Role of Radiation Therapy in Retroperitoneal Sarcomas

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Historically, patients with retroperitoneal sarcomas have had a poor prognosis. Surgical resection continues to be the standard treatment for these tumors. However, their anatomic location and large size at presentation often

Introduction

Retroperitoneal sarcomas account for approximately 15% of the 6,000 new soft-tissue sarcomas diagnosed each year. The prognosis of patients with retroperitoneal sarcomas is poor. The rarity of these tumors, as well as the diverse histologic subtypes and grades, makes it impossible to come to any definitive conclusions about optimal management from the literature. The role of radiation in the treatment of retroperitoneal sarcomas has been controversial. However, several key points and guiding principles can be extracted from the available data.

Presentation and Natural History

Most patients present with an abdominal mass. Because of their anatomic location, these tumors often grow to a tremendous size without causing any systemic symptoms. There are reports of patients presenting with retroperitoneal tumors as large as 40 pounds with relatively few other symptoms.[1] Symptoms, such as weight loss, nausea/vomiting, early satiety, and back pain, occur later in the disease process and are related to pressure exerted by the tumor on adjacent organs. As opposed to soft-tissue sarcomas at other sites, in which pulmonary metastases represent the vast majority of distant failures, retroperitoneal sarcomas also commonly fail in the liver via access of the portal venous system. In addition, peritoneal sarcomatosis is often seen. One must distinguish sarcomas arising from the retroperitoneum from those arising from abdominal viscera. The latter are much more easily resected, are less likely to invade into adjacent structures, and are less apt to require adjuvant therapy.

Histopathology

Soft-tissue sarcomas are derived from the primitive mesoderm. Although the histopathology is diverse, the most common subtypes in the retroperitoneum are leiomyosarcoma and liposarcoma.[2,3] Other frequently seen subtypes include fibrosarcoma, malignant fibrous histiocytoma, lymphangiosarcoma, and neurofibrosarcoma. Despite the diversity of these tumors, histologic sub-type is relatively unimportant and does not play a major role in overall management. In contrast to subtype, histologic grade does influence prognosis and treatment. Higher-grade tumors tend to be more locally invasive and aggressive than lower-grade tumors and have a higher incidence of distant metastases. In soft-tissue sarcomas at all sites, histologic grade has been shown to be the single most important prognostic factor.[4,5] Several institutional reviews have demonstrated that grade is also an important prognostic factor in sarcomas of the the retroperitoneum.[2,6-8]

Diagnosis and Staging

The diagnostic work-up in a patient with a retroperitoneal mass should include a complete blood count, serum electrolytes, serum creatinine, and liver function tests. Computed tomography (CT) or magnetic resonance imaging (MRI) are the best studies for evaluating the extent of the primary tumor. These imaging studies can assess invasion or displacement of neighboring structures, evaluate the liver, and may help guide the diagnostic biopsy. When the primary tumor is located in a region where one kidney is likely to be sacrificed by surgery or damaged with radiation, a renal scan is indicated to evaluate the function of the contralateral

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kidney. Other studies, such as barium enema, upper gastrointestinal (GI) series, or IV pyelography, are rarely necessary.

Incisional biopsy is the preferred means of obtaining a diagnosis, because it provides sufficient tissue for accurate grading of the tumor and provides adequate information for treatment planning. Hemostasis should be ensured following the incisional biopsy to prevent tumor seeding. The work-up for metastasis should include a CT scan of the chest/upper abdomen to rule out pulmonary and/or liver metastases.

Once a diagnosis has been established, a multidisciplinary approach should be undertaken prior to the initiation of therapy for the proper sequencing of each treatment modality. The precise goal of treatment (cure or palliation) should be understood by the treating physicians, as well as the patient. The staging system for soft-tissue sarcomas, as defined by the American Joint Committee on Cancer (AJCC), incorporated histologic grade as the primary determinant in the clinical staging (Table 1).

One of the ironies of the AJCC system is that although the stage grouping is based on tumor, there are no definitive criteria for grading soft-tissue sarcomas. Several grading systems have been proposed, which use a variety of histologic criteria. Trojani et al proposed a three-grade system in which mitotic count, differentiation, and necrosis were found to be the three necessary parameters in attributing a tumor grade.[9] Hajdu described a two-grade system based on differentiation, cellularity, stromal involvement, vascularity, necrosis, and mitotic count.[10] There are no widely accepted criteria for a tumor grade despite its importance in prognosis.

