A PHASE II STUDY OF MULTIMODALITY THERAPY FOR PRIMARY AND RECURRENT RETROPERITONEAL SARCOMAS
INDEX

Schema
Eligibility Check

1.0 Introduction
2.0 Objectives
3.0 Patient Selection
4.0 Pretreatment Evaluations
5.0 Registration Procedures
6.0 Radiation Therapy
7.0 Drug Therapy
8.0 Surgery
9.0 Other Therapy
10.0 Pathology
11.0 Patient Assessments
12.0 Data Collection
13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting Guidelines
Appendix VI - Filgrastim (G-CSF) Drug Request Form
Appendix VII - Returned Medication Packing Slip
RADIATION THERAPY ONCOLOGY GROUP
RTOG S-0124
A PHASE II STUDY OF MULTIMODALITY THERAPY FOR PRIMARY AND RECURRENT RETROPERITONEAL SARCOMAS

SCHEMA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose of Agent (mg/m2)/day</th>
<th>Preop Cycle 1 Days</th>
<th>Preop Cycle 2 Days</th>
<th>Preop Cycle 3 Days</th>
<th>Preop Cycle 4 Days</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna</td>
<td>1500</td>
<td>1-4</td>
<td>22-25</td>
<td>43-46</td>
<td>64-67</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25</td>
<td>1-3</td>
<td>22-24</td>
<td>43-45</td>
<td>64-66</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2500</td>
<td>1-4</td>
<td>22-25</td>
<td>43-46</td>
<td>64-67</td>
<td></td>
</tr>
</tbody>
</table>

G-CSF 5 mcg/kg/d starting on day 5 of each cycle and continuing daily until ANC ≥ 10,000/mm³.

Radiation (within 2-4 weeks after completion of chemotherapy)
External beam irradiation delivering 45-50.4 Gy given in 25-28 once-daily fractions (1.8 Gy/fraction) Monday-Friday.

Surgery
Surgery performed 4-7 weeks after completing irradiation. Attempt complete resection with appropriate removal of any adjacent organs/structures. Immobilization of small bowel out of the boost field for immediate or subsequent treatment. Clips will be used to identify the area at risk.

Radiation Boost
Multiple techniques are acceptable in order to eliminate/reduce the dose to normal structures, primarily the bowel. This can be accomplished during surgery using intraoperative electrons or HDR brachytherapy. Alternatively, if the bowel can be adequately displaced with mesh or tissue expanders then postoperative external beam or brachytherapy can be used. Dose is dependent on method of treatment and residual disease after surgery.

Eligibility: (see Section 3.0 for details) (12/3/02)
- Histologically confirmed, non-metastatic, soft tissue sarcoma of the retroperitoneum and/or pelvis with measurable disease which has not been debulked
- High-grade disease (grade 3/3, 3/4, 4/4 primary or recurrent) > 5 cm or recurrent, moderate grade (grade 2/3, 2/4) disease > 10 cm by CT scan (see Appendix III)
- No evidence of metastases; no multifocal disease suggestive of regional nodal involvement
- Gross total resection (R0 or R1) must be feasible
- Zubrod 0-2
- > 65 years of age patients may be enrolled after evaluation by medical oncologist; two functional kidneys
- Normal cardiac function (Ejection fraction ≥ 50% within the past six months)
- ANC ≥ 1,500/mm³; platelets ≥ 100,000/mm³; bilirubin ≤ 1.5 mg/dl, AST ≤ 3 x the upper limits of normal (ULN); creatinine ≤ 1.6 mg/dl; albumin ≥ 3.5 g/dl
- Oral caloric intake ≥ 1500 kCal/d; no hypersensitivity to E. coli derived products
- No prior radiation therapy to the abdomen or pelvis
- No prior chemotherapy for sarcoma or prior doxorubicin/ifosfamide
- Signed study-specific consent prior to study entry

Required Sample Size: 48
Institution #  
RTOG S-0124  

ELIGIBILITY CHECK (8/1/01, 12/3/02, 12/23/02)  
(page 1 of 3)

Case #  

1. Is the malignancy a primary or recurrent high grade soft tissue sarcoma > 5 cm or recurrent moderate grade soft tissue sarcoma that is > 10 cm?  

2. Is the sarcoma located in the pelvis or retroperitoneum?  

3. Is there radiographically measurable disease?  
   Provide the 3 dimensions of the disease:  
   cm (anteroposterior diameter)  
   cm (medial-lateral diameter)  
   cm (cranio-caudad diameter)  

4. Has the tumor been debulked prior to enrollment on study?  

5. What is the grade? (on a scale of 1 to 3 or on a scale of 1 to 4)  

6. How was the grade determined? (FNA, core biopsy, open biopsy, other)  

7. Was histologic confirmation (biopsy) done within 2 months prior to registration?  

8. If patient is > 65, did a medical oncologist evaluate the patient for tolerance to the protocol therapy?  

9. What is the Zubrod Performance Status?  

10. Is there evidence of metastatic disease?  

11. Is there evidence of multifocal disease suggestive of regional nodal involvement?  

12. Are there any contraindications to surgery?  

13. Is the tumor potentially resectable as indicated by the surgeon?  

14. Has the patient presented with a bowel obstruction at the time of diagnosis?  

15. Has the patient received any prior pelvic/abdominal irradiation, chemotherapy for sarcoma or Adriamycin® and/or ifosfamide?  

16. Has the patient had a previous malignancy other than adequately treated non-melanoma skin cancer or cervical cancer in-situ?  
   If yes, has the patient been disease free for ≥ 5 years?  

17. Is the patient pregnant, lactating or not using effective contraception? (code NA for men and for females without child-bearing potential)  

(cont’d on next page)
Institution #  ____________
RTOG S-0124
Case #  ____________

ELIGIBILITY CHECK  (8/1/01, 12/3/02, 12/23/02)
(page 2 of 3)

18. Does the patient have an active uncontrolled bacterial, viral, or fungal infection?  (N)
19. Has a radiation oncology consult confirmed feasibility of pre-operative radiation therapy?  (Y)
20. Does the patient have any serious medical or psychiatric illness which would prevent informed consent or limit survival to less than 2 years?  (N)
21. Does the patient have two functioning kidneys?  (Y)
22. What is the ANC?  (≥ 1500)
23. What is the platelet count (x 1000)?  (≥ 100)
24. What is the bilirubin?  (≤ 1.5)
25. What is the AST?  (≤ 3 x ULN)
26. What is the creatinine?  (≤ 1.6)
27. What is the albumin?  (≥ 3.5)
28. Has the patient had a normal heart function study done within the past six months?  (Y)
29. Is the patient’s oral caloric intake ≥ 1500 kCal per day?  (Y)
30. Does the patient have any hypersensitivity to E. coli derived products?  (N)

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed?  (Y)
3. Is the patient eligible for this study?  (Y)
4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Name
6. Verifying Physician

(cont’d on next page)
Institution # __________________
RTOG S-0124

ELIGIBILITY CHECK (8/1/01, 12/3/02, 12/23/02)

Case # __________________

(page 3 of 3)

7. Patient’s ID Number

8. Date of Birth

9. Race

10. Social Security Number

11. Gender

12. Patient’s Country of Residence

13. Zip Code

14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Treatment Start Date (must begin within 2 weeks after registration)

17. Is this patient going to receive IMRT?

18. Is the tumor primary or recurrent?

19. Specify tumor grade based on pre-treatment biopsy (prior to protocol treatment):
   Grade 2 or Grade 3 or Grade 4.

20. Specify maximum tumor size: > 5 to < 10 cm or ≥ 10 cm to < 15 cm or ≥ 15 cm to < 20 cm.

21. Medical Oncologist’s Name

22. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ________________________________ Date ________________________________
1.0 INTRODUCTION

1.1 Overview

Soft tissue sarcomas are uncommon tumors estimated to account for 8,100 of the tumor cases diagnosed in the United States in 2000.\(^1\) This corresponds to 0.7% of all estimated cancers diagnosed in the United States. The majority of these tumors arise in the extremities. In one series, the retroperitoneal and intraabdominal origin of soft tissue sarcomas accounted for only 14% of the entire population of soft tissue sarcomas.\(^2\) Hence, it is estimated that 1,100 to 1,200 retroperitoneal sarcomas are diagnosed annually in the United States. Retroperitoneal sarcomas are frequently large at the time of diagnosis. The relatively large size of most of these tumors and critical adjacent (frequently involved) viscera make it difficult to perform R0 surgical resection. As such, the disease is characterized by significant local failure rates. Most studies on the treatment of retroperitoneal sarcomas are retrospective single institution reports with relatively small numbers of patients and do not allow for firm conclusions regarding the role of combined modality therapy. Therefore, the general treatment approach and rationale for combined modality therapy for these tumors is predicated on phase III data from trials performed in extremity sarcoma.

1.2 Surgery

Complete surgical resection is the only known potentially curative therapy for retroperitoneal sarcomas. Published series of surgical resection alone for retroperitoneal sarcoma have shown a wide variation in local control and survival rates with local relapse as high as 70%-80% and low survival rates.\(^3,4,5,6,7,8\) This variability is a function of the anatomic and histologic heterogeneity of these lesions and the relatively short follow-up in most reports. Unfortunately, complete resection may not be feasible in approximately half of the patients at presentation. When gross complete (R0 or R1) resection is performed, microscopic surgical margins are frequently positive because of the normal tissue limitations.\(^3,4,6,7,8\) Indeed, local failure remains the primary site of treatment failure in 22-90% of patients.\(^3,5,6,9,10,11\) In an older series from the Mayo Clinic, in which only 18 of 63 patients received adjuvant postoperative irradiation (dose not indicated) after complete resection of soft tissue sarcomas of the retroperitoneum, a local recurrence rate of 86% was reported.\(^6\) A more modern series from Karakousis reported a local recurrence rate of 30% despite very aggressive resection including en bloc resection of adjacent organs and/or vasculature.\(^9\) A large series from Memorial Sloan-Kettering Cancer Center reported the outcome of 500 patients with retroperitoneal sarcomas.\(^11\) The majority of patients had high grade (64%) lesions and most were greater than 10 cm in size (60%). In patients with primary lesions, local recurrences occurred in 22% of patients at a relatively short median follow-up of 28 months.

1.3 Adjuvant External Beam Irradiation

A significant component of the rationale for postoperative radiotherapy for patients with retroperitoneal sarcomas is based on extrapolation from phase III trials of adjuvant radiotherapy for patients with extremity and superficial trunk sarcomas.\(^12,13\) In these phase III trials, postoperative external beam radiation\(^12\) and brachytherapy\(^13\) were associated with significantly improved local control as compared to control patients treated by surgery alone. It is thus postulated that there may be a comparable local control benefit for similar histology lesions located in the retroperitoneum provided that such treatment can be provided with an acceptable toxicity profile.

In the treatment of retroperitoneal soft tissue sarcomas, radiation has been used in a variety of manners with varied success.\(^5,10,14,15,16\) External beam irradiation (EBRT) alone is limited by the dose tolerance of multiple structures in this region. Radiation doses typically used for extremity soft tissue sarcomas exceed normal tissue tolerances of several organs. Hence, the literature includes a wide range of doses utilized in the treatment of sarcomas arising from the retroperitoneum.

