# Table of Contents

## Original Articles


Stereotactic Hypofractionated Accurate Radiotherapy of the Prostate (SHARP), 36.25 Gy in Five Fractions for Localized Disease: A Case Series Results from King Faisal Specialist Hospital, Saudi Arabia .............................................................................................................................................................12
M.W. Hegazy, R. Mahmood

FOLFOX as Perioperative Chemotherapy of localized Gastric Cancer: Efficacy and Tolerance .............................................................................................................................................................17

Evaluation of localization uncertainty of fiducial markers due to length and position variations induced by motion in CT imaging by measurement and modeling .............................................................................................................................................................21
I. Ali, N. Alsbou, S. Oyewale, J. Jaskowiak, S. Ahmad, O. Algan

Effect of Fractionated Dose of Radiotherapy on Oral Mucosa in Head and Neck Cancer Patients: A Cytological Assessment ...............30
S. Khan, M. Jain, V. Mathur, SMA Feroz

Change in the Quality of Life in Oropharyngeal, Laryngeal and Hypopharyngeal Cancer Patients treated with Volumetric Modulated Arc-Based Concomitant Boost Radiotherapy .............................................................................................................................................................36
P. Kannan, A. Mukherji, K. Reddy, S. Vivekarandam, C. Shamsudheen, V. Santhosh

Prostate biopsy handling: special tissue embedding technique with sponges affects the yield of prostatic tissue available for microscopic examination. .............................................................................................................................................................46
E. Salmo, K. Sitpura

Expression of VEGF-A in Epithelial Ovarian Cancer: Correlation with Morphologic Types, Grade and Clinical Stage .......................49
C.S. Premalata, K. Umadevi, K. Shobha, M. Anurekha, L. Krishnamoorthy

Efficacy of Different Protocols in treatment of Nephroblastoma: A revisit .............................................................................................................................55
O.M. Zakaria, M.Y.I. Daoud, S.H. Farrag, MS Al Mulhim

## Case Reports

Ectopic Intrathymic Parathyroid adenoma demonstrated on Tc–99m Sestamibi SPECT–CT .............................................................................................................................................................61
S. Usmani, A. Javaid, F. Abu Huda, H.G. Amanguno

Is cutaneous leishmaniasis a risk factor for basal cell carcinoma? .............................................................................................................................................................64
M. Chisti, R. Almasri, I. Hamadah

Bilateral Choroidal Metastases from Prostate Cancer revealed in a patient under abiraterone – Fourteen years after diagnosis ..........67
H.R. Kourie, J. Antoun, F. Bteich, A. Jalkh, M. Ghosn

Spectrum of Presentation of Anorectal Malignant Melanoma: Experience of a Tertiary Care Centre of north India..........................70
A. Gupta, P. Prakash, A. Rattan, N. Wadhwa, S. Kumar, V. Rathi

## Review Articles

Metaplastic carcinoma of breast: a case series of seven patients from a tertiary care center and review of literature .......................74
R. Benson, R. Madan, P.K. Julka, G.K. Rath

DNA methylation and Cancer: Identifying and targeting epigenetic modifications may be the future of cancer therapy? ..................77
G. Maresca, P.S. Wismayer

Novel agents in second–line therapy for EGFR wild–type Advanced Non–Small–Cell Lung Cancer ...................................................84

## Conference Highlights/Scientific Contributions

- News Notes ............................................................................................................................................................................................. 89
- Advertisements ........................................................................................................................................................................................ 93
- Scientific events in the GCC and the Arab World for 2016 ........................................................................................................... 94
Abstract

Background

Management of Nephroblastoma (NB) remains a subject of debate despite the fact that it ranked first among primary childhood’s renal neoplasm. We have previously discussed this issue in our previous studies, yet, the sample size was limited.

Aim

The aim of this study was to further evaluate the efficacy of initial surgery in the treatment of stage II & III pediatric NB as a part of the short administration schedule as in National Wilms’ Tumor Study (NWTS)-4 and to evaluate its effectiveness compared to the long administration schedule.

Patients and Methods

The study included 50 children who were primarily diagnosed as stage II & III NB. They were divided into 2 equal groups. Group I (n = 25) included children who have undergone neoadjuvant chemotherapy followed by surgery and postoperative chemotherapy, while group II (n = 25) included children who have undergone primary surgery as an initial management followed by chemotherapy. After a mean postoperative follow-up period of 20±6 months, clinical and radiological evaluation was performed to all patients.

