Profile and Clinical Outcome of Children with Wilms’ Tumor treated at a Tertiary Care Centre, India

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South Asian J Cancer

Abstract

Background Wilms’ tumor (WT) is the most common kidney tumor of the pediatric age group. The outcome of WT has improved due to the evolution of the treatment approach. A prospective observational study was conducted at All India Institute of Medical Sciences (AIIMS), Patna, to analyze the clinical profile along with the response and outcome to neoadjuvant chemotherapy according to the International Society of Pediatric Oncology (SIOP) protocol.

Materials and Methods In total, 28 patients of WT visited the radiotherapy department from January 2015 to December 2019.

Results Gender distribution showed male preponderance with a median age at diagnosis was 31 months. The abdominal lump was the dominant clinical presentation. The median volume of tumor at diagnosis was 359.48 mL (52.67–1805.76). Radiological staging workup shows that stage I, II, III, IV, and V were 7.1%, 39.3%, 39.3%, 10.7%, and 3.6% respectively. Neoadjuvant chemotherapy (NACT) was received by all patients. Also, 71.4% of patients showed >50% of tumor volume reduction, while 28.6% of patients showed <50% of tumor mass reduction. There was a statistically significant decrease in the tumor volume reduction following neoadjuvant chemotherapy ($p < 0.001$). There was a statistically significant stage down ($p = 0.018$) of the disease.

Bivariate correlation studies showed recurrence was correlating statistically significantly with age < 24 months ($p = 0.049$), locoregional lymph nodes ($p = 0.008$), histopathological subtypes ($p < 0.001$), stage of the disease ($p = 0.003$), and risk groups ($p < 0.001$). In addition, 25% of patients developed recurrence during the median follow-up of 25 months. The median disease-free survival (DFS) and overall survival (OS) were not reached. The mean DFS and OS were 48 and 59.13 months, respectively. One- and 3-year DFS were 100% and 64.1%, respectively. One- and 3-year OS were 100% and 75% respectively.
Introduction

Wilms’ tumor (WT) is the most common genitourinary malignancy in the pediatric age group. The WT affects approximately one child per 10,000 worldwide before the age of 15 years. Incidence rates are slightly elevated for the US and African Blacks in comparison with Whites but are only half as compared with Asians.\(^1\) The mean age of presentation is 3 to 4 years. The male to female ratio in unilateral Wilms’ tumor is 0.92:1.00 and for bilateral cases is 0.60:1.00.\(^2\) Most patients are asymptomatic wherein abdominal lump is an incidental finding, however, patients may also present with abdominal pain, hematuria, and fever. Patients often have underlying congenital anomalies associated with such as Wilms’ tumor, aniridia, genitourinary malformations, and mental retardation (WAGR), Denys–Drash, and Beckwith–Wiedemann syndrome.\(^3\) In a developing country, the patients usually present late with advanced disease.\(^4\) The National Wilms’ Tumour Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP) have laid down structured protocols for the management of these tumors that include chemotherapy, surgery, and radiation.\(^5\) The main difference between the two groups is that the SIOP insists on neoadjuvant chemotherapy prior to nephrectomy as a rule. The advantages of giving neoadjuvant chemotherapy include 1) reduction in tumor mass, 2) preventing spillage, 3) decreasing chances of distant spread. The multimodality approach has indeed improved the prognosis in the past few decades. The clinical outcome however depends on the stage and the biology of the disease and the economic setting.\(^6\) We at our center follow the SIOP protocol 9301.\(^7\) We conducted this study to analyze the outcome of patients treated at our center from January 2015 to December 2019.

Materials and Methods

Aims and Objective

The primary objective was to analyze the outcome of multimodality treatment of Wilms’ tumor with SIOP protocol in a referral institute in north India. The secondary objective is to assess the response to neoadjuvant chemotherapy and its toxicity.

Study Design

This is a prospective observational study of children with newly diagnosed WT adapted to local circumstances in a low-income setting done in the department of radiotherapy with collaboration with the departments of pediatric surgery, pathology, and radiology at All India Institute of Medical Sciences (AIIMS), Patna, from January 2015 to December 2019. Patients were registered and their outcome evaluated in a prospective clinical study.