Surgery

Surgical resection continues to be the primary therapy for retroperitoneal sarcomas. Extent of surgical resection has often been reported as the single most important prognostic factor for these tumors.[2,6,8,11] Complete surgical resection provides improved local control and survival rates when compared with a more limited resection.[2,8,12,13] Cody et al, in a review of 158 patients with retroperitoneal sarcomas treated at Memorial Sloan-Kettering Cancer Center (MSKCC), reported a 5-year survival rate of 40% in those patients who underwent complete excision vs a rate of 3% in those with an incomplete resection.[2]

It is likely that tumors with a more favorable prognosis at the outset are also most amenable to surgical resection. Thus, the improved prognosis associated with a complete resection probably represents both a cause and an effect. Despite complete surgical removal of a retroperitoneal sarcoma, the majority of patients experience a local recurrence (Table 2). Storm and Mahvi,[12] in a review of the literature, report a > 90% local recurrence rate at 10 years following complete surgical resection. This local failure is not unexpected given the lack of anatomic barriers in the retroperitoneum and the large size of these tumors. Even with surgical sacrifice of such organs as the kidney, bowel, and pancreas, the anatomic limits of the retroperitoneum prohibit wide surgical margins. Approximately one-half of the patients explored for these tumors are able to undergo complete removal of all gross disease,[12] but clear pathologic margins are the exception, as microscopic extension beyond apparent tumor borders is the rule. Sarcomas often have a pseudocapsule of compressed normal tissue into which there is microscopic tumor invasion. This can lull the surgeon into believing that the operation performed was better than was actually the case. Unlike extremity sarcomas, where wide margins are routinely achieved, a complete "oncologic" resection is rarely accomplished in the retroperitoneum.

Given these limitations of surgery, it is not surprising that a large discrepancy exists between the local recurrence rates of extremity and retroperitoneal sarcomas after surgical resection. The efficacy of adjuvant radiation therapy in decreasing local failure rates following wide surgical excision of extremity sarcomas has been well documented. Surgical excision as the sole treatment of high-grade extremity sarcomas results in local recurrence rates of 35% to 60%, whereas local control rates of approximately 85% can be expected with the addition of radiation therapy.[14] The improvement in local control with radiation therapy seen in extremity sarcomas should also be observed in the retroperitoneum since there is no suggestion that soft-tissue sarcomas at these sites are biologically different.

Radiation Therapy

The contribution of radiation therapy, when used in conjunction with surgical excision, to the local control of retroperitoneal sarcomas is difficult to assess from the literature. This difficulty stems from the limited number of patients, as well as uncontrolled variables, such as tumor size, histologic subtypes, and radiation technique and dose. No randomized series has demonstrated a benefit of
radiation therapy in these tumors, but no study has compared surgery alone to surgery plus radiation. However, the retrospective studies with the best results in terms of both local control and survival have used radiation therapy in combination with surgery.[2,8,11,15-18]

Harrison et al reviewed the literature, as well as 23 patients with retroperitoneal sarcomas treated at Yale. They suggested that with adjuvant radiation doses of 45 to 50 Gy, a moderate degree of local control can be achieved.[16] Cody et al, in their analysis of 158 patients treated at MSKCC between 1951 and 1977, reported a 5-year disease-free survival of 17% (4/23) in patients treated with complete excision alone, as compared with a rate of 33% (5/15) in patients treated with complete excision and radiation therapy.[2] These results suggest an advantage to combined surgery and radiation.

Two major problems that plague radiation therapy for retroperitoneal sarcomas may explain the discrepancy between local control rates seen in sarcomas at this site and sarcomas in the extremities. The first problem is the large size of these tumors at presentation. Tepper and Suit showed an inverse correlation between tumor size and local control in 110 patients with soft-tissue sarcomas treated at Massachusetts General Hospital (MGH).[19]

The second, more important problem is the limited radiation dose that can be delivered to this region because of the sensitive normal structures that are usually within the radiation fields. In the extremity, doses of 65 to 70 Gy are generally well tolerated. In contrast, radiation dose often must be restricted to 45 to 50 Gy in the retroperitoneum because of the limited radiation tolerance of normal tissues, such as the small bowel, stomach, liver, spinal cord and kidneys. As the probability of tumor control is directly correlated to the dose delivered, one would expect a large difference in tumor control between extremity and retroperitoneal sarcomas.