Results

In group I, 15 patients were preoperatively diagnosed as stage II and 10 patients as stage III while in group II, 16 patients were proved to be stage II and 9 patients were stage III. After a follow-up period, clinical and radiological evaluation using CT was performed to all patients. In patients with stage II, evidence of recurrence was noted in 5 patients of group I whereas no patient showed any evidence of recurrence in group II. In patients with stage III, rebound increase in size was seen in 3 patients in group I and only one patient in group II.

Conclusions

This study confirmed our previous conclusions that initial surgical intervention with appropriate adjuvant therapy has a better outcome than the neoadjuvant chemotherapy and delayed surgery for children primarily diagnosed as stage II & III NB. Moreover, it may also act as a short administration schedule for the treatment as it is not less effective than the long administration schedule and can be administered at a substantially lower total treatment cost.

Keywords

Nephroblastoma, SIOP, NWTS4, Children, Chemotherapy and Surgery.

Introduction

Renal neoplasms in childhood are usually malignant, the most common being Nephroblastoma(1). The incidence varies from 10.9 per million in the USA to 2.5 per million in China(2). Therapeutic approach varies geographically(3). Most of the United States and Canada follow the National Wilms’ Tumor Study Group (NWTSG) protocol, which mandates primary nephrectomy for all cases with the exception of the large unilateral or bilateral tumors, while further adjuvant therapy is given based on surgical and pathologic findings(4-6). In Europe and other countries near the continent, patients are treated according to Société Internationale d’Oncologie Pédiatrique / International Society of Pediatric Oncology (SIOP) protocol, which
advocates preoperative chemotherapy for 4–6 weeks relying on initial diagnostic imaging, followed by surgery.\textsuperscript{2–8} The fundamental differences between these 2 large cooperative multinational trials are primary surgery in NWTSG versus initial or neoadjuvant chemotherapy in SIOP8. Despite the debate over whether chemotherapy should be given before surgery\textsuperscript{9–11}, the clinical outcomes are excellent in both groups, and productive debate continues on the merits of each approach.\textsuperscript{6}

The issue at hand here is which approach should supersede the other as a treatment option specifically in stage II and III. Some researchers tried to find the answer\textsuperscript{12} and at present, the decision to follow either approach is the prerogative of cancer centers that are not a part of these groups. We have previously discussed this issue, yet, the sample size was limited\textsuperscript{13, 14}.

The aim of the current study is to review and further evaluate the concept of initial surgery (NWTSG) as a guide in determining an accurate stage and to plan a tailor treatment for children. It is also the aim of this review to evaluate the efficacy of short administration schedule of NWTSG compared with the long administration schedule in SIOP and its effect on lowering the total treatment cost in developing nations with low and/or resource challenged settings.

**Patients and Methods**

The study recruited 50 children who were primarily diagnosed as stage II & III NB over a period of 11 years (2004–2015). The initial assessment was the clinical examination as well as laboratory investigations including complete blood count, urine analysis specially urine catecholamines to rule out neuroblastoma, serum urea and creatinine levels. Abdominal ultrasonography and CT were performed to all patients in order to confirm the diagnosis and to exclude other abdominal masses not originating in the kidney. Chest CT and radiographs were also used for detection of lung metastases.

Inclusion criteria were CT–proved unilateral WT (stage II & III), while the exclusion criteria was the presence of other abdominal malignancies and/or other renal lesions such as hydronephrosis or cystic disease. Cases with hematogenous metastasis were also excluded.

Children were divided into two equal groups. In–group I (n=25): preoperative chemotherapy was decided according to CT diagnosis, whereas precise staging was assigned after surgery. In–group II (n=25): surgical intervention was done as an initial management followed by chemotherapy. Commonly employed chemotherapeutic agents include dactinomycin, vincristine, doxorubicin, cyclophosphamide, etoposide, and carboplatin.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Pediatric dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dactinomycin</td>
<td>0.015 mg/kg IV push qd for 5 days</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.5 mg/m² IV q1-3 weeks; not to exceed 2 mg/dose</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1.2-2.2 g/m² IV qd for 1-3 days</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m² IV cd for 5 days</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>45 mg/m² IV</td>
</tr>
</tbody>
</table>

**Table 1: Chemotherapeutic agents used for treating Wilms’ tumour**

Chemotherapy dosage depends on the particular stage of the disease and the child (Tables 1, 2).\textsuperscript{15, 16} In group I, surgical exploration was performed as soon as the child health was optimized, usually within 6 weeks after the initial diagnosis.

