completion of therapy, need to be surgically removed if possible.

Table 30.2 Recommended radiotherapy doses for metastatic sites in WT under COG treatment protocol (Source: AREN0533 NCT00379340 study trial document) [1, 38]

Lung (whole ± boost) (total/fraction dose)	Liver (whole ± boost) (total/fraction dose)	Brain (whole ± boost) (total/fraction dose)	Bone (total/fraction dose)	Unresected LLN metastasis
12.6 Gy/1.8 Gy ± 9.0 Gy/1.8 Gy (boost to gross residual disease)	10.8 Gy/1.8 Gy (whole liver) ± 9.0 Gy/1.8 Gy (boost to gross residual disease)	21.6 Gy/1.8 Gy (whole brain) + 0.8 Gy (boost to gross residual disease)	25.2 Gy/1.8 Gy (lesion +3 cm)	19.8 Gy/1.8 Gy (entire nodal region)

30.5.2 SIOP-RTSG UMBRELLA 2016 Protocol

Like the COG protocol, the SIOP-RTSG UMBRELLA 2016 protocol recommends 6 weeks of preoperative ChT with three drugs—VCR, AMD, and DOX—followed by response assessment by CT. There is difference though in the cumulative dose of neoadjuvant DOX which is 100 mg/m^2 in this protocol compared to 45 mg/m^2 in the COG protocol. Further treatment is stratified according to the disappearance of pulmonary nodules, size, and histology of pulmonary nodules if persistent, tumor histology, and local tumor stage. In the best-case scenario, that is, complete disappearance of the metastatic tumor along with low- or intermediate-risk stage I–III of primary tumor, lung XRT is avoided and DOX is given at the cumulative dose of 150 mg/m^2. For the rest of the patients, detailed guidelines are provided for the stratification of postoperative ChT, in which the cumulative dose of DOX is kept as low as possible to reduce cardiac toxicity. This involves stratifying patients to VCR and AMD plus DOX either with a cumulative DOX dose of 150 mg/m^2 or VCR, and AMD plus DOX with cumulative DOX of 250 mg/m^2, or a four-drug regimen including ETOP (150 mg/m^2/day), carboplatin (CARB) (200 mg/m^2/day), CTX (450 mg/m^2/day), and doxorubicin (cumulative dose 300 mg/m^2). The detailed stratification and treatment plan post neoadjuvant ChT and nephrectomy are tabulated in another chapter.

The UMBRELLA protocol also strongly encourages resection of any residual metastatic disease by week 10. This gives us a correct histological picture and avoids further treatment intensification in benign lesions. Also, it achieves complete surgical clearance of disease in a large number of cases and help to avoid therapy intensification and consequent late effects. This approach has eliminated the requirement for WLI in 59–67% of patients [2].

Metastatic disease resection should be carried out as soon as possible after nephrectomy and preferably before the start of postoperative ChT. Though extensive surgery can be done to completely eliminate metastatic disease, potentially mutilating surgeries need to be avoided. Thus, whereas wide wedge resections of the lung and liver, segmentectomies, and even lobectomies are acceptable, pneumonectomy should be avoided. Metastasis outside the lung and liver should be resected as far as possible while avoiding damage to vital organs [2].

The XRT protocol in UMBRELLA protocol is in broad accordance with the COG protocol (Table 30.3). In SIOP 2001, the WLI dose was 15 Gy, which was decreased to 12 Gy. This was done considering the previous NWTS experience of high EFS and OS (72% and 78%) for favorable histology (FH) tumors with only 12 Gy XRT to the lungs [24].

30.5.3 UKCCLG Protocol

The UKCCLG protocol is similar to the UMBRELLA protocol in terms of stratifying the postoperative treatment on the basis of residual metastatic disease and tumor histology. It uses similar drugs and dosages [21].