All patients of WT attending to the Radiotherapy and Pediatric Surgery departments, AIIMS, Patna for 5 years were registered, in the study. Staging workup included ultrasonography (USG) and whole abdomen contrast-enhanced computed tomography (CECT). The thorax was evaluated with X-ray and CECT thorax. Fine needle aspiration cytology (FNAC) or Trucut biopsy was done in all prior to the start of chemotherapy. After informed written consent, the patients received preoperative chemotherapy according to SIOP protocol consisting of injection vincristine 1.5 mg/m\(^2\) (maximum dose 2 mg) weekly for 4 weeks (i.e., 4 doses in total), actinomycin-D 45 μg/kg (maximum dose 2 mg) at weeks 1 and 3 (i.e., 2 doses in total) for localized disease. Both drugs are given as intravenous (i.v.) bolus. This was prolonged to 7 weeks and intensified (adding doxorubicin 50 mg/m\(^2\) i.v. over 4 hours on weeks 5 and 9) for those not responding to 4 weeks of chemotherapy based on the CT scan. If metastases were present, neoadjuvant treatment was given for 6 to 9 weeks and consisted of a combination of three drugs, vincristine, actinomycin D, and doxorubicin. Chemotherapy dose modifications (50% dose reduction of all drugs of the regimen) or delay was allowed for patients with toxicities. In this study, chemotherapy drug dose reduction was done by 50% in all patients having age < 12 months.\(^8\) Response assessment was done before the surgical intervention using a CT scan (RECIST 1.1).\(^9\) The tumor volume before at diagnosis and after neoadjuvant chemotherapy was calculated using the equation \(4\pi/3 \times a \times b \times c\), where \(a\), \(b\), and \(c\) are the radii in the three dimensions.\(^10\) Our pediatric surgeons performed surgery after a formal assessment and consent. The surgical procedure for a unilateral WT mostly was a transperitoneal radical nephroureterectomy with ipsilateral lymph node sampling. Stringent postoperative monitoring for complications was done such as bleeding, inferior vena cava (IVC) obstruction, intestinal obstruction (due to adhesions/due to intussusceptions), wound infection, wound dehiscence, hernia (incisional/diaphragmatic). Histopathological findings were evaluated for stratifying the patients for chemotherapy and the indications for radiotherapy. Patients were stratified into low-, intermediate-, and high-risk groups depending on staging and histopathology. Risk-stratified postoperative chemotherapy was delivered based on the SIOP protocol. Radiotherapy was given in patients indicated for the same.

Statistics

The Statistical Package for the Social Sciences (IBM SPSS for Windows, version 25.0) was used for the statistical analysis.  

Conclusion

Our study suggests that most of the patients presented at an advanced stage, thus rendering most of the cases difficult to undergo surgery at presentation. Neoadjuvant chemotherapy followed by surgery may be considered a well-balanced approach with a comparable response and survival outcomes.
Descriptive statistics were used to patient population using frequencies, mean, and median. Continuous variables were analyzed using Student’s t-test. Chi-square test was performed to compare categorical variables. Univariate and multivariate analyses were performed for disease-free survival (DFS) using the Cox regression model. Factors with a p-value < 0.05 in the univariate analysis were included in the multivariate analysis. Kaplan–Meier method was used for the survival analysis. Comparison between the survival curves was performed using the Log-rank test (Mantel–Cox test). A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics and management: Twenty-eight (n = 28) patients were analyzed in this study. The median age at presentation was 31 months (range: 4–96 months); the sex ratio (male/female) was 1.5. Also, 42.9% of the patients were < 24 months old, whereas 57.1% of them were ≥ 24 months. No associated congenital syndrome was found. The median duration of symptoms was 2 months (range: 1–8 months). The median time to diagnosis was 10 (2–22) days from the first visit at AIIMS, Patna. Other clinical characteristics are listed in Table 1 and 2. Clinical features were dominated by abdominal lump (50%), followed by abdominal lump with fever (35.7%), vomiting (7.1%), and hematuria (7.1%). The diagnosis was based mainly on clinical, histopathological, and radiological evidence. Core needle biopsy, CT scan of the abdomen and thorax were done in all cases. Right-sided and left-sided disease were seen in 39.2% and 57.1%, respectively. Only one patient was found to have bilateral disease.

