Section 14

SOFT TISSUE SARCOMAS

Summary and Conclusions

This synthesis of the literature on radiotherapy for sarcomas originating in the body's soft, supportive tissues, ie, muscle, connective tissue, and fatty tissue is based on 71 scientific articles, including 4 randomized studies, 5 prospective studies, and 26 retrospective studies. These studies involve 3 444 patients.

- Over 90% of patients with soft tissue sarcomas in the arms and legs can be treated in a way that preserves the extremities. Subcutaneous and intramuscular sarcomas can be treated surgically with little functional loss or risk for local recurrence without adjuvant radiotherapy. To avoid amputation, surgery is often combined with radiotherapy for treatment of local relapse.
- Adequate surgical margins are usually difficult to achieve for head/neck tumors and retroperitoneal tumors, and therefore surgery is often combined with radiotherapy to reduce the risk for local relapse.
- Pre- and postoperative radiotherapy are similar (1, 2). A disadvantage of preoperative radiotherapy is that it reduces the opportunity for exact diagnosis and determining morphobiologic sarcoma parameters.
- To further improve treatment results for advanced sarcomas, it is necessary to introduce other fractionation schedules, mainly hyperfractionation (1). This places greater demands on radiotherapy, mainly for staff resources.
- Combining radiotherapy and local intraarterial chemotherapy involves greater risks for complications and has not shown better treatment results than pre- or postoperative radiotherapy alone, and it is not recommended as standard treatment for soft tissue sarcomas.
- Intraoperative treatment methods should be targeted for further study and development.

Introduction

Soft tissue sarcomas represent less than 1% of all newly diagnosed malignant diseases, with 287 cases reported in 1992 (II). The annual age-adjusted incidence is 2 per 100 000 persons (XXVI). Approximately 7% of all malignant diseases among children under the age of 15 are soft tissue sarcomas, mostly rhabdomyosarcoma. After age 40, the age-specific incidence of soft tissue sarcomas increases exponentially; most patients are over 60 years of age. In 1992, 149 deaths were reported from the disease in Sweden (III).

Localization. Soft tissue sarcomas may develop in any part of the body, but are most common in the extremities (60%). Two thirds of soft tissue sarcomas occur in the legs, usually the thigh, and one third in the arms. Other sites include the head and neck (10%) and torso, including retroperitoneal sarcoma (30%) (3–11).

Histologically, soft tissue sarcomas are a heterogeneous group of tumors representing approximately 30 different types (12). Most have mesenchymal origins, but neuroectodermal tumors are also included. The most common tumor type (approximately 30% to 40%) is malignant fibrous histiocytoma (13, 14).

Treatment and prognosis depend more on tumor site, tumor size, and histologic malignancy grade than on exact histological type (14–19). A four-grade malignancy scale is used in Scandinavia. Tumors at a malignancy grades I–II are highly differentiated and have little tendency for metastasis. Grade IV tumors are often pleomorphic, grow rapidly, and have a strong tendency to spread, they metastasize in more than one half of the cases. Recently, tumor size, tumor necrosis, and vascular invasion have emerged as much stronger prognostic factors and can be used to improve prognostic systems (20). The strength of prognostic factors is different for different histologic types (20). Attempts to construct different prognostic systems for different types of tumors have been unsuccessful.

Specific chromosomal changes have been detected in many types of soft tissue sarcoma, eg, synovial sarcoma, liposarcoma, and alveolar rhabdomyosarcoma. These chromosomal changes are of importance for classifying soft tissue sarcomas. Whether they are also of prognostic significance is yet unclear.

Staging of soft tissue sarcomas usually follows the American Joint Committee (AJC) System (21) or the Surgical Staging System (SSS) (22). The AJC System represents an extension of the Tumor-Node-Metastasis (TNM) System and is based on tumor size ($</>$ 5 cm), malignancy grade (I–III) and distant metastases. The SSS System is based on tumor compartmentalization (intra/extra), malignancy grade (high/low), and distant metastases. This system, in contrast to the AJC System, provides

guidance for selecting a surgical procedure. The Scandinavian Sarcoma Group's (SSG) System for classifying tumor localization—subcutaneous, intra- and extramuscular—has no prognostic aims, but off ers guidance for selecting patients who can be treated by local surgery without radiotherapy (23).