Surgery entails radical excision of the tumor whenever amenable. A transverse abdominal incision was done to provide adequate exposure, from the tip of the 12th rib on the involved side to the lateral rectus border on the opposite side. Exploration of the contralateral kidney with biopsy as needed was carried out first; reflection of colon and complete mobilization of kidney are required for adequate visualization and manual inspection of front and back surfaces of the kidney. Radical nephrectomy was done whenever possible. Metal clips were left to identify residual masses in stage III patients.

Histopathological examination was performed for all surgically removed specimens. CT follow-up and clinical evaluation was performed to all patients to detect recurrence in stage II and follow-up of the size of the residual mass in stage III.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Chemotherapeutic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II (FH), stage III (FH)</td>
<td>DD-4A (AMD, VCR, and DOX; 24 weeks)</td>
</tr>
<tr>
<td>Stage II or stage III (local or diffuse anaplasia)</td>
<td>I (VCR + CPM + E; 24 weeks)</td>
</tr>
</tbody>
</table>

**Table 2: Chemotherapeutic regimens in relation to the stage of NB**

Abbreviations: FH=favorable histology; AMD=Dactinomycin; VCR=Vincristine; DOX=Doxorubicin; CPM=Cyclophosphamide; E=Etoposide
For statistical analysis, SPSS 22 was used. Collected data were tabulated and analyzed statistically using $\chi^2$ analysis. Continuous variable was analyzed using the independent sample t-test. P values less than 0.5 were considered statistically significant.

Results

Fifty patients were studied; they were 28 males and 22 females with the ratio of 1.3:1. The age of the studied patients in—group I ranged from 1.1 years to 16 years (mean = 7.2 ± 1.4), while in—group II, it ranged from 1.3 years to 15 years (mean = 7.5 ± 1.4) with no statistical significant difference between the two groups. Palpable abdominal mass was the first presentation in 31 patients (62%), recurrent abdominal pain in 9 patients (18%) and hypertension in 10 patients (20%).

In group I, 15 patients were preoperatively diagnosed as stage II, while the remaining 7 patients were preoperatively diagnosed as stage III (Figure 1). After a mean postoperative follow-up period of 20±6 months (mean ± S.D.), 10 patients with preoperatively diagnosed stage II showed CT—evidenced recurrence. On the other hand, remission was noted in 6 patients with stage III whereas rebound increase in size was seen in the remaining (4).

In group II, 16 patients were proved to be stage II (Figure 2) whereas 9 patients were stage III. The postoperative follow—up was identical to that of group I. Yet, no patient with stage II showed any evidence of recurrence. Nevertheless, only one patient with stage III showed relapse. In this group, chemotherapy regimens were modulated taking in consideration the histopathological grade found at biopsy. Table 3 shows the relapses in both groups.

In group I, 8 patients (32%) were found to be under staged at histopathological examination with CT accuracy of 66.7% ($P < 0.03$) compared to surgical exploration and biopsy. This was due to unresectable tumor margins in spite of being stage II on CT (Fig.1,2). On the other hand, histopathological examination confirmed free margins in all patients stage II in group II, ($P < 0.01$).

The overall histopathological results revealed favorable histology (tubular predominance) in 44 patients (88%) whereas unfavorable histology (anaplasia, rhabdoid and clear cell sarcoma) in 6 patients (12%). The most commonly encountered complications among our patients after chemotherapy were tabulated (Table 4).

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Group I</th>
<th>Group II</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>3 (6%)</td>
<td>0</td>
<td>$&lt; 0.02$</td>
</tr>
<tr>
<td>Stage III</td>
<td>5 (10%)</td>
<td>1</td>
<td>$&lt; 0.04$</td>
</tr>
</tbody>
</table>

Table 3: Comparative relapse rate between Groups I and II
Management of NB remains a paradigm for multimodal cancer therapy. Nevertheless, all recent nephroblastoma trials and studies to determine the minimal therapy needed for cure. The goal was survival without morbidity\(^{(5, 15)}\).