A CT scan was used for the assessment of response. The median size of the sum of diameters at diagnosis was 27 cm (14.1–46 cm). The median volume of the disease at diagnosis was 359.48 mL (52.67–1805.76). Renal vein thrombosis was found in 32.1% of cases, infiltration of the renal pelvis was found in 35.7% of patients, and locoregional lymph node involvement was seen in 42.9% of patients. Liver metastasis was found in 10.7% (3) patients, i.e., among them two patients with lung metastasis and one patient with only liver metastasis. CT scan thorax showed 10.7% (3) patients with lung metastasis, i.e., among them two patients with liver metastasis and one patient with only lung metastasis at diagnosis. There was an overlap of two patients with both liver and lung metastasis. Radiological staging workup showed that 7.1% in stage I, 39.3% in stage II, 39.3% in stage III, 10.7% in stage IV, and 3.6% in stage V.

All patients received preoperative chemotherapy according to the SIOP protocol 9301. Also, 89.3% of patients received regimen “VA” (vincristine 1.5 mg/m² intravenous bolus at weeks 1, 2, 3, and 4; actinomycin-D 45 µg/kg intravenous bolus at weeks 1 and 3), “ ” and 10.7% received regimen “VAA” (vincristine 1.5 mg/m² intravenous bolus at weeks 1, 2, 3, 4, 5, and 6; actinomycin-D 45 µg/kg intravenous bolus at weeks 1, 3, and 5; doxorubicin 50 mg/m² intravenous over 4 hours at weeks 1, 5, and 9). Preoperative chemotherapy included weekly chemotherapy for 4 weeks followed by surgical intervention, week 5 chemotherapy was given when planned surgery falls after week 5.

Preoperative chemotherapy toxicity (grade III) was seen in 25% (7) of patients. The most common toxicity was grade III diarrhea, seen in 10.7% of patients. Grade III neutropenia and hepatic toxicity were seen in 7.14% and 7.14% of patients, respectively. Only one patient received the “VAA” regimen among the patients who developed grade III toxicity and the rest six were received the “VA” regimen. Dose reduction was done in 39.3% (11) of patients. Eight out of 11 patients were under 12 months of age group (dose reduction of all drugs of the chemotherapy regimen by 50% was done from week 1 and onward), further dose reduction (by 50%) in the remaining three patients was done due to chemotherapy-related grade III toxicities. Toxicity-related delay in the chemotherapy schedule was a median of 9 days.

Following neoadjuvant chemotherapy, all patients underwent radiological assessment using a CT scan (RECIST 1.1). The partial response was observed in 35.7% of patients, while 64.3% of patients showed stable disease. None of the patients showed a complete response. More than 50% of the tumor volume reduction was seen in 71.4% of patients, while 28.6% of patients showed < 50% of tumor mass reduction.

Twenty-four (85.7%) patients underwent surgical intervention. Surgical treatment consisted of radical nephrectomy in all cases. Histological subtypes and tumor stage were defined according to pathological assessment, which revealed 7.1% low risk, 67.9% intermediate-risk, and 25% high risk, according to the SIOP WT 2001 staging criteria for renal tumors of childhood. On histopathological subtype classification, mesoblastic nephroma, favorable histology, and diffuse anaplasia were 7.1%, 67.9%, and 25%, respectively. Postoperative staging showed 17.9% in stage I, 46.4% in stage II, 21.4% in stage III, 10.7% in stage IV, and 3.6% in stage V. Postoperative chemotherapy was indicated in 75% of cases. Postoperative radiotherapy was indicated in 28.6% of patients. The median time to start radiotherapy following surgical intervention was 18 (9–25) days. Radiotherapy was delivered with a daily fraction of 1.5 Gy (for whole abdomen irradiation) and 1.8 Gy (for flank irradiation). The dose of radiotherapy ranged from 10.8 Gy to 21.6 Gy. Flank radiotherapy was given to patients with stage II high risk (two patients), stage III intermediate risk (three patients), and stage III high risk (one patient). Whole abdomen radiotherapy was given to stage III intermediate risk with per operative bleeding (one patient), and stage III high risk with tumor spillage during surgery (one patient).