Many studies using EBRT alone indicate a persistent high local failure rate. However, in a series of 48 long-term survivors from Memorial Sloan-Kettering Cancer Center where 35 received no irradiation, a local regional control advantage was seen with the use of adjuvant irradiation.\(^10\) The Princess Margaret Hospital reported on 45 patients treated with complete surgical resection of whom 36 received irradiation (40 Gy). Infield failure rate was improved with radiation for those receiving \(\geq 35\) Gy.\(^16\) A series from the Netherlands treated 34 patients, 30 with complete surgical resection.\(^17\) Thirteen of these patients received adjuvant post-operative irradiation of 40-62 Gy. Local recurrence with or without metastatic disease occurred in 23 of the 34 patients. In the 13 patients who received adjuvant post-operative irradiation, local failure was recorded in seven patients, primarily in patients receiving less than 60 Gy. A series of 21 patients from Fox Chase Cancer Center treated with surgical resection and adjuvant irradiation (36-90 Gy, \(18 \text{ with EBRT only}\)) resulted in a local failure rate of 28% at 2 years, but improved control was seen in the eight patients with total doses of \(> 55.2\) Gy.\(^18\) An older series of 17 patients from Massachusetts General
Hospital treated with curative intent using surgery and adjuvant irradiation resulted in a local failure rate of 54% at five years. As in the other series, higher doses appeared to increase the control rate. Although several authors have indicated a relationship between dose and local control, the treatment of the abdominal cavity and its small bowel content to large postoperative doses of irradiation results in a higher number of complications.

1.4 Intraoperative Irradiation With or Without External Beam Irradiation

Intraoperative radiation therapy with electrons (IOERT) has been utilized to maximize the dose to tumor bed/dose to normal tissue ratio. This technique has specific advantages in the retroperitoneum since intraoperative exposure is utilized to move radiosensitive adjacent viscera and neurovascular structure out of the intraoperative treatment field. IOERT in combination with external beam irradiation has been evaluated by multiple institutions in the treatment of retroperitoneal sarcomas. One study was a prospective randomized study and the other experiences are retrospective. The retrospective studies have shown better neurologic tolerance with lower IOERT doses.

1.4.1 National Cancer Institute (NCI): Phase III External Beam Irradiation With/Without Intraoperative Irradiation

The NCI conducted a randomized trial from 1980-1985 in which 35 patients with resectable primary retroperitoneal sarcoma were randomized to receive postoperative EBRT ± IOERT. All patients had a gross total resection, but most had presumed or pathologically positive microscopic residual disease because of marginal resections. Fifteen patients received IOERT (20 Gy), usually to abutting fields using high-energy electrons of 11 to 15 MeV, followed by postoperative EBRT to 35 to 40 Gy. Twenty patients received standard postoperative EBRT alone of 50 to 55 Gy (35 to 40 Gy to an extended field; 15 Gy within a boost field). All patients receiving IOERT also received Misonidazole as a radiosensitizer.

In the final analysis of these patients by Sindelar et al. with a minimum follow-up of 5 years and a median follow-up of 8 years, there was a significant difference in local control between the two groups (Table 1). In the IOERT group, only 3 of 15 patients (20%) had an in-field local recurrence, versus 16 of 20 patients (80%) in the EBRT control group (p < 0.001). The median survival was similar for both groups: 45 months for the IOERT group and 52 months for the control group. Severe small bowel complications were less frequent in IOERT patients at 2 of 15 versus 10 of 20 patients (13% vs. 50% - p <0.05). Peripheral neuropathy rates were higher in the EBRT plus IOERT patients.

### Table 1

Retroperitoneal Sarcoma Resection ± IOERT Series - Treatment Method and Results

<table>
<thead>
<tr>
<th>Series (Author/Institution)</th>
<th>Resection N</th>
<th>Gross complete N (%)</th>
<th>EBRT (Gy) N, Dose</th>
<th>IOERT (Gy) N, Dose</th>
<th>DFS (%) 5-yr</th>
<th>OS (%) 5-yr</th>
<th>In-Field Local Failure % (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. Series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen, Mayo22,7</td>
<td>87</td>
<td>72 (83)</td>
<td>77, 45-52</td>
<td>87, 10-20</td>
<td>----</td>
<td>47</td>
<td>23d</td>
</tr>
<tr>
<td>Willett, MGH21</td>
<td>20</td>
<td>14 (70)</td>
<td>40 - 50</td>
<td>12, 10 - 20</td>
<td>64 (4 yr)</td>
<td>----</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Sindelar, NCI a, 15,20</td>
<td>15</td>
<td>15 (100)</td>
<td>35 - 40</td>
<td>20</td>
<td>----</td>
<td>38b</td>
<td>20b,c</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>20 (100)</td>
<td>50-55</td>
<td>no</td>
<td>----</td>
<td>44b</td>
<td></td>
</tr>
<tr>
<td>European Series</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calvo25</td>
<td>30</td>
<td>21 (70)</td>
<td>23, 40-50</td>
<td>10-20</td>
<td>----</td>
<td>36 (2 yr)</td>
<td>47</td>
</tr>
<tr>
<td>Dubois23</td>
<td>31f</td>
<td>30 (97)</td>
<td>28 - 56</td>
<td>31, ----</td>
<td>----</td>
<td>64.5</td>
<td>30.7</td>
</tr>
</tbody>
</table>

2
a. Randomized study: 35 patients: 15 with IOERT, 20 standard treatment with EBRT
b. from graphs
c. $\Delta p < 0.001$
d. Local failure in only 3 of 43 (7%) with primary disease vs. 17 of 44 (39%) with recurrent disease
e. Only 13 of 31 had retroperitoneal sarcomas

1.4.2 Massachusetts General Hospital: External Beam Irradiation and Intraoperative Irradiation
Willett et al. reported the MGH experience of IOERT in the management of retroperitoneal sarcoma in a group of twenty patients with either primary ($n=14$) or recurrent ($n=6$) disease.21 At MGH, patients were treated with preoperative EBRT (40-50 Gy, 1.7-2.0 Gy fractions in 4-6 weeks) followed by resection and IOERT (10-20 Gy). Seventeen of the 20 patients underwent laparotomy, 14 had a complete resection, 3 had a partial resection and distant metastasis developed during EBRT in 3 patients. IOERT was given to 12 of the 14 patients. The four year actuarial local control and disease-free survival of the 14 patients undergoing complete resection was 81% and 64%, respectively. Five patients developed complications: sensory neuropathy in two (17%), hydronephrosis in two, and small bowel obstruction in one. The series from Massachusetts General Hospital was recently updated with a local control rate of 91% for those who received IOERT in comparison to 61% for those getting EBRT alone.

1.4.3 Mayo Clinic: Intraoperative Irradiation With/Without External Beam Irradiation
A Mayo Clinic analysis reported 87 patients with retroperitoneal or pelvic sarcomas who had resection plus IOERT (10-20 Gy) at Mayo and had ≥ 1 year of follow-up (median 3.5 yrs).22 More tumors were high grade (62%) and recurrent (52%). At the time of the operation at Mayo, all gross disease could be removed in 72 patients or 83%. EBRT usually 45-50.4 Gy was given in 77 patients (all 43 with primary lesions and 34 of the 44 patients with recurrent disease). Forty-nine patients had documented disease relapse with 20 (23%) having local or central failure (central in 7/87 or 8%, local in 16/87 or 18%) (Table 2). Local or central failure occurred in only 3 of 43 patients with primary lesions (7%) versus 17 of 44 (39%) who presented with recurrent disease. If patients with prior EBRT are deleted from the analysis, the incidence of local or central relapse was 8% and 29% for the primary and recurrent disease patients, respectively.

Table 2

Mayo Clinic IOERT Analysis: Incidence of Local or Central Failure in Patients with Retroperitoneal and Intrapelvic Sarcomas22

<table>
<thead>
<tr>
<th>Pattern of Relapse</th>
<th>Primary N=43</th>
<th>Recurrent N=44</th>
<th>Low Grade N=33</th>
<th>High Grade N=54</th>
<th>Total N=87</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>LF</td>
<td>2</td>
<td>11</td>
<td>8</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>LF and CF</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total # (%)a</td>
<td>3 (7%)a</td>
<td>17 (39%)</td>
<td>11 (33%)</td>
<td>9 (17%)</td>
<td>20 (23%)</td>
</tr>
<tr>
<td>Prior EBRT excludedb</td>
<td>3/41 (7%)</td>
<td>9/31 (29%)</td>
<td>6 (22%)</td>
<td>6 (13%)</td>
<td>12/72 (17%)</td>
</tr>
</tbody>
</table>

CF: central failure in IOERT field; LF: local failure in EBRT field or surgical bed (prior EBRT group)

a. Patients with prior EBRT included in numerator and denominator
b. Patients with prior EBRT excluded from numerator and denominator (primary N=2, recurrent N=13)
Five-year overall survival (OS) was 47% with 46 of 87 patients (53%) alive. Five-year OS was unaffected by primary vs. recurrent status (52% vs. 42%) and low vs. high-grade lesions (2-year 97% vs. 75%, 5-year 45% vs. 47%). Patients with gross total resection had a trend towards improved survival over those with gross residual disease (median - 4.7 vs. 3.2 years, 5 year - 49% vs. 36%, p = 0.08).

The influence of multiple prognostic factors on local and distant disease control and overall survival was analyzed separately for patients who presented with either primary (Table 3) or recurrent disease. For patients with primary lesions, both initial lesion size ≤ 5 cm and the surgeon’s ability to achieve a gross total resection prior to IOERT appeared to have a favorable impact on long-term survival (5-year). Disease control appeared to be impaired only by the ability to achieve a gross total resection prior to IOERT. For patients who presented with recurrent disease, the amount of residual disease at time of IOERT had less apparent impact on disease control or survival. Patients with low-grade lesions or recurrent tumor size ≤ 5 cm had more favorable trends for overall survival and disease control.

Severe gastrointestinal intolerance was uncommon in primary disease patients (2/43 or 5%), but 7 of 44 recurrent disease patients developed Grade 3-5 GI fistulae (16%) with one fatality. Grade 3 peripheral neuropathy developed in 4 of 43 patients (9%) with primary disease and 5 of 44 (11%) with recurrent lesions.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic IOERT Analysis: Primary Retroperitoneal and Pelvic Sarcoma - Influence of Prognostic Factors on Disease Control and Survival&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>N</th>
<th>2 yr</th>
<th>5 yr</th>
<th>2 yr</th>
<th>5 yr</th>
<th>2 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual at IOERT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Microscopic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Margin (-)</td>
<td>11</td>
<td>91</td>
<td>62</td>
<td>100</td>
<td>100</td>
<td>71</td>
<td>53</td>
</tr>
<tr>
<td>Margin (+)</td>
<td>25</td>
<td>75</td>
<td>54</td>
<td>100</td>
<td>92</td>
<td>65</td>
<td>41</td>
</tr>
<tr>
<td>Gross</td>
<td>7</td>
<td>71</td>
<td>29</td>
<td>80</td>
<td>60</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (1,2)</td>
<td>9</td>
<td>89</td>
<td>42</td>
<td>100</td>
<td>100</td>
<td>88</td>
<td>25</td>
</tr>
<tr>
<td>High (3,4)</td>
<td>34</td>
<td>75</td>
<td>54</td>
<td>96</td>
<td>84</td>
<td>55</td>
<td>43</td>
</tr>
<tr>
<td>Tumor Size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>7</td>
<td>100</td>
<td>86</td>
<td>100</td>
<td>83</td>
<td>71</td>
<td>43</td>
</tr>
<tr>
<td>&gt;5</td>
<td>35</td>
<td>76</td>
<td>45</td>
<td>96</td>
<td>92</td>
<td>62</td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>22</sup> Montpellier Orthovoltage Intraoperative Irradiation

Dubois et al. from Montpellier, France, reported on their experience with IOERT in 31 patients with soft tissue sarcomas which included 13 patients with lesions in the retroperitoneum or pelvis. Sixteen patients were treated for primary disease and 15 for recurrent disease; this information was not reported separately for patients with retroperitoneal tumors. Patients with primary disease also received postoperative EBRT with doses of 28 to 56 Gy, mean 41.8 Gy. Of the entire group, all but one patient had a gross complete resection. Local recurrence occurred in 4 patients (31%), all of whom had had intra-pelvic or intra-abdominal disease. A five-year survival of 65% was reported for the total group of patients.