This theory is supported by data from Tepper et al, who reviewed 23 patients with retroperitoneal sarcomas treated at MGH between 1971 to 1982. They showed that the probability of local control increases with increasing dose. They reported local failure in 67% of patients who received less than 50 Gy, as compared with a 17% local failure rate in those who received more than 60 Gy.[11]

Fein et al at Fox Chase Cancer Center looked at the issue of dose escalation in a retrospective review of 21 patients treated with surgical resection and radiation therapy for sarcomas of the retroperitoneum. They found that a dose of more than 55 Gy improved the likelihood of local control.[20]

The impact of local control on survival is less clear. This issue is controversial for sarcomas generally. However, there is a suggestion that an increase in local control may translate into a survival advantage in retroperitoneal sarcomas. Karakousis et al reviewed 87 consecutive patients with retroperitoneal sarcomas treated at Roswell Park Cancer Institute between 1977 to 1994. They reported a 49% 5-year survival rate in patients who had a local recurrence vs a rate of 73% in patients without a local recurrence.[8] Unfortunately, this study does not answer the question of whether patients likely to have metastases are also likely to develop a local recurrence. What is clear is that patients cannot be cured if one does not achieve local control.

The challenge, therefore, lies in delivering an adequate radiation dose to the tumor bed while respecting the radiation tolerance of normal adjacent structures. Various approaches have been employed to achieve this end, including preoperative radiation, intraoperative radiation, three-dimensional (3D) treatment planning, and brachytherapy.

**Postoperative Radiation Therapy**

Typically, radiation therapy has been given after surgical resection. Postoperative radiation has the obvious advantage of an immediate resection. However, there are several disadvantages of postoperative radiation:

- Normal radiosensitive structures fall back into the tumor bed following surgical resection and limit the postoperative dose to unacceptably low levels.
- Tissues at risk may not be within the radiation portals each day. For example, tumor peeled away from the small bowel can move in and out of the radiation fields throughout a course of postoperative radiation therapy.
- Potentially larger radiation volumes are used, as compared with the preoperative setting, in an attempt to cover surgically manipulated tissues.

**Preoperative Radiation Therapy**

Preoperative radiation therapy has been used in an effort to improve local control of soft-tissue sarcomas at all sites, including the retroperitoneum.[21] In addition to a delay in surgical resection, a potential disadvantage to preoperative radiation is the risk of compromised wound healing after
Advantages of using radiation in the preoperative setting include:

- Displacement of normal structures, which can significantly reduce morbidity of treatment and may permit dose escalation. This is demonstrated in Figure 1, which shows a typical radiation field used in the preoperative setting and demonstrates the minimal amount of GI tract in the field despite the large treatment volume. This approach, in combination with intraoperative radiation or postoperative brachytherapy, can allow the delivery of a total radiation dose of approximately 60 to 70 Gy with relative sparing of normal structures that lie in close proximity to the tumor.
- Knowledge that tissues involved with tumor are included in the radiation fields. This contrasts with the postoperative setting, in which tissues at risk may not be directly in the tumor bed.
- Other theoretical advantages of preoperative radiation include:
  - Potential radiobiologic advantage of improved oxygenation of tumor cells in the preoperative setting. The absence of oxygen dramatically decreases the sensitivity of cells to radiation. Surgical resection alters the vascularity within the tumor and can render residual tumor cells hypoxic.
  - Decreased potential for tumor seeding at surgery.
  - Sufficient reduction of tumor volume to allow a greater proportion of patients to undergo complete resection.

**Intraoperative Radiation Therapy**

At MGH, a preoperative approach combined with intraoperative radiation therapy has been used in the treatment of retroperitoneal sarcomas.[19] By delivering radiation during surgery, the physician is able to visualize the tumor volume directly and improve the dose distribution. Also, normal structures can be physically moved out of the way of the radiation beam. It is also possible, in some instances, to shield tissues underneath the tumor volume or to adjust the electron energy to spare structures located beneath the tumor.

Willett et al reported on 20 patients who received preoperative radiation therapy to a dose of 45 to 50 Gy with intraoperative doses of 1,000 to 2,000 cGy. Of 19 patients who were explored, 17 underwent complete or partial resection. The 4-year actuarial local control and disease-free survival rates in these 17 patients were 81% and 64%, respectively.[22]

The only randomized, prospective trials of the treatment of retroperitoneal sarcomas were conducted at the National Cancer Institute (NCI). In the most recent study, 35 patients with surgically resected sarcomas of the retroperitoneum were randomized to receive 20 Gy of intraoperative radiation therapy in combination with low-dose postoperative radiation (35 to 40 Gy) or high-dose postoperative radiation alone (50 to 55 Gy). Although median survival times were similar, locoregional recurrences were significantly lower in those receiving intraoperative radiation (6 of 15) than in the control patients (16 of 20). While the incidence of severe radiation-induced enteritis was reduced in the intraoperative radiation therapy arm, the incidence of peripheral neuropathy was increased.[23]

**Three-Dimensional Treatment Planning**

Three-dimensional treatment planning allows the radiation oncologist to shape the high-dose volume to be treated while blocking surrounding normal structures. By utilizing three-dimensional imaging, the target volume can be precisely defined and beams designed to optimize the therapeutic ratio. This approach is optimal in the preoperative setting, where the tumor often displaces normal structures, and may allow for the complete avoidance of sensitive normal structures. This technique can also be extremely useful in planning a boost to a reduced volume.

