Very Large Tumors Not Responding to Chemotherapy/ Locally Infiltrating Tumors

26

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26.1 Introduction

Surgery remains the mainstay of treatment in management of Wilms' tumor (WT). In majority of the cases even when tumor is infiltrating into the adjacent organs, the organs can be freely dissected from the tumor. The goals of surgery are to perform a safe operation, remove the kidney without intraoperative spill, sample adequate number of lymph nodes (LNs), and document all findings such as preoperative or intraoperative tumor rupture, extension into other structures, and the presence of peritoneal metastasis [1, 2]. In case of very large or locally infiltrating tumors, primary surgery may not be feasible. Contraindications to upfront resection of WT are few and include unacceptably high risk of anesthesia or surgery due to the disease burden in cases with very large or locally infiltrating tumors which may cause increased risk of operative morbidity [3]. Preoperative chemotherapy (ChT) in some of these high surgical-risk cases provides a window to improve the nutrition, hydration, and general health status of the patient so that subsequent major surgery can be undertaken with acceptable risk.

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26.2 Definition of Large Inoperable Tumor

Despite an aggressive upfront surgical approach, the recent COG studies (AREN0532 and AREN0533) have incorporated surgeons' judgment for eligibility for resection of large tumors with involvement of contiguous organs, which have often undergone delayed resection to avoid spill, residual disease, and surgical complications [3]. The factors which help the surgeon to decide operability are the size of the tumor, large tumor mass that is immobile or fixed to adjacent organs, tumor that is poorly encapsulated and infiltrating into surrounding structures, and tumor mass lacking clear margins on imaging or seen to be having enlarged LNs extending beyond tumor margins [4].

Relationship of tumor size to prognosis has been addressed in several studies including that of Provenzi et al. from Brazil who observed that tumor volume after preoperative chemotherapy (TVAPQ) was the only variable statistically associated to the prognosis as in their study every increase of 10 ml in tumor volume increased the risk of death by 2% [5].

Japan Wilms Tumor Study-2 (JWiTS-2) has recommended that tumor size greater than 12 cm or tumor volume more than 1000 ml should receive preoperative ChT to reduce surgical risk [6].

26.3 Imaging Technology

Modern advanced imaging technology aids, such as 3-D computer reformatting, and printing models may assist the surgeon in better assessment of tumor operability in management of very large WT [3]. Besides the size of tumor, it was observed in JWiTS-2 that contralateral extension of tumor and compression of great vessels are other important imaging-based surgical risk factors [7]. In their study, more than half of the tumors became stage III due to surgical procedures, and hence their recommendation is that all large tumors with image identified surgical risk factors should undergo needle biopsy for confirmation of diagnosis followed by preoperative ChT instead of attempting aggressive primary tumor resection [6].

26.4 Pre-treatment Core-Needle Biopsy

Pre-treatment core-needle biopsy is advised in only selected patients with specific clinical and imaging characteristics (age above 7 years, with septicemia or UTI or psoas infiltration, hypercalcemia, imaging showing very large LNs or intratumoral calcification or almost totally extrarenal tumor or no visible normal renal parenchyma, or presence of lung metastasis in child below 2 years, or presence of extrahepatic or extrapulmonary metastases) [8]. High proportion of blastemal cells in the needle-biopsy has been known to be associated with greatest decrease in tumor volume; so this may have some prognostic value too [9].

26.5 Preoperative Chemotherapy

The management approach of this subgroup of WT in both COG and SIOP protocols is somewhat similar as preoperative chemotherapy (ChT) is preferred.

In the *COG* protocol, tumors that do not undergo upfront surgery are considered stage III and administered initial chemotherapy with 3 drugs—

Vincristine (VCR), Actinomycin-D (AMD), and Doxorubicin (DOX) for 6 weeks [1, 3]. If sufficient (~30%) tumor shrinkage has occurred, then patient could be taken up for surgery, or another 6 weeks of ChT could be administered (a maximum of 12 weeks of preoperative ChT). If at initial imaging at 6 weeks, no appreciable tumor response is seen, they undergo percutaneous core-needle biopsy (PCNB) or open wedge biopsy for confirmation of diagnosis and treated accordingly. All such patients are considered local stage III from the point of postoperative ChT.