Table 30.3 Radiotherapy guidelines in UMBRELLA-SIOP-RTSG 2016 for metastatic disease [2]

	Lung (whole ± boost) (total/fraction dose)	Liver (whole ± boost) (total/fraction dose)	Brain (whole ± boost) (total/fraction dose)	Bone (total/ fraction dose)
Low-risk	No	No	No	No
Intermediate-risk	12.0/1.5 Gy (± 10–13 Gy)[a]	14.4/1.8 Gy (± 10.8/1.8 Gy)[a]	15.0/1.5 Gy (± 10.8/1.8 Gy)[a]	30.6/1.8 Gy
High-risk	15.0/1.5 Gy (± 15–20 Gy)[a]	19.8/1.8 Gy (± 16.2/1.8 Gy)[a]	25.2/1.8 Gy (± 10.8/1.8 Gy)[a]	30.6/1.8 Gy

[a]Boost dose indicated for residual tumor at the time of XRT only

30.6 Management of Unfavorable Histology Metastatic WT

There is a subgroup of children with unfavorable histology (UH) of the primary tumor (focal or diffuse anaplasia) and metastases. Further treatment intensification is required in these patients. In NWTS-5, these children were treated with Regimen I—VCR, DOX, CTX, and ETOP. The 4-year EFS treated such was 55% [25, 30]. In the AREN0321 study by COG, designed for high-risk unfavorable histology stage II–IV, diffuse anaplasia WT showed that regimen UH-1, a more intensive regimen containing CARB in addition to agents used in Regimen I (CTX, CARB, ETOP, and VCR-AMD-DOX plus XRT for 30 weeks) for patients with stage II–IV and focal anaplasia, and regimen UH-2 (UH-1 plus VCR and irinotecan) for patients with stage II–IV and diffuse anaplasia, improved EFS (69%, 95% CI: 56–80%) [25]. This however comes at the cost of significant toxicity to cardiac, respiratory, and musculoskeletal system along with a high risk of second malignancy. This high toxicity decreases the overall EFS and OS and is stimulating further research for therapies with more favorable therapeutic benefit ratio. The novel approaches are aimed at targeting the tumor via biological therapies rather than intensifying ChT and XRT, which seem to have reached a plateau of therapeutic benefit vs. side effects [26, 27].

The UMBRELLA protocol is also broadly consistent with the above approach for the high-risk metastatic tumors though this is one of the areas that the current ongoing study envisages to prospectively collect data on. High-dose ChT followed by autologous stem cell transplantation is also a suggested approach at the discretion of the treating physician, but the outcomes need to be further studied [28].

30.7 Response, Outcomes, and Late Effects

The AREN0533 study reported CR in 42% of the participants after 6 weeks of neoadjuvant ChT, and lung XRT could be avoided in these patients. The proportion of patients achieving CR at week 6 correlated with the initial maximum lung nodule size: The response rates were 22% CR for nodule size >10 mm, 59% CR for nodule size 6 to 10 mm, 69.2% CR for nodule size 3–5 mm, and 86.2% CR for nodule size 1–2 mm. Also, the response rates depended on the total number of lung nodules: 17.6% for >10, 42.3% for 6–10, 59.5% for 2–5, and 72.9% for a solitary nodule [1].

In contrast, 61–67% of patients have complete metastatic response before surgery following the SIOP protocol. An additional 17% achieved CR by surgical metastectomy [29]. The higher rates of CR in SIOP are probably due to higher dose of DOX in the preoperative ChT (100 mg/m^2) as compared to the COG protocol (45 mg/m^2). Also the fact that SIOP allows pulmonary CR to be achieved by surgical metastasectomy definitely improves the response rates.

30.7.1 Outcome

In the COG AREN0533 study, the EFS and OS in metastatic disease with CR at 6 weeks were 80% and 98.3%, respectively, whereas in *SIR*, it was 88% and 92%. The lower-than-expected EFS in *RCR*, though not significant, is thought to be due to the adverse effect of 1q gain, which can be overcome by Regimen M used in *SIR*. The outcome of high-risk anaplastic stage IV tumors treated with UH1 or UH2 was expectedly poorer with an OS of only 46% [30].

