

Principles of Management of Wilms' Tumor in Resource Challenged Nations

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Abstract

Wilms' tumor is a common malignancy in childhood and poses special challenges in resource challenged nations. The protocols of treatment remain same in principle, and yet some modifications are needed to suit special circumstances. Lack of radiotherapy in many areas, lack of dedicated pediatric medical oncology services in most centres special pose a significant challenge. However, following SIOP framework for LMIC countries, many such challenges can be tackled successfully.

Keywords: Wilms' Tumour; Nephroblastoma; Pediatric Solid Organ Malignancy; Renal Cancer

Introduction

Wilms' tumor (WT) is the fifth commonest childhood malignancy in India [1]. ICMR consensus statement mentions a wide variation in incidence, 0.9% to 5.5% in boys, and 1.9 - 6.8% in girls [2]. Median global incidence of WT is reported to be 7 per million [3]. We have about 1500 practising pediatric surgeons, many working independently, without any institutional backing. We also have about 30 teaching departments of Pediatric Surgery in the country. If all patients went to teaching departments, they will have to treat > 70 patients every year of Wilms' alone. The challenges for patient seeking treatment at teaching centers are unique. They include financial hardship, lack of social support, lack of accommodation and lack of daily needs of caregivers. Sometimes patients have to live on footpaths between admissions for chemotherapy. Teaching centres may not have a focused oncosurgery service for children and they end up in the wider pool of patients seeking tertiary care. Therefore, to provide Optimum treatment to the wider population, authors seek to focus on the principle "WT can be adequately managed at smaller centres" with some support from dedicated centres.

Management of Wilms' tumor involves Surgery, Chemotherapy and Radiotherapy broadly. Particularly, radiotherapy is reserved for a very small number of patients with specific indications. Considering chemotherapy planning and administration, all teaching departments do not have a dedicated pediatric medical oncologist, and a General Medical Oncologist usually takes care of most children with malignancy. Dedicated pediatric surgeons are available in majority cities and districts of India. So, decentralization of Wilms' tumor management can avoid strain on patients, caregivers and tertiary centres. This is contrary to traditional knowledge which dictates higher volume equals better care. But this approach for Wilms' may be counterproductive.

Ease of communication with availability of high speed 4G data networks have made transmission of CT images, histology images, and virtual tumor boards a reality, and patient need not move to a large centre in a metro city to seek care.

This is not to oversimplify Wilms' tumor management. There are circumstances such as IVC thrombus/recurrence/Bilateral disease which require nuance and finer understanding. But barring

these complex cases, renal tumors can be safely resected in a regular operation theatre. Special equipment/instruments are rarely required.

Adjuvant chemotherapy is something that can be carried out by most pediatric surgeons. Therefore, while it is not preferable, it is possible to offer surgical and chemotherapy services to most children with WT in a hospital in their district, where a pediatric surgeon is willing to undertake treatment provided that essential surgical and medical aspects of treatment are considered and done. WHO document on children's cancer mentions 'access to care' as an important factor in recovery from childhood malignancy [4].

SIOP framework document for management of childhood cancer in low and middle income countries also recommends that children be treated where convenient, as referral may not be possible for all, and many are curable in resource constrained settings [5]. The report also mentions that results can be improved by preventing treatment abandonment, adapting treatment strategy to local situation. It states an important principle, 'curing the curable' is ethically mandatory and highly cost-effective even in Low and Middle Income Countries. LMIC [5]. Delay in seeking care, abandonment of treatment is avoidable if appropriate care is available close to the patients.

To begin with, the term, "limited resources" needs to be defined:

- Along with resources such as radiation machines, human resources such as pediatric oncologists or pediatric radiation oncologists are limited in our setting. An adult medical oncologist may not be able to take complete care of a child with WT.
- Therefore, it becomes necessary for the operating surgeon to look after chemotherapy of patients.
- Pathology services in all centers may not be comprehensive, and pathologists may not be confident in typing the tumor. Although, this can be overcome by sending the block to a centre which is able to give complete pathological diagnosis, with grade, type and stage.