Preoperative investigation provides the foundation for treatment (20). Clinical examination, magnetic resonance imaging (MRI), computerized tomography (CT), and sometimes bone scintigraphy or angiography are necessary to determine which structures are affected by the tumor and which fasciae define the area. Preoperative radiography, including computed tomography, of the lungs is necessary to exclude the possibility of metastases. Internationally, open biopsy is generally used in diagnosis. In Sweden, fine needle aspiration is used in most cases, avoiding open biopsy which increases the risk for local recurrence (19, 24–26). TRU-CUT biopsy, a method that uses a larger needle to provide a tissue cylinder, can also be used. In cases where biopsy is necessary, the biopsy should be performed by the same surgeon who is responsible for performing the operation. A poorly planned biopsy can lead to an unnecessarily large intervention, possibly amputation. An excision biopsy to "shell out" the tumor as if it were benign is particularly unfortunate. The procedure is not curative and destroys the opportunity for exactly defining the tumor site, a necessity for adequate surgery. Superficial tumors measuring over 5 cm are suspect to malignancy, as are all deep tumors regardless of size. These tumors should be investigated immediately at specialized orthopedic-oncology departments. The tumors should not be disturbed.

In contrast to the Scandinavian Sarcoma Group's principles, half of sarcoma cases in the United States and England are diagnosed before referral by excision biopsy, often by general surgeons with limited knowledge about treating sarcomas (11). Twenty percent of the patients were diagnosed by incision biopsy, and fine needle aspiration was used in approximately 10% of cases. Hence, only one third of the patients are referred prior to surgery. In recent years, the use of fine needle aspiration for primary diagnosis of soft tissue sarcomas has increased somewhat in the United States and England.

Treatment

Surgery alone, surgery combined with radiotherapy, surgery combined with radiotherapy and intra-arterial chemotherapy, or radiotherapy alone have been used to treat soft tissue sarcomas. The treatment strategies which have emerged have focused on maintaining a low rate of local recurrence and good function in the extremities. Currently, less than 10% of the patients with soft tissue sarcomas in the extremities are amputated.

Surgery

Adequate surgical margins are essential for achieving good local tumor control. The local recurrence rates are high, at least 60%, with marginal excision, ie, "shelling out the tumor" with narrow margins (27–31).

"Wide excision" includes several centimeters of normal tissue in all directions around the tumor. Near the fasciae, the margins can be narrower. All earlier scars, fine needle aspiration channels, and biopsy areas with hematomas should be excised. The risk for local recurrence is approximately 20% in operations with such wide margins. The same surgical principles are applied to sarcomas in the extremities and sarcomas localized to the trunk wall (32–41).

At most international centers, extremity-conserving surgery is always combined with radiotherapy. However, in Sweden radiotherapy is used to a lesser extent. Both low-grade and high-grade sarcomas which are subcutaneously localized or completely surrounded by a muscle fascia (intramuscular sarcoma) can be treated surgically without radiotherapy, and yet remain at low risk for local recurrence ($<10\%$), with little functional loss (23). However, the fascia shall not have been opened by previous biopsy. This requires patients to be referred prior to surgery. In contrast to the situation at many tumor centers, most sarcoma patients in Sweden are referred prior to surgery.

Radiotherapy and surgery

Internationally, a combination of surgery and postoperative radiotherapy is the most common method for treating soft tissue sarcomas. This approach requires adequate excision of all macroscopic disease; excision often ranges between marginal and wide (42).

Frequently, it is impossible to achieve adequate surgical margins for large, deep, extramuscular extremity sarcomas. This also applies to sarcomas in the head and neck and for tumors in the mediastinum and the retroperitoneum. In these cases, surgery is combined with radiotherapy. Reconstructive plastic surgery is often necessary for successful treatment. Amputation, used in less than 10% of the cases, may be indicated for tumors which infiltrate the skeleton, major blood vessels, or nerves.

Preoperative radiotherapy has the following theoretical advantages: inactivation of tumor cells may reduce the risk for tumor implantation and reduce metastatic spread to the vascular area during surgery. The target volume can be limited to clinically and radiologically observable tumors. Since tumors shrink due to irradiation, previously inoperable tumors may become operable. The major disadvantage of preoperative radiotherapy is the delay in surgery, mainly a psychological disadvantages for some patients, but it also increases the risk for complications related to wound healing. Adequate diagnosis of sarcoma may be

difficult with preoperative radiotherapy since large, open biopsies are not systematically performed prior to treatment. Several series reported good results (43–48), the local recurrence rates range between 7% and 11%.