<sup>23</sup> Pamplona Intraoperative Irradiation

Calvo et al. presented the Pamplona results of IOERT for 30 patients with soft tissue sarcomas of central anatomical sites. Of the entire group, 13 had recurrent lesions and 17 had primary tumors. Tumor
location included the retroperitoneum in 8 cases and pelvis in 5 (6-recurrent, 7- primary), trunk in 14 and miscellaneous sites in 3. All patients underwent maximum resection and received IOERT of 10 to 20 Gy. A gross total marginal resection was accomplished in 21 patients, and gross residual remained in the other 9. EBRT was given to 23 patients (40-50 Gy at 1.8 - 2 Gy/fx) excluding the 7 patients who had received previous EBRT. Patients with high-grade tumors also received chemotherapy consisting of ifosfamide, dacarbazine, and Adriamycin® (preoperatively in 5 patients, as maintenance treatment in 12).

Both local recurrence and distant metastases occurred with higher frequency in the 13 patients who presented with local relapse (7 of 13 had received prior EBRT and were treated only with maximal resection and IOERT at time of local relapse). Other factors predicting for an increased risk of local relapse were lesion diameter of > 10 cm vs. ≤ 10 cm and gross (macroscopic) vs. microscopic residual after maximal resection. Local control overall was 53% with better local control in patients with microscopic residual disease (67%) versus gross residual (22%). For the 8 patients with retroperitoneal tumors, five developed a local recurrence (two had distant metastasis in addition to local recurrence), and three were NED at 35, 38, and 63 months.

With a median follow-up of 25 months, the overall survival (OS) for the entire group was 36%. Five-year actuarial survival appeared better in the patients who presented with primary vs. recurrent lesions at 53% vs. 20%. The difference in survival between the Pamplona and Mayo series in patients with recurrent disease may be related to the fact that a higher percentage of patients in the Pamplona series had received prior EBRT.

1.4.6 University of Texas M. D. Anderson Cancer Center: Chemoradiotherapy Plus Intraoperative Irradiation

At the University of Texas M.D. Anderson Cancer Center, investigators have reported preliminary results of a phase I study of preoperative doxorubicin (20 mg/m²/week by continuous infusion for 4 weeks) and concurrent EBRT followed by surgery and IOERT (15 Gy) for patients with resectable retroperitoneal sarcomas.⁵⁻⁶ The external beam radiation dose has been escalated from 18 to 46.8 Gy. Grade 3 or 4 toxicities (diarrhea, n=2; fatigue, n= 1; neutropenia, n=1) have been noted in 4 of 19 patients. No patients have experienced febrile neutropenia or grade 3-4 nausea or vomiting. All patients have undergone complete tumor resection; 1 patient achieved a complete pathologic response. IOERT has been performed without identifiable toxicity.

1.5 Risk for Distant Metastasis/Role for Chemotherapy

In addition to the significant risk for local failure, patients with intermediate and high-grade retroperitoneal sarcomas are at significant risk for hepatic and pulmonary metastases. A series by Karakousis et al. revealed an overall recurrence rate of 30% in 90 patients, 18 of whom received adjuvant chemotherapy. The 5-year rate of distant recurrence for grade 1 tumors was only 6% compared to 50% and 44% for grades 2 and 3 sarcomas, respectively.⁹ The series from Memorial Sloan Kettering Cancer Center (MSKCC) reported that 11 of 48 long term survivors developed distant metastases.¹⁰ The MSKCC data indicates an 11% distant metastases rate among 30 primary retroperitoneal sarcomas with less than three years follow-up.¹¹

Most studies assessing adjuvant chemotherapy in the management of soft tissue sarcomas have not demonstrated a significant improvement in survival. However, the recent Sarcoma Meta Analysis Collaboration (SMAC) meta-analysis of all published phase III trials of adjuvant chemotherapy for patients with soft tissue sarcomas (all anatomic sites) demonstrated improved relapse-free survival and local control with the use of adjuvant doxorubicin-based chemotherapy. However, subset analysis of patients with retroperitoneal sarcomas was not possible.²² More recently, interim analysis of an Italian phase III trial evaluating high-risk extremity sarcoma patients treated by local therapy alone or local therapy plus postoperative epirubicin (120 mg/m²) and ifosfamide (9 gm/m²) reveals a significant survival advantage for patients treated with adjuvant chemotherapy.²³ The aggregate results of the SMAC meta analysis and the positive results of the Italian trial of more modern (i.e. agents, dosing, and schedule) adjuvant chemotherapy has led some investigators to conclude that all patients with high-risk extremity sarcoma should be considered for adjuvant chemotherapy. It is inferred that if a survival advantage exists for patients with high-risk extremity lesions, this benefit may also apply to patients with high-risk lesions in other anatomic sites such as the retroperitoneum.
Given the significant risk for both local recurrence and distant relapse for patients with intermediate and high-grade retroperitoneal sarcomas, integrated combined-modality treatment strategies that target these patterns of failure are warranted. As such, this protocol is designed to explore induction chemotherapy, preoperative radiotherapy, and post-resection radiation boost in an effort to provide maximal treatment for these high-risk lesions.

2.0 OBJECTIVES
2.1 To assess overall survival of retroperitoneal sarcomas after integrated chemotherapy, radiation, and surgery.
2.2 To assess local-regional control of retroperitoneal sarcomas after integrated chemotherapy, radiation, and surgery.
2.3 To assess disease-free survival of retroperitoneal sarcomas after integrated chemotherapy, radiation, and surgery.
2.4 To assess the pathologic response of retroperitoneal sarcoma after integrated chemotherapy, radiation, and surgery.
2.5 To assess toxicities and complications associated with the entire treatment program and its individual components (preoperative chemotherapy, preoperative external beam irradiation, resection with intraoperative or postoperative radiotherapy boost).

3.0 PATIENT SELECTION (12/3/02)
3.1 Conditions for Patient Eligibility
3.1.1 Patients must have a primary or recurrent (post surgery) soft tissue sarcoma of the retroperitoneum/pelvis confirmed by pathology. Biopsy must be done within 2 months prior to registration.
3.1.2 All primary sarcomas must be high-grade (grade 3/3, 3/4, 4/4) > 5 cm. Moderate grade (grade 2/3, 2/4) sarcomas are allowed only if recurrent and > 10 cm.
3.1.3 Gross total resection (R0 or R1) must be felt to be feasible. Surgical consultation should verify this prior to enrollment in the study.
3.1.4 Patients must have radiographically measurable disease (gross disease) > 5 cm (T2) demonstrated by CT/MRI of the abdomen/pelvis.
3.1.5 Radiation consultation shall confirm feasibility of preoperative external beam radiotherapy prior to enrollment in the study.
3.1.6 CT of the chest with < 4 equivocal pulmonary lesions that are all < 3 mm in diameter. This is allowed because of the indeterminate nature of small pulmonary lesions identified on CT.
3.1.7 Medical oncologist should carefully evaluate patients over 65 to determine their tolerance to the doxorubicin and ifosfamide schedule in this protocol.
3.1.8 Zubrod Performance Status 0-2.
3.1.9 ANC ≥ 1,500/mm³, platelets ≥ 100,000/mm³, bilirubin ≤ 1.5 mg/dl, AST ≤ 3 x the upper limits of normal (ULN); creatinine ≤ 1.6 mg/dl, serum albumin ≥ 3.5 g/dl.
3.1.10 Normal heart function (study of EF ≥ 50% within past six months); two functional kidneys.
3.1.11 Oral caloric intake ≥ 1500 kCal/day.
3.1.12 Treatment must begin within two weeks after registration.
3.1.13 Patients must use effective contraception; must not be pregnant or lactating. It is not known what effects this treatment may have on the developing fetus.
3.1.14 No evidence of metastases.
3.1.15 No contraindications to surgery.
3.1.16 Patient must sign a study-specific informed consent form prior to study entry.

3.2 Ineligibility Criteria (12/3/02)
3.2.1 Prior abdominal or pelvic irradiation.
3.2.2 Prior Adriamycin® or ifosfamide.
3.2.3 No radiographically measurable disease (even if prior resection was marginal) or disease ≤ 5 cm.
3.2.4 Subtotal (R2) resection (partial debulking or subtotal tumor resection with residual gross disease).
3.2.5 Sarcomas that cannot allow sparing of at least 2/3 of one kidney within the planned irradiation field shall be excluded.
3.2.6 Histopathologic subtypes: rhabdomyosarcoma, extrasosseus Ewing’s, primitive neuroectodermal tumors, osteosarcoma or chondrosarcoma, Kaposi’s sarcoma or aggressive fibromatosis (desmoid tumors).
3.2.7 Multifocal disease suggestive of regional nodal involvement since this may be a manifestation of sarcomatosis.
3.2.8 Prior or concurrent malignancies other than surgically treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin within the preceding five years.

3.2.9 Patients with obvious bowel obstruction at the time of diagnosis, whether believed to come from direct bowel involvement or by secondary bowel compression.

3.2.10 Patients may have no serious medical or psychiatric illness, which would prevent informed consent or limit survival to less than two years.

3.2.11 Congestive heart failure or myocardial infarction within previous six months.

3.2.12 Left ventricular ejection fraction < 50% or any cardiovascular abnormality resulting in a New York Heart Association functional status \( \geq 2 \) \(^{33} \) (Appendix II)

3.2.13 Patients with a hypersensitivity to E. coli derived products.

3.2.14 Patients with only one functioning kidney.

4.0 PRETREATMENT EVALUATIONS

4.1 Pre-treatment blood tests must be done within two weeks prior to registration; imaging studies to be done within four weeks prior to registration.

4.1.1 History and physical examination.

4.1.2 Measurements of the primary tumor (anteroposterior, medial-lateral, and cranio-caudad).

4.1.3 Computed tomography (CT) of the abdomen/pelvis with measurements of the primary tumor before any therapy. MRI may be done as an alternative for primary tumor evaluation for patients with allergies to intravenous contrast. It is suggested that the same imaging modality be used consistently for tumor evaluation.

4.1.4 AP and lateral CXR.

4.1.5 CT scan of chest.

4.1.6 CBC, differential and platelet count, AST, alkaline phosphatase, BUN, serum creatinine, total bilirubin, serum albumin.

4.1.7 EKG

4.1.8 Pregnancy test as applicable.

4.1.9 Echocardiography or MUGA scan to evaluate left ventricle ejection fraction.

5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Radiation General Guidelines

6.1.1 CT or MRI planning of the preoperative irradiation is essential. All critical organs that are partially or completely within the treatment volume should be identified on the treatment plan. This includes but is not limited to the kidneys, liver, and spinal cord.

6.1.2 If the disease is recurrent after primary treatment, the recurrent disease should be identified as the treatment volume. However, if protocol treatment is done following incomplete surgical resection with gross residual then the original tumor volume should be encompassed in the treatment volume.

6.1.3 Efforts should be made to minimize the small bowel within the irradiation field using patient positions such as lateral decubitus or prone on a belly board.

6.1.4 A minimum of 2/3 of one kidney should receive a dose of less than 20 Gy. A renal scan to determine differential renal function of each kidney is recommended if any renal dysfunction is suspected. Dose to one kidney may exceed 20 Gy as long as the opposite kidney has 2/3 receiving < 20 Gy.

6.1.5 Half of the liver should not exceed 30 Gy.

6.1.6 If IOERT for the boost is planned that may encompass the spinal cord, external beam dose to the spinal cord should be limited to 35 to 40 Gy.