30.7.2 Late Effects

The persisting concern with the intense regimen used in metastatic disease is the possibility of late effects. Regimen M, notably, can lead to an increased risk of secondary leukemia associated with CTX and ETOP [31, 32]. There is also a risk of infertility, particularly in boys, related to the use of CTX, which has a cumulative dosage of 8.8 g/m^2 on Regimen M [33].

Lung XRT is an important factor leading to delayed cardiorespiratory failure, pulmonary fibrosis, breast cancer, and musculoskeletal problems in survivors. With the current concept of treatment stratification, fortunately this can be avoided in 40–60% of cases. It is estimated that there is a substantial increase in premature deaths (22.7% as compared to 5.4%) in WT survivors 30–50 years after treatment. This is attributable mainly to secondary neoplasms and cardiac illness, related primarily to XRT [34].

The presence of liver metastases at diagnosis is not an independent adverse prognostic factor in patients with stage IV WT [35].

30.8 Follow-Up

Meticulous and strict follow-up of recovered patients is imperative to detect early relapses. In addition to routine clinical examination and abdomen ultrasound every 3 months, a chest X-Ray (both AP/PA and lateral view) is recommended 3 monthly for the first 2 years for patients that recovered from metastatic disease. In high- and intermediate-risk cases, the CXR needs to be done 2 monthly. A NCCT chest is recommended after the end of therapy, if complete clearance of metastatic disease was not documented after the neoadjuvant treatment [36]. Six-monthly serum creatinine and 2-yearly echocardiography are also essential to look for delayed effects of treatment. Patients receiving bone irradiation for bony metastasis also need to undergo a yearly X-ray till full growth followed by a 5-yearly spine and pelvis X-ray thereafter [37].

30.9 Future Directions

Even though we have come a long way in treatment of WT, a large amount of work remains to be done to improve the quality of life of WT survivors, especially in metastatic disease.

A very important aspect to be studied is the effect of 1q gain, especially in *RCR* currently being treated only with three-drug regimen and showing more events than expected and consequently a lower EFS of 80% compared to the targeted 85% EFS. Both the COG and UMBRELLA protocol aim at collecting more data about the biomarkers, especially 1q gain and their effect on treatment and outcomes.

High-dose ChT followed by autologous stem cell transplant is an approach showing positive outcomes in many pediatric malignancies and is now being tried in metastatic WT too. Though presently this option rests with the treating physician and the local facilities, it is envisaged to assess this option very seriously.

Another important area of work is the treatment of focal or diffuse anaplastic metastatic WT. Currently being treated with Regimen UH1 or UH2, the treatment is handicapped by the severe side effects of these regimens, and there is a constant effort to attempt dose reduction or replace drugs such as irinotecan with those having higher benefit/side effects ratio.

Recently, dendritic cell-based immunotherapy against the WT1 gene protein is being investigated as a potential new targeted therapy, especially for disseminated/relapsed cancers

which have exhausted all other possible treatment approaches. The vaccine against the WT1 gene protein is hypothesized to act by encouraging an immune response by the host's dendritic cells against the cancer cells containing the WT1 protein. Though this is in a very nascent stage, more research into this may present an entirely revolutionary treatment option in the future [39].

30.10 Conclusions

Whereas almost 100% survival has been achieved in stage I and II WT, nevertheless treatment of metastatic WT is still work in progress. After the initial rapid strides in the EFS and OS with stronger ChT drugs and higher doses, along with XRT, there is now a pause in further improvement owing to the unwanted short- and long-term harmful effects of the therapy. Treatment stratification based on response in all the protocols has definitely helped in choosing the patients requiring treatment intensification while ensuring optimum results with less toxic therapy in others. However, this stratification begs for additional refinement, and further progress will depend on identification and understanding of biomarkers affecting tumor behavior.