In *SIOP* protocol, the neoadjuvant ChT given includes 2 drugs—VCR and AMD for 4 weeks followed by surgery. Response evaluation criteria in solid tumors (RECIST) is a widely accepted imaging-based assessment of the response to neoadjuvant ChT in solid tumors, and 30% or more reduction in maximum tumor size at the end of 4 weeks of ChT is considered as partial response [10]. In children due to concerns of excessive radiation exposure with repeated CT imaging, there is a trend towards favoring functional imaging options such as magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (FDG PET), but still the anatomical response to treatment can best be judged by conventional radiology.

UKW3 study has also shown that delayed nephrectomy preceded by preoperative ChT is associated with fewer surgical complications compared with upfront nephrectomy [11]. It has been reported in another UKW-3 study that downstaging of the tumor with preoperative ChT also helps spare 20% of the patients from XRT or DOX and its attendant toxicity [12].

However, progression or increase in size of localized WT has been also reported in 5% of patients during preoperative ChT in the SIOP 93-01 study, and these patients had poorer event free survival (EFS) and overall survival (OS) independent of the stage distribution and histopathological risk group [13]. Similarly, intratumoral bleeding is also known to result in increased tumor size but without compromising treatment outcome. In SIOP 93-01 and 2001 studies, a cut point volume of 500 ml in patients with

intermediate-risk tumors, excluding those with epithelial and stromal subtypes, showed a significant difference in outcome—the 5-year EFS and OS were 88% and 95% for smaller tumors, compared to 76% and 90% for larger tumors [14]. A worse outcome for post ChT large volume tumors was reported by Graf et al. also [15].

26.6   Tumor Embolization

Occasionally, neoadjuvant ChT may be ineffective or may cause tumor necrosis and hemorrhage into the tumor with sudden significant enlargement of the tumor necessitating early or emergency surgery. In such cases of inoperable WT, in acute life-threatening situations like this, interventional radiology procedure of endovascular selective angio-embolization of affected artery to control the hemorrhage can be undertaken which allows the patient to be stabilized prior to subsequent nephrectomy [16, 17]. In advanced "inoperable" WT, preoperative transcatheter arterial chemoembolization (TACE) has been advocated as an effective modality of treatment. Li et al. have reported that preoperative chemoembolization combined with short-term systemic ChT is safe and effective treatment option in these patients as it helps induce more massive necrosis of tumor and periaortic LN metastases, and thus further improves the tumor complete resection rate and helps achieve a high EFS rate [18].

For children where there is inadequate response to ChT with no tumor shrinkage or progression of tumors despite upgrading the ChT (± TACE), surgery should be performed as soon as possible. R1 resection is acceptable, but it classifies the tumor as stage III and further postoperative ChT and radiotherapy (XRT) has to be given accordingly.