The importance of NB responsiveness as distinguished from its aggressiveness has been emphasized during the last decade of the 20th century (1990s). The two main NB study groups are SIOP and NWTSG. SIOP has advocated preoperative radiotherapy in the first two trials and then used chemotherapy in the following 4 trials for 4–6 weeks. The currently used SIOP–9 has mainly presented survival results for patients older than 6 months, with unilateral localized tumor \(^{(15)}\), who had received preoperative therapy with two drugs\(^{(15)}\).

Moreover, the advantage of SIOP protocol is the reduction in the incidence of tumor rupture, intra–peritoneal tumor spillage, able to obtain a more favorable stage distribution, and in turn, reduce the treatment burden. Besides that, this protocol gives the opportunity to judge responsiveness of the tumor to the standard regimen of chemotherapy so that risk stratification and treatment adjustments are feasible in postoperative period. However, the potential disadvantages of SIOP are not obtaining untreated tissue for proper histopathological study, treatment of a benign condition with chemotherapy and treatment of a different malignant disease with the wrong chemotherapy as well as the relative long time of administration schedule that may be more expensive\(^{(9, 12–13)}\).

The NWTSG approach recommends up–front surgery with certain exceptions: bilateral tumors, tumors in a solitary or horseshoe kidney, extension of tumor thrombus in the supra–hepatic cava or heart, and extensive metastatic disease causing respiratory distress. There are mainly two advantages of this approach: accurate and early complete staging and obtaining an untreated tumor specimen that can be subjected for tissue diagnosis and other biological prognostic studies as well as the short administration schedule that may decrease the cost of treatment\(^{(5)}\). The disadvantage of this approach is a higher rate of surgical complications like tumor rupture and intra–operative spillage \(^{(12–16)}\).

In this study, we have applied the two protocols for children who were primary staged as stage II & III according to the CT findings. Neoadjuvant chemotherapy was adopted as the first line of management in group I children which coincided with researchers who primarily gained their experience from the application of SIOP protocols including a period of preoperative chemotherapy followed by surgery and a period of postoperative chemotherapy\(^{(14, 16–17)}\). In–group II we adopted the National NB Tumor Society protocol (NWTS) with surgery as the first line of treatment followed by chemotherapeutic application\(^{(18–19)}\). This group has the advantage of histological confirmation of the disease as well as accurate staging during surgery. During the operation, the contralateral kidney was also explored to ensure that the disease was indeed unilateral and lymph node dissection was carried out\(^{(21)}\). We did not perform transcutaneous biopsy for any of our cases with the concept that it may complicate the treatment in accordance with the same concept in a previous study \(^{(22)}\).

The study results showed that patients in group I have a significantly less success rate as compared to those in group II. Such results were contradictory to previous published results of SIOP protocols\(^{(21)}\) while coincided with those of National NB Tumor Study Group\(^{(22–24)}\).

Tumor histology and stage are the two most significant prognostic factors for patients with NB Tumor\(^{(25)}\). In group I, the preoperative chemotherapy alters the tumor’s histological features\(^{(26)}\), thus making the pathologist’s job to assign the subtype of histopathology and stage very difficult while patients in group II, the pathologist could properly identify and stage the tumor.

Generally, children can tolerate the acute toxicities of chemotherapeutic drugs better than adults\(^{(27)}\). However, they are more susceptible to delayed side effects of chemotherapy like growth problems, infertility and neuropsychological dysfunction\(^{(28)}\).

In our study, the most commonly encountered complication is bone marrow depression (30%) followed by bowel obstruction (13.3%). This is in agreement with other recent studies\(^{(29–33)}\).
Further to our previously published data\textsuperscript{(13,14)} plus the current study, it can be concluded that initial surgical resection remains a crucial part in treatment of stage II & III Nephroblastoma patients as a short administration schedule that will reduce the cost–effectiveness of treatment especially in resource challenged settings as in our case. It can provide a local primary tumor control, accurate staging, proper histological interpretation and possibly controlling the metastatic spread. However, patient selection for surgery is an important determinant for successful outcome.

References