References

1. Dix DB, Seibel NL, Chi YY, Khanna G, Gratias E, Anderson JR, et al. Treatment of stage IV favorable histology Wilms tumor with lung metastases: a report from the Children's oncology group AREN0533 study. J Clin Oncol. 2018;36:1564–70. https://doi.org/10.1200/JCO.2017.77.1931.
2. Heuvel-Eibrink MMVD, Hol JA, Pritchard-Jones K, Tinteren HV, Furtwängler R, Verschuur AC, et al. International Society of Paediatric Oncology-Renal Tumour Study Group (SIOP-RTSG). Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol. 2017;14:743–52. https://doi.org/10.1038/nrurol.2017.163.
3. Verschuur A, Tinteren HV, Graf N, Bergeron C, Sandstedt B, Kraker JD, et al. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol. 2012;30:3533–9. https://doi.org/10.1200/JCO.2011.35.8747.
4. Grundy PE, Green DM, Dirks AC, Berendt AE, Breslow NE, Anderson JR, et al. Clinical significance of pulmonary nodules detected by CT and not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's oncology group. Pediatr Blood Cancer. 2012;59:631–5. https://doi.org/10.1002/pbc.24123.
5. Warmann SW, Furtwängler R, Blumenstock G, Armeanu S, Nourkami N, Leuschner I, et al. Tumor biology influences the prognosis of nephroblastoma patients with primary pulmonary metastases: results from SIOP 93-01/GPOH and SIOP 2001/GPOH. Ann Surg. 2011;254:155–62. https://doi.org/10.1097/SLA.0b013e318222015e.
6. Green DM. The treatment of stages I–IV favorable histology Wilms' tumor. J Clin Oncol. 2004;22:1366–72. https://doi.org/10.1200/JCO.2004.08.008.
7. Termuhlen AM, Tersak JM, Liu Q, Yasui Y, Stovall M, Weathers R, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2011;57:1210–6. https://doi.org/10.1002/pbc.23090.
8. Chagtai T, Zill C, Dainese L, Wegert J, Savola S, Popov S, et al. Gain of 1q as a prognostic biomarker in Wilms tumors treated with preoperative chemotherapy in the International Society of Paediatric Oncology (SIOP) WT 2001 trial: a SIOP renal Tumours biology consortium study. J Clin Oncol. 2016;34:3195–203. https://doi.org/10.1200/JCO.2015.66.0001.
9. Gratias EJ, Dome JS, Jennings LJ, Chi YY, Tian J, Anderson J, et al. Association of chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's oncology group. J Clin Oncol. 2016;34:3189–94. https://doi.org/10.1200/JCO.2015.66.1140.
10. Cone EB, Dalton SS, Van Noord M, Tracy ET, Rice HE, Routh JC, et al. Biomarkers for Wilms tumor: a systematic review. J Urol. 2016;196:1530–5. https://doi.org/10.1016/j.juro.2016.05.100.
11. Davidoff AM. Wilms tumor. Adv Pediatr Infect Dis. 2012;59:247–67. https://doi.org/10.1016/j.yapd.2012.04.001.
12. Seemayer TA, Harper JL, Shickell D, Gross TG. Cytodifferentiation of a Wilms' tumor pulmonary metastasis: theoretic and clinical implications. Cancer. 1997;79:1629–34. https://doi.org/10.1002/(sici)1097-0142(19970415)79:8<1629::aid-cncr29>3.0.co;2-z.
13. Dokmak S, Cabral C, Couvelard A, Aussilhou B, Belghiti J, Sauvanet A. Pancreatic metastasis from nephroblastoma: an unusual entity. J Pancreas. 2009;10:396–9.
14. Ramdial PK, Hadley GP, Sing Y. Spinal cord compression in children with Wilms' tumour. Pediatr Surg Int. 2010;26:349–53. https://doi.org/10.1007/s00383-010-2563-z.
15. Ehrlich PF, Hamilton TE, Grundy P, Ritchey M, Haase G, Shamberger RC, et al. The value of surgery in directing therapy for patients with Wilms' tumor with pulmonary disease. A report from the National