26.7   Surgical Considerations

Very large tumors are likely to be hyper-vascular and have large areas of necrosis and hence require careful handling of tumor to prevent intraoperative rupture. A generous transabdominal approach (large, transverse supraumbilical incision) is best for resection of these large tumors [4]. For tumors arising from upper pole of kidney and extending up to diaphragm, a thoracic extension of the abdominal incision through the 8th or 9th rib and converting to a thoracoabdominal incision helps with improved exposure for easier and safe tumor resection [1]. Majority of WTs do not invade other organs and are very responsive to ChT; hence, radical en-bloc resection of part of liver, spleen, pancreas, or colon are generally not required and should be avoided as this is associated with increased frequency of complications [1, 4]. In rare cases, advanced right-sided tumors may extend into the liver, and en-bloc wedge resection or even hepatic lobectomy may be necessary in these patients. In cases where tumor is adherent to a small part of diaphragm or psoas muscle or tail of pancreas, then that small part can be resected in continuity at the time of nephrectomy. Adrenal glands were found to be involved in 4.4% of patients in NWTSG data, and intraoperative tumor spill was reported to be higher in patients undergoing adrenalectomy which is likely to be due to larger tumor size or technical factors [19]. Hence, adrenalectomy should not be considered mandatory during radical nephrectomy for WT, and adrenal glands should be preserved but not at the risk of incomplete excision of tumor or rupturing the tumor. In large tumors, it may not be possible or safe to ligate the hilar vessels first, and in such cases tumor mass is adequately mobilized by lateral and posterior dissection so as to clearly visualize, isolate, and ligate the vessels at the hilum [4]. The risk of duodenal and mesenteric vascular injuries is also higher.

After removal of tumor mass, titanium clips should be placed to outline the extent of the tumor area or to mark any suspicious residual disease. Placement of titanium clips helps in providing further targeted XRT with minimal side effects.

26.8   Role of MIS

In very large tumors, minimally invasive surgery (MIS) has very little role except for may be helping with tissue diagnosis which is more safely done with image-guided percutaneous core-needle biopsy. MIS is recommended only for small tumors involving less than one-third of kidney, with less than 300 ml volume, those which are centrally placed with a rim of normal renal tissue and not infiltrating extrarenal structures. No outcome advantage has been reported with MIS in WT [20].

26.9   Adjunct Therapy

Post-operative ChT is continued as per the stage and histological risk category. In the SIOP protocol, only patients who have stage III disease because of positive lymph nodes (LN), positive surgical margins, tumor rupture, or peritoneal implants receive flank or abdominal XRT. This cohort of patients usually receive 10 cGy flank XRT; whole abdomen radiation (40 cGy) reserved for those with intra-operative ruptures with diffuse contamination and anaplastic histology [1, 3]. Unlike COG protocol, the patients who had needle biopsy and/or preoperative ChT but no other indications mentioned above are not upstaged to stage III and are not administered flank XRT in SIOP protocol. Irtan et al. [21] observed that in the UKW3 trial, the patients with initially large, inoperable WT at diagnosis, after receiving fairly prolonged three-drug preoperative ChT, ultimately did not have stage III tumor and had a good outcome without abdominal XRT. UKCCLG has shown that omission of XRT does not have an adverse impact on survival in these patients [22].

26.10   Situation in Developing Countries

In developing countries like India where large tumors with advanced stage are common due to delayed presentation and in children with poor nutritional status, the importance of neo-adjuvant chemotherapy increases many folds [23, 24]. Hence, it is prudent to recommend neo-adjuvant ChT for all patients of WT in India although high volume centers, that have developed expertise over the years, can develop the best strategy suited to their population. Meta-analysis of the effect of preoperative ChT on WT published by Liu et al. has concluded that preoperative ChT combined with surgery can increase the EFS and OS and improve the prognosis of patients with WT [25]. In a recently published study by Qureshi et al., more objective criteria for delayed surgery, after a biopsy and preoperative ChT, have been suggested based on image identified high-risk features, including perinephric spread or adjacent organ infiltration, tumors crossing the midline, intravascular thrombus, and extensive adenopathy, which are associated with increased risk of rupture or incomplete resection [26]. In their experience with customization of the timing of surgery, the outcomes with delayed nephrectomy remained similar to that reported in the UKW3 study, while there was favorable improvement in the stage and outcomes in the upfront nephrectomy group.

26.11   Conclusion

Although this subset of very large, locally infiltrating WT, not responding to ChT, requires special considerations in their management, yet it is apparent that with proper risk stratification and an individualized approach involving delayed nephrectomy after neo-adjuvant ChT, has made it possible to achieve favorable oncologic outcome in these children.

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