6.1.7 Customized blocking using cerrobend blocks or multi-leaf collimation is required to achieve the above criteria.

6.2 Preoperative Radiation

6.2.1 Radiation shall start within 2-4 weeks after completion of chemotherapy.
6.2.2 Initial treatment volume shall encompass the tumor with 5 cm of circumferential margin; however, margins of 3 cm are acceptable in regions required to spare dose to kidneys/liver/spinal cord. If the tumor has been recently subtotally resected then the initial tumor volume should be encompassed in the original treatment volume.

6.2.3 Dose to the initial volume should be 39.6 Gy in 1.8 Gy fractions delivered daily, Monday through Friday.

6.2.4 A subsequent additional dose of irradiation shall be delivered to a reduced field consisting of the tumor volume with a 3 cm margin. This volume should receive 5.4 Gy in 3 fractions for a total cumulative dose of 45 Gy.

6.2.5 A final boost of preoperative irradiation should be delivered if within acceptable toxicity to the tumor volume with a 2 cm margin for an additional 5.4 Gy in 3 fractions.

6.2.6 Total preoperative dose of external irradiation shall be 45-50.4 Gy delivered in 25-28 fractions.

6.3 Boost Irradiation

6.3.1 General Issues

6.3.1.1 Options for boost of the tumor bed allow for any method that can minimize the dose to normal tissue especially small bowel and kidney.

6.3.1.2 The site(s) of highest risk should be identified by the radiation oncologist and surgeon. Proximity of enteric and vascular anastomoses and the risk of radiation to these anastomoses should be carefully considered in the feasibility assessment of intra-operative and post-operative boosts.

6.3.1.3 Treatment choice is at the discretion of the radiation oncologist.

6.3.1.4 Boost therapy can be delivered intraoperatively using electron beam therapy (IOERT) or high dose rate brachytherapy (IOHDR).

6.3.1.5 Alternatively, tissue expanders or slings can be used to displace normal small bowel out of the tumor bed and boost therapy can be delivered postoperatively.

6.3.1.6 Clips identifying the tumor bed should be placed by the surgeon in order to identify the area to be treated. In the case of IOERT or IOHDR, these may be placed at the completion of these treatments.

6.3.2 Intraoperative Electron Beam Radiation Therapy (IOERT)

An operative report describing the intraoperative radiation therapy procedure and dosimetry information must be sent to RTOG Headquarters. If possible, intraoperative radiographs and/or photographs should be taken of the IOERT treatment area and forwarded to RTOG Headquarters.

6.3.2.1 Applicator selection should allow for treatment of the at risk site with 1-2 cm radial margins to the cone edge.

6.3.2.2 Dosimetry on available applicators should be available to the radiation oncologist upon request in the operating suite.

6.3.2.3 The dose should be prescribed to the 90% isodose line.

6.3.2.4 Energy of the electrons is at the discretion of the radiation oncologist taking into consideration the area at risk and normal tissues. However, if 6 MeV electrons are utilized use of bolus material to increase the surface dose should be considered.

6.3.2.5 Dose delivered should vary with the surgical and pathologic findings:
- Patients with wide margins (≥ 10 mm): 7.5-10 Gy
- Narrow but negative histologic margins (< 10 mm): 10-12.5 Gy
- Microscopic residual: 12.5-15 Gy
- Gross residual: 15-20 Gy

6.3.2.6 If more than one applicator is required to treat adjacent areas at risk, the abutting field edges should be demarcated during the procedure by suture, marking pen, or clips (different type than utilized to mark tumor bed). Lead shielding (appropriate for the energy utilized) should be considered at the edge of abutting fields to minimize dose overlap. The treating physician should make every effort to avoid any overlap of adjacent IOERT fields; in some settings, it may be necessary to consider using a small “gap” between adjacent fields to avoid potential overdose of critical structures.

6.3.2.7 All critical structures such as kidney, bowel, and large amounts of the liver should be removed or shielded from the treatment field.

6.3.3 Intraoperative High Dose Rate Brachytherapy (IOHDR)

An operative report describing the intraoperative radiation therapy procedure and dosimetry information must be sent to RTOG Headquarters. If possible, intraoperative radiographs and/or photographs should be taken of the IOHDR treatment area and forwarded to RTOG Headquarters.

6.3.3.1 Treatment intraoperatively with HDR brachytherapy requires prior dosimetric planning with pre-existing constructed implant apparatus. (e.g.: HAM applicator)
6.3.3.2 Placement of the applicator in the operating room should ensure contact of the applicator with the surface being treated.

6.3.3.3 Dummy sources should be placed in the channels of the applicator and intraoperative films taken for documentation of the site being treated. Some anatomical positions will prohibit filming.

6.3.3.4 Dose is calculated to 0.5 cm radial depth (from the tissue surface of the applicator) for patients with gross total resection with negative or positive margins. Optimally the 150% isodose line should be non-contiguous between catheters. For patients with gross residual, thickness or radial depth must be \( \leq 1.0 \) cm and the dose calculated at 1.0 cm from the tissue surface of the applicator.

6.3.3.5 Dose to the skin (if applicable) should be \(< 75\%\) of the prescribed dose.

6.3.3.6 Lead shielding of appropriate tissue may be employed as needed.

6.3.3.7 Dose delivered should vary with the surgical and pathologic findings:
- Patients with wide (\( \geq 10 \) mm) margin: 7.5-10 Gy
- Narrow but negative histologic margins (\(< 10 \) mm) margin: 10-12.5 Gy
- Microscopic residual: 12.5-15 Gy
- Gross residual: 15-20 Gy

6.3.3.8 All critical structures such as kidney, bowel, and large amounts of the liver should be removed or shielded from the treatment field.

6.3.4 Postoperative HDR Brachytherapy

6.3.4.1 The tumor bed should be implanted with afterloading catheters at 1.0-1.5 cm spacing extending 1-2 cm beyond the area at risk as determined intraoperatively and marked by clips.

6.3.4.2 Appropriate tissue expanders/slings should be utilized to remove small bowel and other critical structures from the immediate area of the implant. All small bowel should be \( > 2.0 \) cm from any active source.

6.3.4.3 Treatment planning should be done prior to the first therapy.

6.3.4.4 Planning should allow for the prescription dose to cover contiguously a radius of 0.5 cm (from the tissue surface of the applicator) for patients with gross total resection with negative or positive margins. Optimally the 150% isodose line should be non-contiguous between catheters. For patients with gross residual, thickness or radial depth dose must be \( \leq 1.0 \) cm and the dose calculated 1.0 cm from the tissue surface of the applicator.

6.3.4.5 Dose to the skin (if applicable) should be \(< 75\%\) of the prescribed dose.

6.3.4.6 Treatments should not commence before 5 postoperative days. A total of 3-4 fractions shall be delivered over 2-3 days. If two treatments are delivered in the same day they shall be separated in time by at least 6 hours.

6.3.4.7 Dose delivered should vary with the surgical and pathologic findings:
- Patients with wide (\( \geq 10 \) mm) margin: 2.5-3 Gy x 3 fractions
- Narrow but negative histologic margins (\(< 10 \) mm) margin: 3.5-4 Gy x 3 fractions
- Microscopic residual: 4 Gy x 3 fractions
- Gross residual: 3.5-4 Gy x 4 fractions

6.3.5 Postoperative LDR Brachytherapy

6.3.5.1 The tumor bed should be implanted with afterloading catheters at 1.0-1.5 cm spacing extending 1-2 cm beyond the area at risk as determined intraoperatively and marked by clips.

6.3.5.2 Appropriate tissue expanders/slings should be utilized to remove small bowel from the immediate area of the implant. Ideally small bowel should be \( > 2.0 \) cm from any active source.

6.3.5.3 Treatment planning should be done prior to the first therapy.

6.3.5.4 Iridium 192 is the preferred isotope for low-dose rate brachytherapy. The strength of each source can vary to allow for treatment of the at risk volume. The radial depth of the implant shall be 0.5 cm for patients with gross total resection and \( \leq 1.0 \) cm for patients with gross residual. Optimally the 150% isodose line shall be non-contiguous between catheters.

6.3.5.5 Dose to the skin (if applicable) should be \(< 50\%\) of the prescribed dose.

6.3.5.6 Treatments should not commence before 5 postoperative days and should be delivered at a dose rate of 30-50 cGy/hour.

6.3.5.7 Dose delivered should vary with the surgical and pathologic findings:
- Patients with wide (\( \geq 10 \) mm) margin: 7.5-10 Gy
- Narrow but negative histologic margins (\(< 10 \) mm) margin: 10-12.5 Gy
- Microscopic residual: 12.5-15 Gy
- Gross residual: 15-20 Gy

6.3.6 Postoperative External Beam Boost
6.3.6.1 External beam irradiation should be initiated within 3 weeks after surgery. An upper GI may be requested if necessary to visualize organ movement into the boost field.

6.3.6.2 The tumor bed (as depicted by clips left at surgery) should be treated with a 2 cm margin.

6.3.6.3 Small bowel should be demonstrated by small bowel series or CT to be completely out of the boost field. If some small bowel is within the field, the dose to that small bowel should not exceed a total dose of 54 Gy (adding preoperative and postoperative treatment).

6.3.6.4 Treatment shall be given using multiple field techniques to cover the tumor bed and eliminate small bowel, kidney, and liver.

6.3.6.5 External beam therapy shall be delivered daily using 1.8 Gy fractions given Monday-Friday.

6.3.6.6 Dose delivered should vary with the surgical and pathologic findings:

<table>
<thead>
<tr>
<th>Margin Description</th>
<th>Dose Range</th>
<th>Fraction Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide (&gt; 10 mm)</td>
<td>7.2-10.8 Gy</td>
<td>4-6 fractions</td>
</tr>
<tr>
<td>Narrow (10 mm)</td>
<td>10.8-12.6 Gy</td>
<td>6-7 fractions</td>
</tr>
<tr>
<td>Microscopic residual</td>
<td>12.6-16.2 Gy</td>
<td>7-9 fractions</td>
</tr>
<tr>
<td>Gross residual</td>
<td>16.2-19.8 Gy</td>
<td>9-11 fractions</td>
</tr>
</tbody>
</table>

6.4 Dose Specifications

6.4.1 For two opposed coaxial equally weighted beams: on the central ray at separation of beams.

6.4.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.4.3 Any other field arrangement: at the center of the target volume.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Preop Cycle 1 Days</th>
<th>Preop Cycle 2 Days</th>
<th>Preop Cycle 3 Days</th>
<th>Preop Cycle 4 Days</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna</td>
<td>1-4</td>
<td>22-25</td>
<td>43-46</td>
<td>64-67</td>
<td>See 7.1.1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1-3</td>
<td>22-24</td>
<td>43-45</td>
<td>64-66</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1-4</td>
<td>22-25</td>
<td>43-46</td>
<td>64-67</td>
<td></td>
</tr>
</tbody>
</table>

7.1 Dose

7.1.1 Neoadjuvant Chemotherapy

Patients will receive a maximum of four cycles of preoperative chemotherapy. The preoperative chemotherapy shall start within 14 days after registration. Delays beyond 35 days will be considered a major protocol deviation.

7.1.1.1 Mesna: 1500 mg/m² as a continuous intravenous infusion administered via central venous access (preferably double lumen) over 24 hours days 1-4 with an extra bolus of 500 mg/m² mixed with ifosfamide on day 1 of each cycle and a bolus as needed for gross hematuria. Mesna is put in two liters of D5W and 100 meq/L of Na acetate, 40 meq/L of K acetate, and 4 meq/L of MgSO₄ to run over 24 hours qd x 4 via a double channel pump. Doses are repeated at each 21-day cycle (provided patients have recovered from their toxicities).