Wilms' Tumor Study Group (National Wilms' Tumor Study 5). J Pediatr Surg. 2006;41:162–7. https://doi.org/10.1016/j.jpedsurg.2005.10.020.
16. Meisel JA, Guthrie KA, Breslow NE, Donaldson SS, Green DM. Significance and management of computed tomography detected pulmonary nodules: a report from the National Wilms Tumor Study Group. Int J Radiat Oncol Biol Phys. 1999;44:579–85. https://doi.org/10.1016/s0360-3016(99)00086-3.
17. Fletcher BD, Glicksman AS, Gieser P. Interobserver variability in the detection of cervical-thoracic Hodgkin's disease by computed tomography. J Clin Oncol. 1999;17:2153–9. https://doi.org/10.1200/JCO.1999.17.7.2153.
18. Wilimas JA, Kaste SC, Kauffman WM, Winer-Muram H, Morris R, Luo X, et al. Use of chest computed tomography in the staging of pediatric Wilms' tumor: Interobserver variability and prognostic significance. J Clin Oncol. 1997;15:2631–5. https://doi.org/10.1200/JCO.1997.15.7.2631.
19. Owens CM, Veys PA, Pritchard J, Levitt G, Imeson J, Dicks-Mireaux C, et al. Role of chest computed tomography at diagnosis in the management of Wilms' tumor: a study by the United Kingdom Children's cancer study group. J Clin Oncol. 2002;20:2768–73. https://doi.org/10.1200/JCO.2002.02.147.
20. Smets AM, van Tinteren H, Bergeron C, Camargo BD, Graf N, Pritchard-Jones K. The contribution of chest CT -scan at diagnosis in children with unilateral Wilms' tumour. Results of the SIOP 2001 study. Eur J Cancer. 2012;48:1060–5. https://doi.org/10.1016/j.ejca.2011.05.025.
21. Howell L, Messahel B, Powis M, Vujanic G, Saunders D, Alam F, et al. Children's Cancer and Leukaemia Group clinical management guidelines, Wilms tumour. 2015. https://www.cclg.org.uk/media/uploads/treatment_guidelines/pdf. Accessed 10 Jul 2020.
22. Grundy PE, Breslow NE, Li S, Perlman E, Beckwith JB, Ritchey M. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2005;23:7312–21. https://doi.org/10.1200/JCO.2005.01.2799.
23. Begent J, Sebire NJ, Levitt G, Brock P, Pritchard Jones K, Ell P, et al. Pilot study of F(18)-Fluorodeoxyglucose positron emission tomography/computerised tomography in Wilms' tumour: correlation with conventional imaging, pathology and immunohistochemistry. Eur J Cancer. 2011;4:389–96. https://doi.org/10.1016/j.ejca.2010.09.039.
24. D'Angio GJ, Breslow N, Beckwith JB, Evans A, Baum H, deLorimier A, et al. Treatment of Wilms' tumor. Results of the third National Wilms' tumor study. Cancer. 1989;64:349–60. https://doi.org/10.1002/1097-0142(19890715)64:2<349::aid-cncr2820640202>3.0.co;2-q.
25. Daw NC, Chi YY, Kalapurakal JA, Kim Y, Hoffer FA, Geller JI, et al. AREN0321 Study Committee. Activity of vincristine and irinotecan in diffuse anaplastic Wilms tumor and therapy outcomes of stage II to IV disease: results of the Children's oncology group AREN0321 study. J Clin Oncol. 2020;38:1558–68. https://doi.org/10.1200/JCO.19.01265.
26. Geller JI. Current standards of care and future directions for "high-risk" pediatric renal tumors: anaplastic Wilms tumor and Rhabdoid tumor. Urol Oncol. 2016;34:50–6. https://doi.org/10.1016/j.urolonc.2015.10.012.
27. Maschietto M, Williams RD, Chagtai T, Popov SD, Sebire NJ, Vujanic G, et al. TP53 mutational status is a potential marker for risk stratification in Wilms tumour with diffuse anaplasia. PLoS One. 2014;9:e109924. https://doi.org/10.1371/journal.pone.0109924.
28. Kremens B, Gruhn B, Klingebiel T, Hasan C, Laws H-J, Koscielniak E, et al. High-dose chemotherapy with autologous stem cell rescue in children with nephroblastoma. Bone Marrow Transplant. 2002;30:893–8. https://doi.org/10.1038/sj.bmt.1703771.
29. Verschuur A, Tinteren HV, Graf N, Bergeron C, Sandstedt B, de Kraker J. Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy. J Clin Oncol. 2012;30:3533–9. https://doi.org/10.1200/JCO.2011.35.8747.
30. Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: "state-of-the-art" update. Semin Pediatr Surg. 2016;25:250–6. https://doi.org/10.1053/j.sempedsurg.2016.09.003.
31. Le Deley M-C, Leblanc T, Shamsaldin A, Raquin MA, Lacour B, Sommelet D, et al. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Societé Française d'Oncologie Pediatrique. J Clin Oncol. 2003;21:1074–81. https://doi.org/10.1200/JCO.2003.04.100.
32. Smith DC, Esper P, Strawderman M, Pienta KJ. Phase II trial of oral estramustine, oral etoposide, and intravenous paclitaxel in hormone-refractory prostate cancer. J Clin Oncol. 1999;17:1664–71. https://doi.org/10.1200/JCO.1999.17.6.1664.
33. Green DM, Liu W, Kutteh WH, Ke RW, Shelton KC, Sklar CA, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude lifetime cohort study. Lancet Oncol. 2014;15:1215–23. https://doi.org/10.1016/S1470-2045(14)70408-5.
34. Wong KF, Reulen RC, Winter DL, Guha J, Fidler MM, Kelly J, et al. Risk of adverse health and social outcomes up to 50 years after Wilms tumor: the British childhood cancer survivor study. J Clin Oncol. 2016;34:1772–9. https://doi.org/10.1200/JCO.2015.64.4344.
35. Ehrlich PF, Ferrer FA, Ritchey ML, Anderson JR, Green DM, Grundy PE, et al. Hepatic metastasis at diagnosis in patients with Wilms tumor is not an independent adverse prognostic factor for stage IV Wilms tumor: a report from the Children's Oncology Group/National Wilms Tumor Study Group. Ann