**Brachytherapy**

Brachytherapy is a reasonable alternative to intraoperative radiation therapy in the attempt to improve dose distribution. The afterloading of catheters placed strategically at the time of surgery permits a high-dose of radiation to be delivered to a very limited area with rapid dose fall-off as the distance from the radioactive sources increases. At the University of North Carolina (UNC) at Chapel Hill, a dose of 12 to 20 Gy is delivered to the residual tumor over 36 to 60 hours using iridium-192 seeds (in combination with preoperative external-beam radiation of 4,500 cGy). With this approach, one must be certain that the small bowel does not lie on top of the implant and thus receive an excess dose.

**Palliative Radiation**

A brief mention of palliation should be made. Although radiation therapy is most effective against microscopic disease, it can provide effective palliation for patients with large retroperitoneal
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sarcomas. When palliation is the goal, several general principles should guide management. First, one should determine that the tumor is the actual cause of the symptoms to be palliated. Second, the specific goal(s) of treatment should be established and communicated to the patient. Third, total treatment time, as well as recovery from the treatment, should be minimized, especially in patients with a short life expectancy. Finally, the treatment should give the patient a reasonable likelihood of symptomatic improvement with minimal morbidity. Careful attention to technique is critical for optimizing the therapeutic ratio. It is essential to minimize radiation to sensitive organs, such as the stomach and small bowel, which can result in unacceptable side effects during and after radiation.

There have been rare reports of patients with large, unresectable retroperitoneal sarcomas achieving a complete response and long-term survival when treated with radiation therapy.[16,24]

Chemotherapy

Retrospective studies have not shown a benefit from the addition of adjuvant chemotherapy in retroperitoneal sarcomas.[7,8] In addition, a randomized study from the NCI showed no advantage to the use of adjuvant doxorubicin, cyclophosphamide (Cytoxan, Neosar), and high-dose methotrexate after surgical resection and postoperative radiation therapy. Only 15 patients were randomized, but the 2-year actuarial survival rate in patients treated with chemotherapy was inferior to that in those who did not receive chemotherapy (47% vs 100%).[3]

Given the high likelihood of liver and lung metastases, as well as peritoneal sarcomatosis, in patients with retroperitoneal sarcoma, there is reason to believe that chemotherapy could have a favorable impact. Extrapolation of data from other sites suggests that chemotherapy may be beneficial in patients with adequate local control of the primary tumor. Existing data from several randomized studies of soft-tissue sarcomas suggest that adjuvant chemotherapy may improve disease-free survival, although this is statistically significant in only a few studies and is most apparent in sarcomas of the extremities.[14]

Chemotherapy has been used in the neoadjuvant setting in patients with retroperitoneal sarcomas. Up-front chemotherapy can provide valuable information regarding tumor response to systemic therapy and can identify a subgroup of patients who are likely to respond to adjuvant chemotherapy. At UNC-Chapel Hill, a trial is underway in which patients with retroperitoneal sarcoma are treated with two cycles of neoadjuvant ifosfamide (Ifex) and doxorubicin. Patients who respond (more than 50% tumor reduction) receive an additional two cycles of chemotherapy followed by preoperative radiation therapy and then surgical resection. Patients who do not respond after two cycles of chemotherapy receive radiation followed by surgical resection. For either group of patients, brachytherapy or a postoperative radiotherapy boost is considered.

Summary

The management of patients with retroperitoneal sarcomas remains a challenge. A multimodality approach should be employed at the outset. Complete surgical resection is clearly the mainstay of treatment. However, even with "complete" surgical resection of all gross tumor, the majority of patients will experience local failure.

Radiation therapy can improve local control but is limited by the large size of these tumors and the close proximity of normal radiosensitive structures. The use of higher doses of radiation has been associated with an improvement in local control. The use of preoperative radiation therapy plus intraoperative radiation or brachytherapy allows the delivery of the high doses required to afford a reasonable likelihood of achieving local control of these tumors. Chemotherapy has not been shown to be beneficial in the treatment of retroperitoneal sarcomas. However, as the control of local disease improves and better drug regimens are developed, chemotherapy may yet play a role.

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