Most patients with WT can be managed under these constraints with satisfactory results.

All childhood malignancies are covered under one of the Central or state government schemes with significant reimbursement. Scheme covers surgery, and chemotherapy. Therefore, any patient, howsoever poor he may be can receive appropriate treatment. There is no longer financial constraint in the country, when it comes to treatment of Wilms' tumor.

This is our concept of resource constraint.

Verma and Kumar mention drug shortage, malnutrition, poor supportive care and lack of surgical expertise responsible for poor outcomes in Wilms' tumor in India [6].

We will try to highlight this unique problem and address solutions in this chapter under following heads:

1. Diagnosis of WT
2. Surgical management
3. Histology and immunohistochemistry
4. Staging
5. Virtual tumor board
6. Surgical management
7. Chemotherapy planning and protocols. Administration of chemotherapy and monitoring
8. Management of complications during chemotherapy
9. Evaluation during chemotherapy and at completion of therapy
10. Long term follow up for recurrence, second malignancy
11. Rescue chemotherapy plans
12. Palliative care for non-responders
13. Counseling, social, financial support
14. Current status of Wilms' tumor management in RCN across the world.

Diagnosis of WT

Diagnosis of Wilms' tumor can be made by imaging such CT-IVP in most districts. If a tissue diagnosis is needed, a tru-cut biopsy from posterior flank (retroperitoneal) has been found to be reliable by Cost., *et al.* in seven patients [7]. There were no complications. Kurian and others describe 76 patients with suspected WT who underwent tru-cut core biopsy from posterior flank, under USG guidance [8]. Of 62 patients with WT, diagnosis was made in 61 patients. However, subtyping was possible in 25% patients only. Core biopsy correlated accurately with nephrectomy biopsy in 57/61 patients. Biopsy site recurrence occurred in one patient. There were no other complications. In a large series of 286 biopsies for WT, by UKCCSG Wilms Tumor Study 3, 204/241 tumours showed WT, while 28/241 showed other tumor [9]. Rikki John and others also mention safety of tru-cut biopsy in a group of 59 patients [10].

Thus, it can be ascertained that diagnosis of WT by radiology or biopsy will not pose a special challenge in the hands of a competent pediatric surgeon. A solid tumor in one kidney, in a child is presumed to be Wilms' tumor unless proved otherwise.

Diagnosis of Wilms' tumor can be made by any competent pathologist, though everyone may not be able to sub-type the tumor. If necessary, the sample can be sent to a centre where such services are available. There are regional cancer centres in every state which can liaise with local centres to provide a detailed pathology report. Depending upon the subtype of tumor, chemotherapy can be planned.

Diagnosis of tumor thrombus changes surgical management. This thrombus classification system has been proposed by Abdulah., *et al* [11].

Histology and immunohistochemistry

Gross pathology diagnosis of Wilms' tumor is straightforward. Even histology classification is not always difficult, if the tumor is well differentiated. A triphasic pattern can be identified by most pathologists. Further differentiation and subtyping may require pediatric oncopathological expertise. However, this can be obviated by sending block/unstained slide to a centre which provides this service.

Staging and subtyping

Staging initially is based on imaging and further complimented by histopathology. If there has been neoadjuvant chemotherapy administered, response to this can be assessed. Surgeons themselves can identify macroscopic findings such as capsular invasion and gross tumor residue during surgery. Based on all of these factors, final stage and subtype is reached and further chemotherapy and radiotherapy can be planned.

Virtual tumor board

Virtual tumor board is an especially valuable tool in a country like India where expertise is available but not widely. It uses the available technology to help surgeons and oncologists benefit from expertise available at dedicated Cancer centres. One such example is the virtual tumor board run by Tata Memorial Centre, Mumbai. Each hospital has to register and identify the key person. During tumor board meetings, patients can be presented, and experts on panel will recommend treatment plans and protocols. They can provide additional support such as review of histopathological blocks, Immunohistochemistry studies and can also be used as points of referral for more complicated cases. The value of these is

immense especially to a surgeon where multidisciplinary support is unavailable. This constraint is overcome and patients in remote locations have virtual access to a wider panel of experts.