7.1.1.2 Doxorubicin: 25 mg/m² as a continuous intravenous infusion administered via central venous access (preferably double lumen) on days 1-3 (total of 75 mg/m² continuous infusion) and repeated on day 22 (provided patients have recovered from their toxicities).

7.1.1.3 Ifosfamide: 2500 mg/m² in 500 ml of normal saline as an intravenous infusion administered via central venous access (preferably double lumen) as a continuous 3 hour infusion on days 1-4 starting on day 1 of the drug cycle and repeated on day 22 (provided patients have recovered from their toxicities). (12/3/02)

7.1.1.4 G-CSF: 5 mcg/kg/d administered as a subcutaneous injection starting on day 5 (24 hours after completion of the chemotherapy) after each cycle of chemotherapy and continuing daily until ANC recovers to >10,000 (post nadir).

7.1.1.5 Chemotherapy response assessment: (12/3/02) response will be assessed after the first two cycles of chemotherapy. Patients will be considered to have responding or stable disease disease if they have evidence of:

- RECIST criteria for complete response (CR), partial response (PR), or stable disease (SD) (see Section 11.2.2.1);
- CT density changes with increased qualitative necrosis.

Patients with responding or stable disease as defined above will receive two more cycles of preoperative chemotherapy. Patients who do not meet these criteria for responding or stable disease after the first two cycles of chemotherapy will proceed with preoperative radiation (i.e., no further chemotherapy should be administered).

### 7.2 Mesna (Mesna)

#### 7.2.1 Dose Formulation: Mesna is available as an injectable sterile preservative-free aqueous solution. The colorless solution is supplied in clear glass ampules containing 4 and 10 ml of a 100 mg/ml solution. Mesna may be further diluted in 5% dextrose, 5% dextrose and 0.45% normal saline or normal saline to a final concentration of 1 to 20 ml. Mesna should be given as a continuous intravenous infusion via central venous access.

#### 7.2.2 Mechanism of Action: Mesna is a uroprotective agent used to prevent hemorrhagic cystitis induced by the oxazaphosphorines (ifosfamide, cyclophosphamide). It has no intrinsic cytotoxicity, no antagonistic effects on radiotherapy or chemotherapy. Mesna binds with acrolein, the urotoxic metabolite produced by the oxazaphosphorines to produce a non-toxic thioether, and slows the rate of acrolein formation by combining with 4-hydroxy metabolites of oxazaphosphorines.

#### 7.2.3 Drug Availability: Mesna is commercially available in 4 and 10 ml ampules containing 100 mg/ml.

#### 7.2.4 Storage: Intact ampules are stored at room temperature. Diluted solutions are physically and chemically stable for 24 hours under refrigeration.

#### 7.2.5 Side Effects: At the doses used for uroprotection, mesna is virtually non-toxic. However, adverse effects that have been attributable to mesna include: nausea, vomiting, diarrhea, abdominal pain, rash, lethargy, headache, arthralgia, myalgias, fatigue, and bad taste in the mouth.

### 7.3 Doxorubicin (Adriamycin®, Rubex®)

#### 7.3.1 Dose Formulation: Doxorubicin is available as a red powder for injection in 10, 20, 50, 100 and 150 mg vials. Add 5, 10, 25, 50 or 75 ml of preservative-free normal saline to the 10, 20, 50, 100 or 150 mg vials respectively to produce a solution containing 2 mg/ml. Doxorubicin should be given as a continuous intravenous infusion via central venous access.

#### 7.3.2 Mechanisms of Action: Doxorubicin is an anthracycline antibiotic. It causes intercalation between adjoining nucleotide pairs in the DNA helix causing inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

#### 7.3.3 Drug Availability: Doxorubicin is commercially available.

#### 7.3.4 Storage: Adriamycin RDF® or Rubex® intact vials are stable protected from light at room temperature. Adriamycin PFS® vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF® 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

#### 7.3.5 Side Effects:

1. Hematologic: leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
2. Dermatologic: alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.
3. Gastrointestinal: nausea and vomiting sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule.
4. Cardiovascular: arrhythmias, EKG changes; rarely, sudden death. Congestive heart failure due to prior mediastinal irradiation, pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.
5. Other: red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
6. Local effects: vesicant if extravasated; flush along vein, facial flush.

### 7.4 Ifosfamide (Ifex®)

#### 7.4.1 Dose Formulation: Ifosfamide is available as a white crystalline powder in 1 and 3-gram single dose vials. When the 1 and 3 gram vials are reconstituted with 20 and 60 ml of sterile water respectively, each vial will contain 50 mg/ml. The solution's pH is approximately 6. Ifosfamide should be given as a continuous 3 hour intravenous infusion via central venous access. (12/3/02)

#### 7.4.2 Mechanism of Action: Ifosfamide is an alkylating agent which is activated by hepatic microsomal enzymes to reactive alkylating substance. The reactive metabolites, ifosfamide mustard and aldophosphamide, are capable of covalent binding and cross-linking of DNA and cellular proteins.
7.4.3 Drug Availability: Ifosfamide is commercially available.
7.4.4 Storage: The intact, unreconstituted vials are stored at room temperature. The sterile reconstituted solution is stable for 1 week at 30°C or 3 weeks at 5°C. Ifosfamide liquifies at temperatures above 35°C.
7.4.5 Side Effects:
1. Hematologic: leukopenia, thrombocytopenia (dose-limiting); anemia.
2. Gastrointestinal: nausea, vomiting, anorexia, constipation, diarrhea, salivation, stomatitis.
3. Dermatologic: alopecia, rash, urticaria.
5. Genitourinary: hemorrhagic cystitis (incidence related to dose and schedule; more common with a single high dose); elevated creatinine.
7. Other: hyponatremia, hypokalemia, phlebitis, fever, hypo- or hypertension.

7.5 G-CSF - Filgrastim (r-metHuG-CSF, Neupogen®)
7.5.1 Dose Formulation: Commercial Neupogen® is available in 1 ml and 1.6 ml vials at a concentration of 300 mcg/ml. Discard unused portions. Use only one dose per vial; do not reenter the vial. Do not save unused drug for later administration.

Neupogen® is also available as single-dose, preservative-free, pre-filled syringes with 26 gauge, 5/8 inch needles containing 300 mcg (0.5 ml) of Filgrastim (600 mcg/ml) and 480 mcg (0.8 ml) of Filgrastim (600 mcg/ml). If required, Neupogen® may be diluted in 5% dextrose. Neupogen® diluted to concentrations between 5 and 15 mcg/ml should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/ml. Do not dilute with saline at any time; product may precipitate. For this study, G-CSF will be supplied in 480 mcg/1.6 ml vials; initial order quantities will be 100 vials; reorder quantities will be in 30 vial increments.

7.5.2 Mechanism of Action: Filgrastim is a human granulocyte colony stimulating factor (G-CSF), produced by recombinant DNA technology. Neupogen® is the Amgen Inc. trademark for Filgrastim, recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

7.5.3 Drug Availability: (9/12/01) G-CSF (Filgrastim) is commercially available. However, for this study it is being supplied free-of-charge by Amgen, Inc. and is available from UintaVision. To obtain a supply of G-CSF, complete the G-CSF (Filgrastim) Drug Request Form supplied in Appendix VI, and fax or send the form to the following address:

UintaVision, Inc./Axion, Inc.
232 Castro Street, Suite #2
San Francisco, CA 94114
General Phone: (800) 370-2508
Fax: (650) 745-3877

UintaVision’s office hours are 6:30 a.m. to 1 p.m. PST; a phone message may be left at other times. Phone messages after 1 p.m. will be returned the next business day.

Orders received by 11:30 a.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 11:30 a.m. PST on Friday will be shipped for receipt the following Monday. G-CSF orders from USA sites only will be accepted. Patients must be registered to the study before study drug can be obtained. When the study is terminated, unused drug at the site will be returned to UintaVision, Inc./Axion, Inc. with a completed Return Medication Packing Slip (see Appendix VII) included to identify for which study the drug was originally shipped.

7.5.4 Storage: Neupogen® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, Neupogen® may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

7.5.5 Side Effects: Neupogen® is contraindicated in patients with known hypersensitivity to E. coli-derived products, Filgrastim, or any component of the product. The only consistently observed clinical toxicity described with Neupogen® is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare
reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.

7.6 Drug Dose Modifications

The doses of chemotherapy will be attenuated as noted below. The most severe toxicity should determine the degree of attenuation.

7.6.1  Hematologic Toxicity (12/3/02)

7.6.1.1  Ifosfamide and doxorubicin doses are to be modified based on both the nadir counts of the previous cycle and counts obtained on the day treatment is given. No new treatment course may begin unless the patient's absolute neutrophil count is > 1500/mm$^3$ and platelet count is >100,000/mm$^3$. If these counts are not adequate on day 22, then repeat counts weekly; if after 2 weeks the patient's counts are not adequate for therapy, contact the medical oncology study chair.

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on Interval Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC &lt;500 and associated with fever or documented infection</td>
<td>Ifosfamide</td>
<td>Decrease Ifosfamide to 8 gm/m$^2$</td>
</tr>
<tr>
<td>PLT &lt;20,000 with associated severe bleeding, requirement of transfusion for &gt; 7 days</td>
<td>Ifosfamide Doxorubicin</td>
<td>Discuss with medical oncology study chair</td>
</tr>
<tr>
<td>CNS toxicity: grade 3</td>
<td>Ifosfamide</td>
<td>Decrease Ifosfamide to 8 gm/m$^2$</td>
</tr>
<tr>
<td>CNS toxicity: persistent grade 3 toxicity or grade 4</td>
<td>Ifosfamide</td>
<td>Decrease Ifosfamide to 6 gm/m$^2$ and discuss with medical oncology study chair</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urotoxicity: grade 2-3</td>
<td>Mesna i.v. fluids</td>
<td>Increase to match ifosfamide dose Increase i.v. fluids</td>
</tr>
<tr>
<td>Urotoxicity: grade 3 toxicity and not responding to above measures</td>
<td>Ifosfamide</td>
<td>Decrease Ifosfamide to 8 gm/m$^2$</td>
</tr>
<tr>
<td>Urotoxicity: grade 4</td>
<td>Ifosfamide</td>
<td>Discuss with medical oncology study chair</td>
</tr>
<tr>
<td>Cardiotoxicity: ECHO / cardiac scan with EF &lt; 50% or signs/symptoms of CHF develop</td>
<td>Doxorubicin</td>
<td>Discontinue doxorubicin</td>
</tr>
<tr>
<td>Mucositis: grade 3</td>
<td>Doxorubicin</td>
<td>Decrease infusion to 48 hours, same dose, wait until complete recovery to initiate next cycle</td>
</tr>
<tr>
<td>Mucositis: recurrent grade 3 after above</td>
<td>Doxorubicin</td>
<td>60 mg/m$^2$ as a 48-hour continuous infusion. If grade 3 occurs again, decrease doxorubicin to 50 mg/m$^2$ as a 48-hour continuous infusion.</td>
</tr>
</tbody>
</table>

At time of treatment

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>AGENT</th>
<th>DOSAGE CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity: creatinine of 1.8-2.0 prior to subsequent course</td>
<td>Ifosfamide</td>
<td>Decrease Ifosfamide to 8 gm/m$^2$</td>
</tr>
<tr>
<td>Nephrotoxicity: creatinine of &gt; 2.0 prior to subsequent course</td>
<td>Ifosfamide</td>
<td>Discontinue ifosfamide</td>
</tr>
<tr>
<td>Any non-hematologic grade 3 toxicity</td>
<td>Ifosfamide Doxorubicin</td>
<td>Delay Rx until &lt; grade 3 toxicity. Any delay &gt; 2 weeks contact the medical oncology study chair</td>
</tr>
<tr>
<td>Hematologic ANC &lt; 1500 and/or PLT &lt; 100,000</td>
<td>Ifosfamide Doxorubicin</td>
<td>Delay Rx until counts recover to ANC ≥1500 and platelets ≥100,000. Then Rx as per nadir. Any delay &gt; 2 weeks contact the medical oncology study chair</td>
</tr>
</tbody>
</table>

7.7 Adverse Drug Reaction Reporting Guidelines

7.7.1  This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0.
This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.7.2 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days and telephoned to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery:

7.7.2.1 Any ADR which is both serious (life threatening, fatal) and unexpected.
7.7.2.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
7.7.2.3 Any death on study if clearly related to the commercial agent.
7.7.2.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.7.3 The ADR report should be documented on form FDA 3500 and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone: (24 hours) (301) 230-2330
Fax: (301) 230-0159

7.7.4 Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

8.0 SURGERY

8.1 Initial Biopsy
8.1.1 Patient will undergo a biopsy to confirm the histologic diagnosis. This ideally will be done using radiologic guidance into the area of suspected highest grade tumor using a core needle biopsy. The site of core biopsy shall be made with consideration for the site of the planned surgical incision.
8.1.2 Patients who have had recent incisional biopsy within two months prior to registration will not require re-biopsy. (12/3/02)

8.2 Definitive Surgery

General considerations: The choice of incision, patient position and exposure will be left to the discretion of the operating surgeon based on tumor location and prior experience. Complete resection (R0 or R1) of the post-treatment tumor mass will be performed with additional en-bloc organ resection as necessary based on the operative findings. Clearly uninvolved organs will be mobilized and preserved whenever possible. Perioperative antibiotics, drains, gastrostomy tubes, and feeding jejunostomy tubes will be placed at the discretion of the operating surgeon.