Correlation (bivariate) studies: Recurrence correlated statistically significantly with age < 24 months (p = 0.049), locoregional lymph nodes (p = 0.008), histopathological subtypes (p < 0.001), stage of the disease (p = 0.003), and risk groups (p < 0.001). There was statistically significant reduction in the tumor volume following neoadjuvant chemotherapy while comparing the means of the tumor volume (p < 0.001). Preoperative and postoperative comparisons of
stages using paired t-test revealed that there was a significant down staging following chemotherapy (p = 0.018).

Univariate analysis using Cox regression model showed that DFS was statistically significant dependent on locoregional lymph nodes (p = 0.018; confidence interval [CI], 1.562–111.854); percentage tumor volume shrinkage > 50% (p = 0.043; CI, 1.052–22.374); histopathological subtype of tumor (p = 0.045; CI, 1.024–7.449), risk group (p = 0.008; CI, 2.147–146.540), and postoperative stage (p = 0.002; CI, 1.981–20.828). Multivariate analysis using Cox regression model showed that postoperative stage (p = 0.019; CI, 1.344–26.823) was the only independent factor for DFS (►Table 4).

Survival analysis: At the time of analysis, 25% of patients developed recurrence during the median follow-up of 25 months. The median DFS was not reached, the mean DFS was 48 months (95% CI: 36.892–61.038). The median OS was also not reached, the mean OS was 59.13 months (95% CI: 49.738–68.527), shown in ►Figs. 1 and 2. The 1- and 3-year DFS were 100% and 64.1%, respectively. Three-year DFS of stages I and II was 100%, 40% in stage III, 0% in stages IV and V (►Fig. 3). Three-year DFS was 100%, 89%, and 33% for low risk, intermediate risk, and high risk, respectively (►Fig. 4). The 1- and 3-year OS was 100% and 75% respectively. Three-year OS of stages I and II was 100%, 60% in stage III, 0% in stages IV and V.

Discussion

This analysis provides an outcome of WT cases at a tertiary care center. The total number of patients enrolled during this period was 28. All were histologically confirmed cases of WT. Bilateral WT was seen only in one patient. The age and sex distribution of this study were similar to another large Indian study.12 The male to female ratio was 1.5:1, which was
similar to other studies. In our study, the most frequent presenting complaint was abdominal mass (50%), and 35% of the patients presented with an abdominal lump with fever. Western studies reported 74% of patients presenting with an abdominal mass. A study by Guruprasad et al reported that 90% of their patients presented with abdominal mass, which was almost similar to our findings. Only 17.9% of patients were in stage I in our study. This is in contrast to other larger studies showing a larger number of patients in the early stages. This may be due to the late presentation of the majority of the patients possible reason includes poor access to the health care facility. These advanced stage presentations of our study patients caused most of them in upfront inoperable disease. Our cohort showed 25% of patients with high-risk histopathological features, while in other Indian studies this varied from 7% to 37.5%. The high-risk histopathological features in Western studies ranged from 7% to 28.8% (►Table 5). Total surgical excision is the standard of the treatment of unilateral WT. In this study, we adopted the SIOP study group protocol, which included neoadjuvant chemotherapy followed by surgical intervention. Most of our patients presented with advanced