Surgical management

Surgical management of WT is rarely as complex as resection of malignant tumors in adults.

Most Wilms' tumors are localized and rarely invade adjacent structures. It is possible to resect a stage II or even stage III tumor, with lymph node sampling without much difficulty in a hospital with good OT and instrumentation by a trained pediatric surgeon. During surgery ambitious resection at the cost of tumor spill should be avoided. Imaging should be carefully discussed with radiologist and neoadjuvant chemotherapy can be considered if there are concerns about resectability. If patient has tumor thrombus in IVC, up-front surgery should be deferred, and neo-adjuvant chemotherapy should be administered. If surgery is considered essential, patient will require surgery in a centre which can provide cardio-pulmonary bypass.

If tumor thrombus is absent, patient undergoes a transperitoneal resection of tumor, via a long transverse incision. It used to be recommended that other kidney be mobilized and palpated for tumor, before the primary tumor is resected. However, that may not be necessary if there has been an adequate contrast CT scan.

Blood transfusion is not required in every patient. Nor is general anesthesia different from any other major surgical procedure. Intensive care is rarely required.

In a country like India where access to services is a major concern, only complex Wilms' such as recurrences, bilateral disease, with IVC thrombus should be considered for referrals to dedicated centres. Otherwise, Wilms' nephrectomy should be offered by all pediatric surgeons, with adequate multidisciplinary inputs. This will avoid burdening of a few centres while providing access to treatment to a wider population.

Chemotherapy planning and protocols. Administration of chemotherapy and monitoring

One important function of tumor board is determining chemotherapy protocols for the given patient. Depending upon pathological stage and subtype, chemotherapy drugs will be selected, and standard NWTS/SIOP protocols followed for schedule, dose, frequency of drug administration.

If patient develops a complication during administration, we can go back to tumor board and seek advice.

During chemotherapy, patient is given a printed schedule of the whole cycle, with clear mention of number of cycle, date of injection of every drug, date of checking blood reports. The method of administration of drug should be mentioned in detail, whether by bolus, whether diluted, with which diluent, duration of administration, drugs to be administered before the chemotherapeutic agent. This is necessary as the cycles last over 6 months, and the nursing staff, and residents may change during the period [2].

The senior member of team should examine the patient every time, personally look at the reports, and check chemotherapy schedules. This will avoid errors in medication.

ICMR guidelines recommend pre-operative chemotherapy in resource constrained settings, especially in large tumours, which may be difficult to resect up-front [2].

Management of complications during chemotherapy

What complications can happen during chemotherapy administration and how they are to be managed, is a vexing question. Common complication of anti-cancer chemotherapy is bone marrow depression. Regular screening of patient's TLC, Hb and Platelet count can detect bone marrow depression.

Before administering any cycle of chemotherapy, CBC is performed. If necessary, patient can receive a blood transfusion.

If counts are less, administration of G-CSF generally improves the situation. G-CSF is associated with bone pain, but children tolerate it well.

Chemotherapy drugs, G-CSF, anti-emetics are available in all district headquarters and do not pose a logistic problem.

Other complications like infection is managed with specific antibiotics and monitoring. This too can be carried out at most places. If necessary, help of a pediatrician can be obtained.

Other complications like temporary alopecia, are managed by counseling parents and patients.

Evaluation during chemotherapy and at completion of therapy

Unless there is a complication during chemotherapy, or new symptoms appear, imaging is not necessary. During chemotherapy, hematologic monitoring is done before every cycle. This can be done at district level. Those receiving Vincristine are examined for

neurological deficit. Myasthenia like symptoms have been reported in some children. Those who receive Adriamycin should have undergone 2-D echocardiography, assessment of ventricular function before starting chemotherapy. This may be repeated midway and once again after completing. Adriamycin has cumulative toxicity, depending upon total dose received. Ultrasound scan of abdomen is done at completion of chemotherapy for identification of residual disease if any.