8.2.1 Definitive surgery shall take place at 4-7 weeks after completing irradiation.
8.2.2 All patients shall have initial assessment of the abdominopelvic cavity upon opening the peritoneum.
8.2.3 Evaluation of any suspicious areas for peritoneal seeding shall include frozen section analysis.
8.2.4 Subsequently the primary tumor shall be evaluated for resection. Resection should ideally be performed en-bloc. Adjacent organs involved with tumor should be removed as indicated by the operative findings. This includes but is not limited to nephrectomy, bowel resection, partial liver resection, and vascular resection.

8.2.5 Resection will be graded and recorded by the operative surgeon as:

8.2.5.1 Wide resection – complete resection with a circumferential soft tissue margin of greater than 1 cm.

8.2.5.2 Close resection – complete resection of all gross tumor with a closest margin of less than 1 cm.

8.2.5.3 Marginal resection – complete resection of all gross disease where the closest margin is immediately adjacent to the tumor edge or tumor pseudocapsule. Area of closest margin shall be recorded and marked with clips.

8.2.5.4 Gross residual – resection with residual gross disease. Area of gross residual shall be recorded and marked with clips.
8.2.6 Small bowel exclusion technique will depend on the site of highest risk for relapse and subsequently the site of the planned post-operative boost dose. The technique may employ the use of a tissue expander, synthetic absorbable mesh, omental sling, or other methods designed to protect the small intestine.

8.2.7 Surgical clips of stainless steel will clearly mark the treatment volume.

9.0 OTHER THERAPY

9.1 Nutritional Assessment and Dietary Support

9.1.1 Initial Evaluation: It is suggested that all patients have an initial evaluation of their nutritional status including baseline pre-treatment serum albumin and caloric intake before initiating chemotherapy. Initial caloric intake must be ≥ 1500 kCal/day and baseline albumin must be ≥ 3.5 g/dl.

9.1.2 Interval Nutritional Evaluation

9.1.2.1 Interval nutritional assessment will occur before each cycle chemotherapy, before the start of radiation therapy, and weekly during radiation treatment. This limited nutritional assessment will include serum albumin and weight.

9.1.2.2 Treating physicians are encouraged to involve a dietician for periodic assessment of nutritional status, protein-calorie intake, and assessment of options for intervention as needed.

9.1.2.3 Specific intervention with oral or intravenous nutritional support should be considered if the patient loses ≥ 10% of their pre-treatment body weight, albumin drops by 0.4 g/dL from pre-treatment levels, or if other clinical criteria suggest that nutritional supplementation is necessary.

9.1.3 Nutritional Supportive Care Options

9.1.3.1 Oral nutritional supplements should be started as soon as it is apparent that disease or treatment-related anorexia and hypocaloric intake are present. This can be assessed by serial evaluation of weight and albumin levels.

9.1.3.2 Patients with progressive hypoalbuminemia and weight loss should be evaluated for the need for intravenous nutrition. Intravenous nutrition should be strongly considered for all patients who develop disease or treatment-related decline in albumin to 2.2 g/dl or lower. Intravenous nutritional support should be managed with the aid of a dietitian, gastroenterologist, or nutrition-support team.

10.0 PATHOLOGY

10.1 Assessment of Pre-treatment Biopsy Specimen

10.1.1 Central Pathology Review

a) Recuts of all histology slides, a representative paraffin tissue block and a copy of the surgical pathology report must be mailed with a Pathology Submission Form to:

Dr. Antonio Nascimento  
Department of Pathology  
Mayo Clinic  
200 First Street SW  
Rochester, MN 55905

b) Immunohistochemistry slides should be made available upon request. A small sample should be snap-frozen and saved in the tissue bank (see Section 10.4). A small sample should be also fixed in glutaraldehyde for possible electron microscopy and should be sent upon request.

10.1.2 Type of Specimen

a) Needle core biopsy  
b) Incisional biopsy  
c) Excisional biopsy (must include assessment of surgical margins: positive, close, negative)  
d) Fine needle aspiration not acceptable for accurate grading and phenotyping

10.1.3 Histopathologic Assessment

a) Sarcoma phenotype as categorized by the WHO (1994)²⁹  
b) Histologic grade (grade 2 or 3). Grading of soft tissue sarcomas is an imperfect endeavor, not without limitations and pitfalls. This stems from the markedly different histologies between different sarcoma types. All primary tumors in this study must be at least intermediate grade (grade 2 using a 3 or 4-tiered system). Tumors may be separated by features such as mitotic rate (usually > 6 mitotic figures per 10 HPF), percent necrosis, cellularity, pleomorphism, and differentiation. Mitotic rate and necrosis appear to be the most important prognostic factors, and should be useful for separating grade 2 from 3.³⁰ Costa et al.³¹ recommend separating grade 2 and 3 based upon presence or absence of necrosis. Another 3 scale system by Trojani and et al.³² employs degree of tumor
differentiation, mitotic activity, and tumor necrosis; each assigned a quantitative value, with the sum of these three values used to determine grade. A three-scale system would provide two separate groups in our study, as only high and intermediate grade sarcomas will be evaluated. The 3 scale grading system is widely used and should be readily adaptable to this study.

c) Mitotic rate (> 6 per HPF): Yes/No
d) Necrosis (0, < 50%, or ≥ 50%)
e) Tumor matrix (sparse, myxoid, fibrous, etc.)
f) Vascular space invasion (Yes/No)
g) Host lymphoplasmacytic response (+/-)
h) Margin of infiltration (pushing, infiltrative, not evaluable)

10.2 Assessment of Resected Tumor
10.2.1 Central Pathology Review
   a) Recuts of all histology slides, the surgical pathology report, and a representative paraffin block and a Pathology Submission Form should be submitted to Dr. Antonio Nascimento per Section 10.1.1.

10.2.2 Gross Parameters of Tumor
   a) Tumor size (cm greatest dimension).
   b) Description of margins including cm or mm to closest margin.
   c) Gross photograph of tumor desirable.

10.2.3 Handling of Gross Specimen
   a) External surface specimen should be painted with India ink prior to sectioning.
   b) Tumor should be thoroughly sampled (at least 1 section per 1 cm of greatest tumor dimension).

10.2.4 Histopathologic Assessment
   a) Percent of viable neoplasm (0, < 25%, 25-50%, > 50-75%, > 75%)
   b) Percent necrosis (0, < 50%, ≥ 50%)
   c) Degree of fibrosis/hyalinization (0, < 50%, ≥ 50%)
   d) Tumor margin (pushing, infiltrative)
   e) Host lymphoplasmacytic response (+/-)
   f) Vascular space invasion (Yes/No)
   g) Surgical resection margin (+, close, wide) Actual, close and wide margins are to be indicated in millimeters.
   h) Degree of intratumoral hemorrhage (0, < 50%, ≥ 50%)

10.3 Ancillary Studies
10.3.1 Additional biologic studies will be performed on the paraffin sections including immunohistochemistry for p53 protein, multi-drug resistance protein (p-glycoprotein), and proliferation marker (e.g. Ki-67). DNA content may be determined by image analysis.

10.4 Frozen Tissue Bank
10.4.1 Many informative biological studies can be done with snap-frozen tissue samples. These include molecular biologic studies of oncogenes and tumor suppressor genes, including frozen-section immunohistochemistry (e.g. for MDM2 protein), polymerase chain reaction and DNA sequencing techniques. Frozen tissue may also be put in tissue culture or used in flow cytometry for determination of DNA content. Many additional studies will be possible. Details and methods will be determined as the study progresses.
## 11.0 PATIENT ASSESSMENTS

### 11.1 Study Parameters

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Pre-Treatment</th>
<th>Prior to each cycle of chemotherapy</th>
<th>Prior to RT</th>
<th>Every Week During RT</th>
<th>Prior to Surgery</th>
<th>F/U Every 3 Months to Year 2</th>
<th>F/U Every 6 Months Years 3-5</th>
<th>F/U &gt;5 Years Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and PE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wgt (kg), nutritional assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Body Surface ($m^2$)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Biopsy (core needle or incisional)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT of Chest</td>
<td>$X^a$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT of Primary Tumor (or MRI)</td>
<td>$X^b$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor size</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography or MUGA Scan for Ejection Fraction</td>
<td>$X^c$</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
<td>As Indicated</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>$X^a$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EKG</td>
<td>$X^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, diff, platelet</td>
<td>$X^a$</td>
<td>$X^b$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum chemistries: Creatinine, AST, LDH, ALK Phos, Total Bilirubin, BUN</td>
<td>$X^a$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>$X^a$</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td></td>
<td>$X^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Within two weeks prior to study entry. *(12/3/02)*  
b. Within four weeks prior to study entry. *(12/3/02)*  
c. Patients with history of myocardial infarction (MI) may participate in study if they are greater than 6 months post-MI and have evidence of an ejection fraction of ≥ 50%. Ejection fraction may be assessed with echocardiography or MUGA scan.  
d. To be performed in all females of child-bearing age.  
e. To be obtained weekly between cycles of chemotherapy. To be obtained every other day if ANC < 500/mm$^3$ or PLT <100,000/mm$^3$.  
f. Imaging of the primary tumor should occur prior to the third cycle of preoperative chemotherapy.

### 11.1.1 Treatment Summary *(12/3/02)*

- Induction chemotherapy – two cycles *(see Section 7.0)*;  
- Response assessment *(see Sections 7.1.1.5, 11.2.2)*;  
- Further chemotherapy – two cycles for stable or responding patients only;  
- Preoperative radiation *(see Section 6.0)*;  
- Surgical resection with intraoperative boost *(see Sections 6.3, 8.2)*;  
- Postoperative boost – for patients not boosted intraoperatively *(see Sections 6.3.4, 6.3.5, and 6.3.6)*.

