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CLINICAL INVESTIGATION **Sarcoma**

INTRAOPERATIVE RADIATION THERAPY FOR LOCALLY ADVANCED AND RECURRENT SOFT-TISSUE SARCOMAS IN ADULTS

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Purpose: To analyze the outcomes of and identify prognostic factors for patients treated with surgery and intraoperative radiotherapy (IORT) for locally advanced and recurrent soft-tissue sarcoma in adults from a single institution.

Methods and Materials: We retrospectively reviewed 50 consecutive patients treated with IORT to 62 sites of disease. Primary sites included retroperitoneum-pelvis (78%), extremity (8%), and other (14%). Seventy percent of patients had recurrent disease failing prior surgery (70%) and/or radiation (32%). Mean disease-free interval (DFI) before IORT was 1.9 years (range, 2 weeks–5.4 years). The IORT was delivered with orthovoltage X-rays using individually sized beveled cone applicators. Clinical characteristics were as follows: mean tumor size, 10 cm (range, 1–25 cm); high-grade histologic subtype (72%); and mean dose, 1,159 cGy (range, 600–1,600 cGy). Postoperative radiation or chemotherapy was administered to 37% of IORT Sites and 32% of patients, respectively. Outcomes measured were infield control (IFC), locoregional control (LRC), distant metastasis-free survival (DMFS), disease-specific survival (DSS), and treatment-related complications. Mean and median follow-up of alive patients were 59 and 35 months, respectively.

Results: Kaplan-Meier 5-year IFC, LRC, DMFS, and DSS probabilities for the entire group were 55%, 26%, 51%, and 25%, respectively. Prognostic factors found to be significant ($p < 0.05$) on multivariate analysis were prior DFI and tumor size for LRC, extremity location and leiomyosarcoma histologic subtype for DMFS, and prior DFI for DSS. Our cohort had five Grade 3/4 complications associated with treatment or a 5-year Kaplan-Meier Grade 3/4 complication-free survival rate of 85%.

Conclusions: IORT after tumor reductive surgery is well tolerated and seems to confer IFC in carefully selected patients.

Intraoperative radiation, Sarcoma, Prognostic factors, Orthovoltage.

INTRODUCTION

Soft-tissue sarcomas (STSs) are rare malignant tumors, with approximately 9,000 cases diagnosed annually in the United States. The STSs develop from mesenchymal tissue anywhere in the body. Complete resection is the primary therapy for most STSs in adults, but patients with large, deep-seated, or recurrent STSs have poor local control and survival (1–10). Adjuvant radiation therapy (XRT) commonly is recommended for patients with high-grade, large (>5 cm), margin-positive, and retroperitoneal tumors, with the main benefit of XRT being improved local control (9–17). Retroperitoneal tumors comprise 15% of all STSs, but have a worse prognosis than the more common extremity STSs (18). Those who underwent previous irradiation to the site of recurrence or had gross residual disease after attempted resection had particularly dismal local control and survival rates (1, 2, 4–7, 9, 19).

Intraoperative radiotherapy (IORT) is a unique modality that allows the sterilization of microscopic disease *in situ*. Mobilization of normal tissues out of the treatment field and selective shielding of adjacent structures permits protection of organs during IORT, allowing high single doses of radiation to be delivered while minimizing dose to adjacent normal tissues. For these reasons, IORT is well suited as an adjunct to resection of tumors in patients with recurrent and locally advanced malignancies. The available literature suggests that use of IORT in patients undergoing surgery

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for STSs may result in improved local control (12, 20–25). In a prospective trial from the National Cancer Institute for retroperitoneal STS, patients with resectable tumors were randomly assigned to IORT (followed by low-dose postoperative XRT) or higher dose postoperative XRT alone. The number of locoregional recurrences was significantly less in those who received IORT (6 of 15 patients) than those treated without IORT (16 of 20 patients) (26). The objectives of this study are to review our experience using IORT in patients with locally advanced, persistent, or recurrent STSs; analyze results as a function of pretreatment and treatment parameters; and identify prognostic factors for treatment outcomes and complications associated with treatment.

METHODS AND MATERIALS

We conducted an institutional review board–approved retrospective review of consecutive patients treated between Sept 1986 and Jan 2006 with IORT for STSs by the Department of Radiation Oncology, Stanford University Medical Center, Stanford, CA. Our cohort of 50 patients was selected for IORT based on locoregional recurrence or a high likelihood of failure after resection with or without additional external beam radiation (EBRT) or systemic therapy.

Pretreatment evaluation included patient history; complete physical examination; routine laboratory studies; and, depending on the individual patient, chest X-ray; examination under anesthesia; intravenous pyelography; computed tomography scan of the chest, abdomen, and/or pelvis; magnetic resonance imaging scan of the region of disease; cystoscopy; and/or rectoscopy/sigmoidoscopy. Informed consent was obtained from all patients before treatment.