Long term follow up for recurrence, second malignancy

Patients are evaluated for local recurrence and distant metastases by an abdominal USG scan, chest x-ray, CBC at 3 monthly intervals, and at any time, symptoms appear. If patient remains asymptomatic and investigations do not reveal local/distant recurrence at two years, further follow-up is done every year. This may have to be continued for at least 5 years after end of treatment after which the investigations may be discontinued and clinical/telephonic follow-up could continue till the patient is 18. If there is suspicion of late recurrence or second malignancy, PET scan can be performed.

Rescue chemotherapy plans

Failure of first line chemotherapy calls for rescue chemotherapy with different agents like cyclophosphamide, etoposide and carboplatin. The decision regarding which drugs to use and schedules is difficult. This may require referral to special centres. However, if a plan can be formulated, the administration can be done wherever convenient.

Palliative care for non-responders

Some patients with aggressive disease, advanced disease, recurrence may require palliative care. This requires multidisciplinary discussion regarding all treatment options including palliation. Parents and carers need careful counseling. If it is apparent that the patient is not likely to recover, the condition must be discussed with parents by the senior most member of team. The essence of the multidisciplinary meeting must be conveyed. Parents are given the option of palliative care and avoidance of extraordinary measures. Their decision should be respected. Clear, written instructions about pain medication should be issued. If possible, help of a local pediatrician should be obtained for support. Last minute hospitalizations, admission to intensive care unit should be avoided if parents have chosen palliative care.

Counseling, social, financial support

Counseling should be done by a senior member of team, preferably the operating surgeon so that there is no confusion and parents

understand the gravity of situation. This is best done at the very beginning, soon after making diagnosis. If parents are informed that operation is only the first step, and the child will require repeated visits to hospital, at regular intervals for chemotherapy, they are more likely to accept it after operation is over. It is necessary to inform them of the possible complications of chemotherapy, such as alopecia, anemia, loss of appetite, loss of weight, risk of infections, so that they are sensitized and respond properly if a complication should occur. Dropouts and loss to follow up occurs mostly because of gaps in communication. In spite of low literacy and financial constraints, most parents are motivated to complete treatment for their child if carefully counselled.

During chemotherapy, it is necessary that the senior member examine the patient once during every visit, look at the blood reports himself. This is to improve patient compliance and avoid errors.

Many patients have to come to hospital from their place of residence which can be at any distance. This puts additional financial burden of transport cost. Most state transport units provide concession for patient and one relative. We should help the patient obtain this by providing certificates from office.

Surgery, chemotherapy and hospitalization costs are covered under most government schemes in India, be it Ayushman bharat, MPJAY in Maharashtra, RGJAY in Karnataka, and other states. This requires submission of documents to the scheme office in hospital. We need to help the patient in this matter, so they do not have to bear the cost of treatment.

Often a patient comes for follow-up, while another is admitted for chemotherapy. It is good if the recovered patient pay a visit to provide reassurance, comfort to other patients and parents.

Service of a social support team like a social worker and an NGO would be of great help in providing the above. Each centre and relevant doctor should be encouraged to build this link and service.

Current status of Wilms' tumor management in resource challenged countries across the world

India does not have a centralized government health service, where any patient can be referred anywhere for treatment, and the government will take care of all medical/surgical/logistic considerations. Many patients when they go to a metro city for treatment are on their own. The hospital may provide surgery/chemotherapy free of cost, but patients have to bear the cost of staying in the city,

food, transport and so on. These costs are considerable. Lack of good, clean accommodation compels them to stay on the footpath, outside the hospital in unsanitary surroundings. This is not desirable. Similar situation exists in other countries like Pakistan, Cambodia, Thailand, Laos, Vietnam.