Surg. 2009;250:642–8. https://doi.org/10.1097/SLA.0b013e3181b76f20.
36. Scott RH, Walker L, Olsen ØE, Levitt G, Kenney I, Maher E, et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child. 2006;91:995–9. https://doi.org/10.1136/adc.2006.101295.
37. de Kraker J, Graf N, Pritchard-Jones K, Pein F. Nephroblastoma clinical trial and study SIOP 2001, protocol. SIOP RTSG 2001. https://www.skion.nl/workspace/uploads/Protocol-SIOP-2001.pdf. Accessed 25 May 2020.
38. Combination chemotherapy with or without radiation therapy in treating young patients with newly diagnosed stage III or stage IV Wilms' tumor: information provided by Children's Oncology Group in US National Library of Medicine; posted June 14, 2017. https://clinicaltrials.gov/ct2/show/NCT00379340. Accessed 25 May 2020.
39. Shimodaira S, Hirabayashi K, Yanagisawa R, Higuchi Y, Sano K, Koizumi T. Chapter 4. Dendritic cell-based cancer immunotherapy targeting Wilms' tumor 1 for pediatric cancer. In: van den Heuvel-Eibrink MM, editor. Wilms tumor [Internet]. Brisbane: Codon Publications; 2016; https://www.ncbi.nlm.nih.gov/books/NBK373361/. Accessed 25 May 2020. https://doi.org/10.15586/codon.wt.2016.ch4.