### 11.2 Response Assessment

#### 11.2.1 Measurement of Response

Response will be evaluated in this study using both the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors *(RECIST)* Committee [JNCI 92(3):205-216, 2000] and the response criteria utilized in the previous high-risk sarcoma study, RTOG 95-14, based upon measurement of perpendicular dimensions *(see Section 11.2.2.2)*. Changes in only the largest diameter
Target Lesions: All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a standard institutional algorithm. This applies to tumors of the chest, abdomen, and pelvis. Response to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen (see pathology section). (12/3/02)

Response Criteria (12/3/02)

Chemotherapy response assessment: response will be assessed after the first two cycles of chemotherapy. Patients will be considered to have responding or stable disease if they have evidence of:

- RECIST criteria for complete response (CR), partial response (PR), or stable disease (SD) (see Section 11.2.2.1);
- CT density changes with increased qualitative necrosis.

Patients with responding or stable disease as defined above will receive two more cycles of preoperative chemotherapy. Patients who do not meet these criteria for responding or stable disease after the first two cycles of chemotherapy will proceed with preoperative radiation (i.e., no further chemotherapy should be administered).

Response and progression to pre-operative chemotherapy and radiation will be measured by comparing tumor size at time of registration with measurements taken 0-2 weeks prior to surgical resection. Response will be measured through evaluation of the MRI change, CT change, or change in physical examination. In addition, pathologic response will be recorded at the time of pathologic review of the resected specimen (see pathology section 10.0).

Evaluation of target lesions-RECIST criteria

- Complete Response (CR): Disappearance of all target lesions as measured by MRI, CT, or physical examination. This is the order of preference for measurement.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions. The order of preference for measurement is MRI, CT, or physical examination.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. The order of preference for measurement is MRI, CT, or physical examination.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of target lesions-95-14 criteria

(unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.
• **Complete response (CR):** Disappearance of all measurable tumor as measured by MRI, CT or physical examination (PE). This is the order of preference of items for measurement of size.

• **Partial response (PR):** 50% or greater decrease in product of perpendicular dimensions as measured on MRI, CT or PE. This is the order of preference of items for measurement of size.

• **Progression (P):** Progression is defined as an increase in size of the lesion by > 25% as defined by the product of the perpendicular dimensions on MRI, CT or PE. This is the order of preference of items for measurement of size.

### 11.3 Wound Complications

Wound complications will be classified and recorded as specified below:

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Secondary operation required for wound dehiscence, infection, fluid collection, hematoma</td>
</tr>
<tr>
<td>2</td>
<td>Readmission to hospital required for wound care</td>
</tr>
<tr>
<td>3</td>
<td>Invasive procedure required for wound care (drainage of seroma, hematoma, or infected fluid collection)</td>
</tr>
<tr>
<td>4</td>
<td>Wound infection requiring opening of the wound, removal of skin sutures/staples with or without wound packing</td>
</tr>
<tr>
<td>5</td>
<td>Prolonged wound care including dressing changes and/or packing for greater than 6 weeks from the date of wound breakdown</td>
</tr>
<tr>
<td>6</td>
<td>Cellulitis of the wound with cutaneous erythema plus fever and or leukocytosis</td>
</tr>
</tbody>
</table>

### 11.4 Definition of Relapse

Relapse represents the time when locally recurrent, metastatic or persistent disease is noted. Biopsy of suspected recurrent disease should be performed if feasible.

### 11.5 Time to Relapse

Time to relapse represents the time from registration to time that relapse is documented on follow-up cross-sectional imaging studies.

### 11.6 Survival

Survival represents the time from registration to the time of death.

### 11.7 Follow-up

Patients will be followed until death. Follow-up must include CT scans (or MRI for patients with intravenous contrast allergies) as indicated. Every effort should be made to obtain an autopsy to document the extent of disease at the time of death.

### 12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

#### 12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>At end of each treatment cycle</td>
</tr>
<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>Complete Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Pre-op CT/MRI <em>(with tumor volume outline)</em> (C1)</td>
<td></td>
</tr>
<tr>
<td>Pre-op CT/MRI Scan Report (C3)</td>
<td></td>
</tr>
<tr>
<td>Supplemental Dose Calculation (TL)</td>
<td></td>
</tr>
<tr>
<td>Supplemental Localization Films <em>(simulation and portal films)</em> (TP)</td>
<td></td>
</tr>
<tr>
<td>Dose Volume Histograms (DVH)</td>
<td></td>
</tr>
</tbody>
</table>
**Surgery Form (S1)**
Within 2 weeks of surgery

**Operative Notes (S2)**

**Surgical Pathology Reports (S5)**

**Pathology Slides/Blocks (P2)**

**Initial Follow-up Form (FS)**
At end of treatment

**Follow-up Form (F1)**
Every 3 months from treatment start for 2 years; q 6 months for years 3-5, then annually. Also at progression/relapse and at death.

**Perioperative Form (PO)**
Due within 6 weeks of surgery

**Autopsy Report (D3)**
As applicable

**Long-Term Follow-up Form (FF)**
Yearly after 5 years in place of the F1 form, as applicable. See FF form for instructions.

### 13.0 STATISTICAL CONSIDERATIONS

#### 13.1 Study Endpoints

13.1.1 Overall survival
13.1.2 Local-regional control
13.1.3 Disease-free survival
13.1.4 Tumor response
13.1.5 Toxicities and complications associated with the entire treatment program and its individual components (preoperative chemotherapy, preoperative radiotherapy, and resection with intraoperative or postoperative radiotherapy boost).

#### 13.2 Sample Size

Treatment of this rare disease has not been well studied in multi-institutional, prospective trials. This trial seeks to estimate various efficacy rates not only to evaluate the effectiveness of the protocol treatment but also to use the rates as baseline data for planning subsequent trials. It seeks to estimate the rates of overall survival, local-regional control and disease-free survival and the rates of complete and partial tumor response for patients with intermediate and high-grade retroperitoneal or pelvic sarcomas treated with preoperative chemotherapy, preoperative radiotherapy, and resection with intraoperative or postoperative radiotherapy boost. A sample size of 43 evaluable patients will allow us to estimate (with 95% confidence intervals) these rates within a margin of error \( \leq 15\% \). Allowing for an ineligible/inevaluable rate of up to 10%, the total sample size required will be 48 patients.

#### 13.3 Patient Accrual

The patient accrual in the previous RTOG retroperitoneal sarcoma trial, RTOG 85-07, was approximately 0.60 patients per month. The number of institutions now participating in RTOG trials has doubled since the previous trial ended in 1989 (personal communication). The study will be opened in other cooperative groups as well. In addition, participation of the University of Texas M.D. Anderson Cancer Center Sarcoma Group is expected to add 1 patient per month to this trial. Thus, the accrual is projected to be approximately 2.0 cases per month. At this rate, the accrual period will be completed in 24 months. If the average monthly accrual rate is less than 0.5 cases a month, the study will be re-evaluated with respect to feasibility.

#### 13.4 Suspension of Accrual Due to Morbidity

If there is any fatal treatment complication, the event will be immediately reported to the study chairman for review. If there are three such fatal events, accrual will be immediately suspended and the study chairman will review all data pertaining to the events. The results from this review along with recommendations will be reported to the RTOG Research Strategy Committee, which in turn, will decide about the future course of action.

#### 13.5 Inclusion of Women and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered differences in prognosis by race
and gender. In an analysis of the RTOG sarcoma database, we found no difference. No other study so far has indicated any significant racial or gender differences in treatment effects for retroperitoneal sarcoma cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races. The following table gives the projected number of patients in each race and gender group, based on data from the previous RTOG retroperitoneal study, RTOG 85-07.

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian</th>
<th>Black or African American</th>
<th>Hispanic or Latino</th>
<th>Native Hawaiian or Pacific Islander</th>
<th>White</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>44</td>
<td>0</td>
<td>48</td>
</tr>
</tbody>
</table>

### 13.6 Analysis Plans

#### 13.6.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about: the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription; the quality of submitted data with respect to timeliness, completeness, and accuracy; the frequency and severity of toxicities. Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for the study, and, if necessary, the RTOG Research Strategy Committee, so that corrective action can be taken.

#### 13.6.2 Analysis for Reporting the Initial Treatment Results

The analysis for reporting the initial treatment results will be undertaken when each patient has been potentially followed for a minimum of 24 months. The usual components of these analyses are: tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion; reporting of institutional accrual; distribution of important prognostic baseline variables; observed results with respect to the endpoints described in Section 13.1; tabulation of all cases entered, and any excluded. The two-year overall survival, local-regional control and disease-free survival rates, and the complete and partial response rates will be estimated with 95% confidence intervals. The patient accrual rate to this study will be used as a gauge in determining the feasibility of conducting a phase III trial. If this rate is insufficient, the next study will likely be a phase II trial. If this rate is sufficient, then a phase III trial will be considered. A series of patients of comparable risk treated with surgery alone at Sloan-Kettering had 2-year and 5-year overall survival rates of 76% and 51%, respectively. A phase III trial will be considered if we observe a 10% increase in 2-year survival. The distribution of grades 2 and 3 in this patient series is unknown at this time, however, and adjustments for grade will need to be made when it is compared with the 2-year estimate with this protocol treatment.

#### 13.6.3 Analysis for Reporting the Final Treatment Results

The analysis for reporting the final treatment results will be undertaken when each patient has been potentially followed for a minimum of 60 months. The usual components of these analyses are: tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion; reporting of institutional accrual; distribution of important prognostic baseline variables; observed results with respect to the endpoints described in Section 13.1. The five-year overall survival, local-regional control and disease-free survival rates, and their respective medians will be estimated with 95% confidence intervals.

21
REFERENCES


34. MF Brennan, personal communication.
APPENDIX I
RTOG S-0124

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II STUDY OF MULTIMODALITY THERAPY FOR PRIMARY AND RECURRENT RETROPERITONEAL SARCOMAS

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have cancer of the abdomen and/or pelvis.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) chemotherapy followed by radiation followed by surgery and then a boost of radiation have on preventing your cancer from coming back. We also want to see how well this treatment can be tolerated.

The standard treatment for this kind of cancer is surgery. However, surgery has not been effective in preventing this kind of cancer from coming back. This research is being done to see if chemotherapy followed by radiation and then surgery with an additional radiation boost will prevent your cancer from coming back.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 48 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (12/3/02)

If you take part in this study you will have up to four cycles (one cycle every three weeks) of chemotherapy. For each cycle, you will receive mesna, doxorubicin, and ifosfamide. You will receive mesna continuously through a tube in your vein (intravenously) on days 1-4 of each cycle. You will receive ifosfamide intravenously for three hours on days 1-4 of each cycle at the same time you are receiving the mesna. You will receive doxorubicin continuously on days 1-3 through a tube in your vein.
In order to get this treatment, a special tube is placed into a large vein in your neck or chest region or through a large vein in your arm. This is called a central venous line. When the line is placed into a vein in the arm, a needle is inserted through the skin and into the arm vein; the central line is then passed through the needle into the arm vein and into the central vein. When the central venous line is placed through a vein in the neck or chest, a small incision is made and the line is either passed through a needle into the central vein or a cutdown procedure is used to insert the line directly into the vein.

There are several possible risks associated with placement of a central venous line. The two most likely complications are infection and clotting (thrombosis) of the central vein or the central line. Treatment of central line infection typically includes antibiotics and may require removal of the infected central line and placement of another central venous line. Clotting of the central vein or central line is treated with medications and may require removal of the central line. Two less likely risks include puncture of the axillary artery (with swelling and bruising) and pneumothorax (air around the lung). Treatment of puncture of the axillary artery generally includes application of pressure at the site of the bleeding. Treatment of pneumothorax generally includes observation, aspiration (suctioning out the air), or insertion of a tube into the chest to remove the air. Two very unlikely risks include central line migration (movement) or breakage of the central line.

A small pump is then used to give the drug. This pump is worn by the patient and is the size of a pack of cigarettes and weighs about 7 oz.