Hospital medical records, clinic charts, and radiation oncology records were reviewed. We updated follow-up information in all patients within 1 month before the present study by using examination, data from the referring physician, or direct correspondence with patients or relatives. Follow-up for surviving patients was determined from the day of IORT.

Treatment of patients

Patients were eligible for IORT if, at the time of surgical resection, surgeons did not achieve negative margins by frozen sections or there was clinical suspicion for residual disease. Surgery was carried out in a dedicated operating suite containing a Philips RT-250 IORT radiation unit (Philips Medical Systems, Best, The Netherlands). Treatment was delivered with 200–250-kVp orthovoltage x-rays directly over the tumor bed (27, 28). Choice of half-value layer filters, 0.57–2.45 mm copper, was based on consideration of dose rate (50–100 cGy/min), residual tumor thickness, and underlying tissues. For example, when there is normal bone in the exit of the beam, higher half-value layer beam (with higher kilovoltage peak) was used to minimize excess bone dose caused by the contribution from the photoelectric effect. Treatment fields were designed to encompass a 0.5- to 1-cm margin around the tumor bed. The IORT was administered by using a series of specially designed nickel-plated brass circular cones with diameters ranging from 2.5–12.5 cm (one site with a 2.5-cm cone, three sites with the 2.85-cm cone, one site with the 3.85-cm cone, 15 sites with the 5-cm cone, 28 sites with the 7.5-cm cone, 13 sites with the 10-cm cone, and one site with the 12.5-cm cone) and bevels of 0°, 15°, 30°, and 45°. All doses were prescribed to the surface, and no bolus was used. Before administration of IORT, maximal efforts were made to mobilize and pack uninvolved small and large intestines, ureters, and pelvic vasculature out of the proposed radiation field for retroperitoneal tumors, and major uninvolved nerves or vessels for tumors at all sites. If this was not possible, customized lead shielding was used to prevent overdosing of vital structures. The IORT dose to normal bowel and major nerves was limited to 12.5 Gy or less when possible.

Follow-up

After completion of treatment, patients were evaluated at 3- to 6-month intervals for disease status and treatment-related complications. Routine evaluation included physical examination, hematology and chemistry profiles, and chest radiograph, computed tomography, and/or magnetic resonance imaging as indicated based on tumor site and at the discretion of the physician (29).

Parameters analyzed to assess impact on in-field control (IFC), locoregional control (LRC), distant metastasis-free survival (DMFS), and disease-specific survival (DSS) included patient age, American Joint Committee on Cancer stage (Stage I vs. II vs. III vs. IV), tumor grade, site of origin of the primary cancer, prior surgery, prior radiation, primary vs. recurrent disease, tumor size, tumor histologic subtype, number of prior recurrences (0–1 vs. >1), prior disease-free interval (DFI) in cases of recurrent disease, IORT dose, postoperative EBRT, and use of postoperative chemotherapy. Margin status was confirmed by pathology report of frozen/permanent sections, and if not available or noninformative, IORT and/or surgical reports were used. Microscopic disease was defined as disease 5 mm or less from the inked edge of the resected tumor, and a greater than 5-mm margin was considered negative. We also analyzed the effect of LRC on DMFS and DSS. Intervals were defined from day of IORT to last follow-up or first reported site of failure or death from cancer. Disease relapse in the IORT field was defined as an infield failure, whereas relapse within the compartment of IORT, for example, the pelvis or abdomen, was defined as locoregional failure. The DMFS was defined as survival without distant recurrence (outside the locoregional compartment), and other events were censored. Similarly, DSS was scored as death from STS or, if information was lacking, death likely from STS; other competing causes of death were censored. Recurrence outside the IORT compartment was defined as distant failure.

Complications were scored according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (30). Parameters evaluated to assess their impact on freedom from Grade 3/4 (G3/4) complications (complication-free survival [CFS]) were those used to analyze LRC. The interval for CFS was defined as day of IORT to first reported G3/4 complication.

Statistics

The Cox proportional hazards model was used for multivariate analysis to assess the effect of patient variables and treatment factors on the end points described. All variables with $p \leq 0.25$ on univariate analysis were entered into the model, and backwards elimination was carried out. The final model consisted of variables with $p \leq 0.05$ using the Wald test to analyze the function of covariates in our model. Survival graphs were generated by the Kaplan-Meier product limit method, and log-rank analysis was used for differences between proportions. Pairwise comparisons were performed using the two-tailed Mann-Whitney method. Analysis was facilitated using R freeware by the GNU project (GNU, Not Unix, Boston, MA) and Prism, version 4.0, by GraphPad (San Diego, CA).