Postoperative radiotherapy and surgery represents the most common combination. The advantages of postoperative radiotherapy include immediate surgery, no delayed wound healing, and the fresh tumor specimen is available for histopathologic investigation via immunohistochemistry, electromicroscopy, and DNA and chromosome analysis.

Several published studies of surgery and postoperative radiotherapy report local recurrence rates between 10% and 28% (8, 23, 49–54). The series from the MD Anderson Cancer Center is one of the first and largest, involving 300 patients (7). Surgery in this series was inadequate, compared to current surgical principles. Their method may be classified as a "shell-out" procedure with excision of macroscopic tumors. Patients received between 60 Gy and 70 Gy for 6 to 7 weeks. The target volume did not include the entire muscle or anatomic compartment. The frequency of local recurrence was 22% for extremity-localized sarcomas. Low-grade sarcomas are included in the series. Local recurrence was 10% in one series of 29 patients who received 55 Gy and 70 Gy postoperatively for extremity-localized soft tissue sarcomas (50).

The National Cancer Institute (NCI) conducted a randomized prospective clinical study where patients with high-grade, extremity-localized sarcomas were randomized to limb-sparing surgery plus postoperative radiotherapy, or amputation only (52). The radiation dose averaged 63 Gy. 17 patients were randomized to amputation, and 27 to limb-sparing surgery and postoperative radiotherapy. No significant difference in the local recurrence rate was observed in this small series of patients. The rate of local recurrence is approximately 15%. Yang, NCI, randomized 90 patients to surgery and chemotherapy or surgery, chemotherapy, and radiotherapy. With an median followup of 5 years, patients who received postoperative radiotherapy had no local recurrence, while local recurrence was reported in 9 of 46 patients who received no radiotherapy. Survival in both groups is the same. Yang and associates concluded that selected patients who receive optimal surgery for prognostically favorable tumors may not require radiotherapy.

In a study by the Scandinavian Sarcoma Group, 34 patients received postoperative radiotherapy for marginal surgery of soft tissue sarcomas. The dose was 51 Gy, with a 3 Gy daily fractionation and a CRE value of 18.2. The rate of local recurrence was 14% (53). 3 Gy fractionation increased side effects, and the Scandinavia Sarcoma Group subsequently returned to a fractionation of 2 Gy.

A reason behind the dominant international approach to treatment—surgery and radiotherapy—is that patients are generally referred to cancer centers only after they have received procedures involving risks for local tumor dissemination.

Intraoperative radiotherapy, with high single-dose electron irradiation, has been used mainly on tumors localized to the retroperitoneum. This treatment has not demonstrated better results concerning the frequency of local recurrence and survival compared to conventional postoperative irradiation (55). Intraoperative radiotherapy may reduce the frequency of radiation-induced intestinal inflammation. This approach remains under development and is not considered standard treatment (56).

Postoperative brachytherapy was addressed by Brennan and associates in a randomized prospective study of 117 patients with soft tissue sarcomas localized to the extremities and the trunk wall (54). Fifty-two patients were randomized to brachytherapy and the remainder received no brachytherapy. Two of 52 patients who received brachytherapy developed local recurrence compared to nine of the 65 in the group not receiving brachytherapy ($p = 0.06$). No differences in survival were observed. Similar results were reported by Habrand and Gemer (57, 58). The advantages and disadvantages of brachytherapy are similar to preoperative radiotherapy, but treatment times are substantially shorter. Treatment results are similar to those achieved from external irradiation.

Combined Intraarterial Chemotherapy, Radiotherapy, and Surgery. Eilber and associates used preoperative intraarterial chemotherapy concurrently with radiotherapy for extremity-localized sarcomas (59). Seventy-seven patients with high-grade, extremity-localized sarcomas were treated with intraarterial doxorubicin (30 mg per day, by 24-hour infusion for three days), and external radiotherapy (3.5 Gy × 10 for a total dose of 35 Gy). A block-resection of the tumors was performed one to two weeks following the conclusion of radiotherapy. The frequency of local recurrence was 4%, but 35% of the patients had complications, mainly fractures and problems with wound healing. Another 105 patients received postoperative radiotherapy, 17.5 Gy total, and the same dose of doxorubicin. The frequency of complications decreased, but local recurrence increased to 8%.