Table 2 Age and other tumor characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>37</td>
<td>30</td>
<td>4</td>
<td>96</td>
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<tr>
<td>Body surface area (BSA)</td>
<td>0.66</td>
<td>0.64</td>
<td>0.40</td>
<td>0.94</td>
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<tr>
<td>Duration of symptom (months)</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Sum of diameters of tumor at diagnosis (cm)</td>
<td>27.29</td>
<td>27.00</td>
<td>14.10</td>
<td>46.00</td>
</tr>
<tr>
<td>Volume of disease at diagnosis (cc)</td>
<td>450.37</td>
<td>359.48</td>
<td>52.67</td>
<td>1805.76</td>
</tr>
<tr>
<td>Sum of diameters of tumor after neoadjuvant chemotherapy (cm)</td>
<td>20.6</td>
<td>20.8</td>
<td>7.2</td>
<td>40.8</td>
</tr>
<tr>
<td>Percentage change in size</td>
<td>26.12</td>
<td>25.42</td>
<td>7.84</td>
<td>50.76</td>
</tr>
<tr>
<td>Volume of disease after neoadjuvant chemotherapy (cc)</td>
<td>178.07</td>
<td>120.70</td>
<td>3.75</td>
<td>1257.76</td>
</tr>
<tr>
<td>Time to diagnosis (days)</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Delayed schedule of chemotherapy (days)</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Time to start radiotherapy after surgery (days)</td>
<td>17</td>
<td>18</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

Table 3 Grade III toxicity associated with neoadjuvant chemotherapy regimen

<table>
<thead>
<tr>
<th>Grade 3 toxicity</th>
<th>Patients</th>
<th>Percentage</th>
<th>Chemotherapy regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>7.14</td>
<td>VAA</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>10.70</td>
<td>VA</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2</td>
<td>7.14</td>
<td>VA</td>
</tr>
</tbody>
</table>

*VAA-vincristine, actinomycin D, doxorubicin; VA- vincristine, actinomycin D.

Table 4 Univariate and multivariate Cox regression analysis of different factors associated with disease free survival

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>HR</td>
<td>p-Value</td>
<td>95% CI</td>
<td>HR</td>
<td>p-Value</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age &lt;24 months</td>
<td>2.887</td>
<td>0.052</td>
<td>0.345–24.162</td>
<td>1.159</td>
<td>0.905</td>
<td>0.104–12.962</td>
</tr>
<tr>
<td>Locoregional lymph nodes</td>
<td>13.217</td>
<td>0.018</td>
<td>1.562–111.854</td>
<td>1.334</td>
<td>0.812</td>
<td>0.124–14.319</td>
</tr>
<tr>
<td>Renal pelvis infiltration</td>
<td>0.287</td>
<td>0.156</td>
<td>0.051–1.607</td>
<td>0.077–1.620</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>0.354</td>
<td>0.181</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to NACT</td>
<td>1.301</td>
<td>0.754</td>
<td>0.251–6.743</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor volume shrinkage by &gt;50%</td>
<td>4.852</td>
<td>0.043</td>
<td>1.052–22.374</td>
<td>1.159</td>
<td>0.905</td>
<td>0.104–12.962</td>
</tr>
<tr>
<td>Histopathological subtypes</td>
<td>2.762</td>
<td>0.045</td>
<td>1.024–7.449</td>
<td>1.334</td>
<td>0.812</td>
<td>0.124–14.319</td>
</tr>
<tr>
<td>Risk group</td>
<td>17.739</td>
<td>0.008</td>
<td>2.147–146.540</td>
<td>9.289</td>
<td>0.218</td>
<td>0.268–321.820</td>
</tr>
<tr>
<td>Post operative stage</td>
<td>6.423</td>
<td>0.002</td>
<td>1.981–20.828</td>
<td>6.004</td>
<td>0.019</td>
<td>1.344–26.823</td>
</tr>
</tbody>
</table>
disease with a median tumor volume of 359.48 mL and 37.5% of patients had renal pelvis involvement as interpolated from the radiological information. Delay in presentation and advanced disease at diagnosis SIOP study group approach seemed to be more feasible for most of the patients presented to us.