The next three cycles of chemotherapy will be the same. The beginning of each cycle will be separated by a time period of three weeks. The day after each cycle of chemotherapy ends, you will also receive a drug, G-CSF, that should reduce the incidence of fever caused by low blood counts from the other chemotherapy drugs. G-CSF will continue until your blood counts improve.

Your chemotherapy may be given as an outpatient or as an inpatient in the hospital, depending on the facility where you are being treated.

After two cycles of chemotherapy, your tumor will be reassessed. If your condition worsens or your tumor has grown, you will stop receiving chemotherapy and begin radiation.

About 2-4 weeks after completing the chemotherapy, you will receive radiation treatments on a daily basis, Monday through Friday, for a total of 25-28 treatments.

Between 4-7 weeks following the radiation, you will have surgery to remove the remaining tumor. After your surgery, you will receive additional radiation. This may be done immediately after your surgery or several weeks after your surgery.
If you take part in this study, you will have the following tests and procedures:

**Prior to study entry:**
- Biopsy
- Examination
- CT scan of chest and tumor
- Heart scan
- Chest X-ray
- Blood tests

**Prior to each cycle of chemotherapy:**
- Examination
- Chest X-ray
- Blood tests
- CT scan of tumor prior to third cycle of chemotherapy

**Prior to radiation therapy:**
- Examination
- CT scan of the chest and tumor
- Blood tests

**Every week during radiation therapy:**
- Examination
- Blood tests

**Prior to surgery:**
- Examination
- CT scan of the chest and tumor
- Blood tests
- Other tests as indicated

**During follow-up:**
- Physical exam every 3 months for the first 2 years, every 6 months for years 3-5, and then every year after that
- CT scan of the chest and tumor every 3 months for the first 2 years, every 6 months for years 3-5, and then every year after that
- Chest X-ray every 3 months for the first 2 years, every 6 months for years 3-5, and then every year after that
- Blood tests every 3 months for the first 2 years, every 6 months for years 3-5, and then every year after that
• Other tests as indicated

At the time of your surgery, all or some of your tumor was removed. As is usually done, this tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

**HOW LONG WILL I BE IN THE STUDY?**

This study will take approximately 10 months to complete. Follow-up visits will be scheduled every 3 months for the first two years, then every 6 months for years 3-5, and then yearly after that.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or if new information becomes available and this information suggests that the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

**WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the chemotherapy and radiation are stopped, but in some cases side effects can be serious or long-lasting or permanent.

**Risks Associated with Chemotherapy**

The usual effect of the chemotherapy drugs are loss of hair, nausea, and/or vomiting, loss of appetite and decreased blood counts that may increase the chance of infection or bleeding.

**Risks Associated with Mesna:**

Very likely:
- Bad taste in mouth
- Diarrhea
Headache
Nausea/vomiting
Joint and muscle pain
Fatigue
Low blood pressure
Allergic reaction

Less likely:
Abdominal pain
Rash
Lethargy

**Risks Associated with Doxorubicin:**

Very likely:
Nausea/vomiting
Mouth sores
Hair loss
Discoloration of nails, skin and urine
Decrease in blood counts which can lead to a risk of infection and bleeding
Loss of appetite
Hardening of the veins where the drug is injected
Damage to the colon
Congestive heart failure

Less likely:
Damage to the skin if the drug leaks out of the vein
Fever, chills
Conjunctivitis, tearing
Anorexia
Diarrhea

Less likely but serious:
Allergic reaction
Leukemia

**Risks Associated with Ifosfamide:**

Very likely:
Nausea, vomiting
Bladder inflammation
Blood in urine
Decrease in blood counts which can lead to risk of infection and bleeding
Anorexia
Diarrhea
Hair loss
Confusion
Drowsiness

Less likely:
- Inflammation of veins
- Mouth sores
- Fever
- Dizziness, disorientation
- Constipation
- Lethargy
- Rash

Less likely but serious:
- Abnormalities in kidney and liver blood tests
- Kidney damage
- Decrease in sodium and potassium levels in the blood
- High/low blood pressure
- Seizures, coma
- Heart damage
- Allergic reaction

**Risks Associated with G-CSF:**

Very likely:
- Mild to moderate bone pain
- Redness, swelling, itching, pain at injection site

Less likely:
- Rash
- Allergic reaction
- Abnormally large number of white blood cells
- Inflammation of blood vessels
- Increase in uric acid and some enzyme levels in the blood

Less likely but serious:
- Irregularity of heartbeat
- Decrease in blood pressure
- Enlargement of spleen

**Risks Associated with Radiation Therapy to the Abdomen and Pelvis:**

Radiation therapy may cause reddening or tanning of the skin, hair loss in the treatment area, nausea, vomiting, loss of appetite, weight loss, and weakness.
Heart, lung, liver, kidney, or stomach damage may occur if these organs are in the field of radiation.

**Very likely:**
- Decrease in blood counts which can lead to a risk of infection and bleeding
- Reddening or tanning of the skin
- Hair loss in treatment area
- Nausea and vomiting
- Loss of appetite
- Weight loss
- Fatigue
- Diarrhea
- Delayed wound healing after surgery

**Less likely but serious:**
- Small bowel injury
- Spinal cord injury
- Radiation may cause tumors in treated tissues
- Damage to other organs if they are in the field of treatment

Reproductive risks: Because the drugs and the radiation in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. The treatment may result in a decrease in the size of your tumor and longer survival. We hope the information learned from this study will benefit other patients with this kind of cancer in the future.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Another option may be to get the treatment plan described in this study at this center and other centers even if you do not take part in the study.
Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. You will receive no payment for taking part in this study. However, the drug G-CSF will be provided to you at no cost by the drug company. If this free G-CSF is not available for the length of the study, you or your insurance company will be charged for subsequent supplies.

**WHAT ARE MY RIGHTS AS A PARTICIPANT? (12/3/02)**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in abdominal/pelvic cancer from the RTOG Sarcoma Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

________________________________________________________________________
Name ___________________________  Telephone Number _______________________

For information about this study, you may contact:

________________________________________________________________________
Name ___________________________  Telephone Number _______________________

For information about your rights as a research subject, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

________________________________________________________________________
Name ___________________________  Telephone Number _______________________

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615


SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

________________________________________________________________________
Patient Signature (or legal Representative) ___________________________ Date ____________

32
TISSUE AND BLOOD TESTING *(RTOG S-0124)*

I agree to the use of my tissues/other samples for research studies related to my cancer.

☐ Yes ☐ No

Patient Signature *(or legal Representative)* ___________ Date ___________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activity with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

<table>
<thead>
<tr>
<th>New York Heart Association Functional Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>Class II</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td>Class IV</td>
</tr>
</tbody>
</table>
APPENDIX III

STAGING SYSTEM (AJCC, 5th edition - 1998)

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor 5 cm or less in greatest dimension
   T1a Superficial
   T1b Deep
T2 Tumor more than 5 cm in greatest dimension
   T2a Superficial
   T2b Deep

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph metastasis

Regional Lymph Nodes. The regional lymph nodes are those appropriate to the site of the primary tumor.

Unilateral Tumors

Head and neck  Ipsilateral preauricular, submandibular, cervical, and supraclavicular lymph nodes
Thorax  Ipsilateral axillary lymph nodes
Arm  Ipsilateral epitrochlear and axillary lymph nodes
Abdomen, loins and buttocks  Ipsilateral inguinal lymph nodes
Leg  Ipsilateral popliteal and inguinal lymph nodes
Anal margin and perianal skin  Ipsilateral inguinal lymph nodes

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Metastatic Sites. The lung is the most common site, but any body site may be involved.
### STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histologic Grade (G)</th>
<th>Tumor Stage (T)</th>
<th>Regional Lymph Node (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>G1-2</td>
<td>T1a-1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>G1-2</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>G2</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>G3-4</td>
<td>T1a-1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>G3-4</td>
<td>T2a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>G3-4</td>
<td>T2b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any G Any T</td>
<td>Any N</td>
<td>Any N</td>
<td>Any M</td>
</tr>
</tbody>
</table>

### HISTOPATHOLOGIC GRADE (G)

After the histologic type has been determined, the tumor should be graded according to the accepted criteria of malignancy, including cellularity, cellular pleomorphism, mitotic activity, and necrosis. The amount of intercellular substance, such as collagen or mucoid material, should be considered as favorable in assessing grade.

- **GX** Grade cannot be assessed
- **G1** Well differentiated
- **G2** Moderately differentiated
- **G3** Poorly differentiated
- **G4** Undifferentiated
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

   A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions (≥ grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities (≥ grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (IDB)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent. As above

- All life threatening (grade 4) events which may be due to agent. As above

- First occurrence of any toxicity (regardless of grade). Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters. **A written report may be required.

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal (grade 5) and life threatening (grade 4) known adverse reactions due to investigational agent. Report by phone to RTOG Headquarters and the Study Chairman within 24 hours. **A written report must be sent to RTOG within 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours. **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report in writing to RTOG Headquarters and IDB within 10 working days.
# APPENDIX VI (9/12/01)

Filgrastim (G-CSF) Drug Request Form

**Amgen Study No:**   **Group Study No:** RTOG S-0124: “A Phase II Study of Multimodality Therapy for Primary and Recurrent Retroperitoneal Sarcomas”

**Requested by:**

- Pharmacist: ____________________________
- Institution: _____________________________
- RTOG Study Number: _____________________
  *(must be included)*
- Principal Investigator: ____________________

**Ship To:**

- Name: ___________________________
- Address*: ___________________________
- Phone #: ___________________________
- Fax: _______________________________

<table>
<thead>
<tr>
<th>Pt. ID</th>
<th>Pt Initials (Last, First)</th>
<th># of Vials*</th>
<th>RTOG Case#</th>
<th>Starter Supply (For this pt.)</th>
<th>Re-order (For this pt.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reminder: See protocol section on drug formulation for instructions regarding amounts of drug to order.

G-CSF will be shipped refrigerated. Orders received by 11:30 a.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 11:30 a.m. PST on Friday will be shipped for receipt the following Monday.

---

Date of Drug Request ____________________________

Pharmacist Signature _______________________________________________________________________

---

Return Completed, Signed, and Dated form to:

UintaVision, Inc./Axion, Inc.
232 Castro Street, Suite #2
San Francisco, CA 94114
Fax: 650-745-3877

---

40
APPENDIX VII (9/12/01)

RETURNED MEDICATION PACKING SLIP

Institution Name:_____________________________________________________________________

Address:_____________________________________________________________________________

Principal Investigator:_________________________________________________________________

Amgen Study No: Group Study No: RTOG S-0124

“A Phase II Study of Multimodality Therapy for Primary and Recurrent Retroperitoneal Sarcomas”

Instructions:
Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to UintaVision, Inc./Axion, Inc., 232 Castro Street, Suite #2, San Francisco, CA, 94114. Only drug returns are to be sent to this address, no other correspondence. Questions may be directed to (800) 370-2508, Monday through Friday 6:30 am - 1:00 pm Pacific Standard Time. Voice Mail is available at all other times.

Study in progress? Person Shipping Drug: ____________________________
Yes No
Drug being returned by: Fed Ex UPS US Mail

Study completed per protocol? Date: ____________________________ No. of cartons: _______
Yes No
Research Associate’s/Pharmacist’s Signature: ____________________________ Date: ______________

Reason drug returned? (Please check one) Return receipt requested: Yes No
Drug Expired

Unused drug being returned

Fax number: ____________________________

DESCRIPTION OF RETURN SHIPMENT

<table>
<thead>
<tr>
<th>Drug Name &amp; Vial Description</th>
<th>Lot Number</th>
<th>Number of Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>mcg/ml/vial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comments:__________________________________________________________________________

TO BE COMPLETED BY AMGEN
Returned shipment received on ____________________________ and checked by: ____________________________

(Name)