A report from Vietnam by Ba Hoang and Tran, describes 33 children with Wilms' tumor treated with nwts-5 protocol all stages, had 90% EFS and 96.7% OS, mean follow up 30.4 months [12]. Those with SIOP protocol, all stages, had estimated EFS 77.5% and 84.1% OS. they recommend NWTS-5 protocol.

However, the experience from Nigeria has not been equally rewarding [13]. The report mentions 42 patients over 10 years, from 1995 to 2004. Out of 25 children on follow-up, 4 died of complications of treatment, 11 had recurrence. Survival was 40%. Most patients were stage III or IV. No patient was stage I. All patients could not receive adequate chemotherapy, as they could not afford cost of treatment.

With pediatric surgeons in all parts of the country and availability of schemes like Ayushman bharat, RGJAY, MPJAY, more and more children can be treated without their parents facing a financial burden.

A report by Rikki John and others from CMC Vellore [11] is more heartening. They report 59 patients of Wilms' tumor, treated from 2004 to 2014. SIOP protocol was followed. Despite IVC thrombus in 11, distant metastases in 18 and b/l tumors in 6, 55 patients could undergo definitive surgery. OS was 80% and EFS was 73%, 42 months after completing chemotherapy. They found posterior flank core tumor biopsy safe and beneficial. No patient received radiation therapy.

This is a protocol which can be followed by many hospitals and individuals.

Zakaria, Hokkam., *et al.* propose a different model of management [14]. In their study of 40 children with Stage II Wilms' tumor, NWTS 4 and SIOP protocols were followed in 20 children each. They found recurrence in 4/15 stage II patients in SIOP arm, and no recurrence in NWTS arm. Rebound increase in size was observed in 2/5 stage III patients in SIOP arm, and 0/4 patients in NWTS arm. They conclude that NWTS protocol serves better than SIOP in developing countries. However, this study does not provide any statistical analysis or comparison of results. It is not possible to draw fair conclusions.

In another report by same authors [15], a group of 30 patients with Wilms' tumor, is evaluated. Here too, they draw the same conclusions, i.e. NWTS doing better than SIOP. Again, without any statistical analysis.

A report by Wilde., *et al.* describes 40 children with WT treated in a tertiary care hospital in Malawi [16]. 39/42 received adjuvant chemotherapy and 36/42 could undergo nephrectomy. Chemotherapy was completed in only 15% patients. 15/36 operated patients had recurrence. This can certainly be improved with better counseling, government sponsored treatment. India has made some progress in this regard.

SIOP framework for LMIC countries addresses these issues comprehensively. It recommends that if radiotherapy is not available, additional chemotherapy be provided. Omission of two doses of Adriamycin and using prophylactic antibiotics is also mentioned. It defines optimal therapy as therapy which provides the highest possibility of cure and not necessarily whatever is possible in High Income Countries. Management of WT in Low and Middle Income Countries will evolve over time, as surgical expertise, diagnostic expertise improves, and clinicians gain more experience with chemotherapy. Along with core competency, other areas like improving hygiene, improving nutrition, bone marrow stimulating agents, subsidized transport are also mentioned as contributing to improved survival [6].

Wilde., *et al.* have recommended that to improve outcomes in children with Wilms' tumor, the following conditions are necessary, viz good pre-operative ultrasound, good and rapid histological assessment of the tumour, availability of the essential chemotherapeutic agents and a more pro-active follow-up strategy [16]. All this is easily possible in our country and other countries with limited resources.

Therefore, we recommend that all children with Wilms' tumor be provided all possible medical help, including surgery, chemotherapy at a place of convenience, to obviate overloading few urban centres and reduce the financial, social burden on the family.

Conclusion

Children with Wilms' tumor can be managed in most places where surgery can be carried out safely. Pre-operative tru-cut biopsy is a safe option if SIOP protocol is to be followed. Advanced tumors, renal vein thrombus can be managed with pre-op chemotherapy with Adriamycin. Lymph node sampling is desirable. Chemotherapy in standard protocols can be managed safely in most

hospitals. Provision of treatment in a centre nearby is likely to improve compliance to treatment and improve outcomes.

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