Radiotherapy alone

Indications for radiotherapy alone for soft tissue sarcomas are limited to patients with locally advanced, inoperable, recurrent, or metastatic disease. The aim of treatment is often palliation. An analysis of experiences with radiotherapy alone, reported by Tepper and Suit (60), showed an inverse relationship between tumor size and the opportunity to achieve local tumor control. For tumors under 5 cm, 5 cm to 10 cm, and larger than 10 cm, local control with radiotherapy alone was achieved in 88%, 53%, and 33% of cases respectively. The dosage needed to inactivate viable tumor cells increases with the number of tumor

cells; radiotherapy in treatment of microscopic disease is more effective than in treatment of macroscopic tumors (61). Local tumor control can be achieved by radiotherapy alone but requires aggressive treatment with high radiation doses, carrying a substantial risk for side effects. Radiotherapy alone is much less effective at local tumor control than is combined surgery and radiotherapy.

Radiotherapy methods

The target volume should include the entire anatomic region at risk for tumor cell dissemination. In tumors localized to the extremities, the target volume should include the entire engaged anatomic compartment and post-surgical scars and drainage with a margin of at least 5 cm. Booster treatment should include the tumor bed with an approximate 2 cm margin. The extremity should be immobilized and individual dose planning should be used. The dosage for marginal surgery is usually 50 Gy in 25 fractions. The dosage for intralesional surgery is 50 Gy in 25 fractions followed by a 10 Gy to 20 Gy boost in 5 to 10 fractions. For large abdominal fields, the daily fraction dose should be reduced to 1.5 to 1.8 Gy, but the total dose should be 50 Gy (62–64). Approximately one third of the extremity's circumference should, if possible, be excluded from the radiation field to optimize function and minimize lymphedema. Determination of target volumes and dose planning is best done in cooperation with the surgeon.

Neutron therapy is an emerging method which has been used at the MD Andersen Cancer Center and the University of Washington (65, 66). Usual complications include severe subcutaneous fibrosis and radiation enteritis.

Treating recurrence

Local recurrence of extremity-localized soft tissue sarcomas following surgery and radiotherapy is often treated by amputation. Due to radiotherapy-related complications and poor opportunities to achieve local tumor control, physicians have generally avoided additional radiotherapy and opted for local excision. Essner reports on 32 patients with extremity-localized soft tissue sarcomas who were irradiated a second time, followed by local excision (67). A total dose between 28 Gy and 50 Gy was used for the second series of radiotherapy, with a total dose between 88 Gy and 105 Gy, including the first series of radiotherapy. Local tumor control was achieved in 15 of 18 patients by a second series of preoperative radiotherapy and excision. However, local recurrence was experienced by 8 of 14 patients receiving the second series postoperatively. The authors conclude that preoperative radiotherapy and excision of local residuals in the upper extremities and proximal thigh is an acceptable treatment approach before surgery alone, ie, amputation. Surprisingly few complications appeared. Similar results were reported by Graham (68).

Literature

The articles that appear in the reference list were classified and graded as follows: (Number of studies/Number of patients)

	1 = High	2 = Moderate	3 = Low	Total
M		–	–	–
C	1/117	3/107	–	4/224
P	3/83	2/74	–	5/157
R	25/2 948	1/25	–	26/2 973
L	24	–	–	24
O	12	–	–	12
Total	65/3 148	6/206	–	71/3 354

Since soft tissue sarcomas appear infrequently, and since the care of patients with these tumors is not often centralized, institutions have mainly reported on their own experiences. This may explain why there are so few randomized studies with so few patients. The infrequency of the disease highlights the importance of centralizing the diagnosis and treatment of these patients (69–71).

The pioneering work by Suit and associates in developing pre-and postoperative radiotherapy for soft tissue sarcomas stands out among the group of prospective studies. The National Cancer Institute and the Scandinavian Sarcoma Group are attempting to identify patients with soft tissue sarcomas in whom radiotherapy is not indicated.

The group of miscellaneous studies includes several descriptions of technical advancements which have been judged as particularly relevant in this context.

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