Preoperative chemotherapy was mainly associated with hematological and gastrointestinal toxicity. In this study, we

**Fig. 1** The median disease-free survival (DFS).

**Fig. 2** The median overall survival (OS).
observed grade III neutropenia in 7.14% of patients and grade III diarrheas in 10.7% of patients. Israels et al. in their study reported 27% of grade III neutropenia. This low incidence of neutropenia in our cohort of patients may be due to reduction of dose by 50% in patients with age < 12 months.

Preoperative response to neoadjuvant chemotherapy in this study showed partial response in 35.7% and stable disease in 64.5% of patients. In our study, 71.4% of patients showed > 50% reduction in the tumor mass. Other studies reported > 50% tumor mass in 82.7% of cases.

Fig. 3  DFS was significantly differing according to risk group (Log rank Mantel–Cox; $p < 0.001$).

Fig. 4  DFS was significantly differing according to stage of the disease (Log rank Mantel–Cox; $p < 0.001$).
Table 5 Wilms tumor series

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>Number of patients</th>
<th>High-risk histopathology</th>
<th>Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>John et al10</td>
<td>Wilms tumor</td>
<td>59</td>
<td>7%</td>
<td>Indian</td>
</tr>
<tr>
<td>Guruprasad et al12</td>
<td>Wilms tumor</td>
<td>81</td>
<td>16.4%</td>
<td>Indian</td>
</tr>
<tr>
<td>Kumar et al15</td>
<td>Wilms tumor</td>
<td>8</td>
<td>37.5%</td>
<td>Indian</td>
</tr>
<tr>
<td>Reinhard et al16</td>
<td>Wilms tumor</td>
<td>519</td>
<td>7%</td>
<td>Western</td>
</tr>
<tr>
<td>D’Angio et al14</td>
<td>Wilms tumor</td>
<td>1439</td>
<td>11.2%</td>
<td>Western</td>
</tr>
<tr>
<td>Tröbs et al17</td>
<td>Wilms tumor</td>
<td>77</td>
<td>19%</td>
<td>Western</td>
</tr>
<tr>
<td>Rais et al18</td>
<td>Wilms tumor</td>
<td>52</td>
<td>28.8%</td>
<td>Western</td>
</tr>
</tbody>
</table>

difference in response may be due to dose reduction in patients with age < 12 months (9 of 28 patients).

We observed in this study that there was significant downstaging following neoadjuvant chemotherapy. Twenty-five percent of our patients had anaplastic histology. The presence of anaplasia had a significant impact on the DFS and OS and this finding was supported by larger studies including the NWTS group and SIOP.22–26 In this study, recurrence was statistically significantly found to be associated with age > 24 months, the presence of locoregional lymph nodes, histopathological subtypes, risk groups, and stage of the disease. The finding of our study is supported by larger studies NWTS-3.26 Univariate analysis showed tumor volume shrinkage > 50%, histopathological subtypes, risk group, and postoperative stage were the dependent risk factors for DFS, and the postoperative stage was the only independent risk factor of DFS on multivariate analysis. The present study showed a 3-year DFS of 100% in stages I and II and 40% in stage III. Findings in the SIOP-9 study showed that almost 70% of DFS in stage III,27 this difference might be due to a small number of patients in our study, genetic or ethnic factors, and health care access facility or delay in diagnosis due to late presentation at the health care facility.

Conclusion

Presentation of the pediatric WT dominated with advanced stage probably due to difficulty in access of health care facility or ignorance by parents. This advanced stage leads to a large voluminous tumor and renders most of the cases upfront inoperable. Neoadjuvant chemotherapy followed by surgical intervention seems to be a good and feasible option for these subsets of patients with comparable outcomes and toxicities in comparison with western studies.

Ethical Approval

The Institutional Research Committee (IRC) at the All India Institute of Medical Sciences, Patna has approved the study (Ref. number – IEC 20; dated 23/12/14).

Authors’ Contributions

PS, DS, BK, PK, and PD participated in the acquisition of data and drafting the manuscript. All authors read and approved the final manuscript.

Funding

None.

Conflict of Interest

None declared.

References


