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Phase II trial

Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: Long-term results of a prospective trial

Myles J.F. Smith [a,b], Paul F. Ridgway [c], Charles N. Catton [a,d], Amanda J. Cannell [a,b], Brian O'Sullivan [a,d], Lynn A. Mikula [e], Julia J. Jones [f], Carol J. Swallow [a,b,*]

[a] The University of Toronto Sarcoma Group, Princess Margaret Hospital and Mount Sinai Hospital; [b] Department of Surgery, University of Toronto, Canada; [c] Department of Surgery, Adelaide and Meath Hospital, Dublin 24, Ireland; [d] Department of Radiation Oncology, University of Toronto; [e] The Peterborough Clinic, Peterborough; and [f] The R. S. McLaughlin Durham Regional Cancer Centre, Oshawa, Canada

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ABSTRACT

Background: Late failure is a challenging problem following resection of retroperitoneal sarcoma (RPS). We investigated the effects of preoperative XRT plus dose escalation with early postoperative brachytherapy (BT) on long-term survival and recurrence in RPS.
Methods: From June 1996 to October 2000, eligible patients with resectable RPS were entered onto a phase II trial of preoperative XRT (45–50 Gray) plus postoperative BT (20–25 Gray). Kaplan Meier survival curves were constructed and compared by log rank analysis (SPSS 21.0).
Results: All 40 patients had preoperative XRT and total gross resection as part of the prospective trial, nineteen received BT (48%). Median follow-up was 106 months. For the entire cohort, OS at 5 and 10 years was 70% and 64%, respectively; RFS at 5 and 10 years was 69% and 63%. RFS was significantly reduced in high versus low grade RPS at 5 years (53% vs. 88%, $p = 0.016$), but not at 10 years (53% vs. 75%, $p = 0.079$). RFS and OS at 10 years were reduced in patients who presented with recurrent compared to primary disease (RFS 30% vs. 74%, $p = 0.015$; OS 36% vs. 76%, $p = 0.036$). At 10 years, neither RFS nor OS was improved in patients who received BT compared to those who did not (RFS 56% vs. 69%, $p = 0.54$; OS 52% vs.76%, $p = 0.23$).
Conclusions: In this prospective trial with mature follow-up, long-term OS and RFS in patients who underwent combined preoperative XRT plus resection of RPS compare favourably with those reported in retrospective institutional and population-based series. Postoperative BT was associated with unacceptable toxicity and did not contribute to disease control.
Condensed abstract: In a prospective trial with mature follow-up, preoperative radiation combined with complete resection of retroperitoneal sarcoma resulted in favourable long-term RFS and OS compared to historical controls. Dose escalation with postoperative brachytherapy was not associated with better disease control.
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Abdominal relapse of retroperitoneal sarcoma (RPS) presages death from sarcoma, even if resection of the recurrent disease is possible [1–3]. Unlike soft tissue sarcoma at other sites, RPS continues to recur up to and beyond 10 years after initial resection. Few patients die from distant metastatic disease – at 10 years, overall survival (OS) mirrors abdominal recurrence-free survival. Historically, OS at 10 years is reported to range from 14–50% in retrospective surgical series [4–6]. A recent population based analysis using the SEER database, found the 10 year OS after resection of primary RPS to be 27% [7].

Strategies to reduce abdominal recurrence of RPS include extended resection and adjuvant therapy. The sarcoma groups in Milan and Paris have demonstrated the safety of upfront extended radical resection in high volume centres, with Gronchi et al. documenting a relatively low rate of abdominal recurrence of 28% at five years, versus historical rates of 49% [8,9]. Nevertheless, the anatomic constraints inherent to the retroperitoneum limit the ability to achieve widely clear margins of resection [3].

Adjuvant radiotherapy is of proven benefit in high risk soft tissue sarcoma of the extremity [4–6,10,11]. This success has prompted attempts to translate this strategy to the management of RPS [1]. There are practical difficulties in administering an effective dose of external beam radiation to the retroperitoneum postoperatively, with uncertainty as to the appropriate target

* Corresponding author. Address: Mount Sinai Hospital, 600 University Avenue, Suite 1225, Toronto, ON M5G 1X5, Canada.
E-mail address: cswallow@mtsinai.on.ca (C.J. Swallow).

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volume, potential delays when postoperative recovery is prolonged and dose limitations due to toxicity [1]. Indeed, the minority of patients complete the prescribed course of postoperative XRT [4]. Neoadjuvant external beam radiotherapy (XRT) for RPS has several potential advantages: target volume is apparent from preoperative imaging and the tumour acts as a displacement device, shielding adjacent viscera from toxicity [1,12–14]. Our group previously described the safety and tolerability of preoperative XRT for RPS [15].

Focal radiotherapy applied directly to the tumour bed can escalate the total dose to areas at particular risk for recurrence. Techniques such as intraoperative radiotherapy (IORT) and high dose rate brachytherapy (BT) delivered via afterloading catheters have potential in RPS, with the caveat of significant rates of ureteric stricture and neuropathy [16–18].

We previously reported the short term outcomes in a prospective trial of combined preoperative XRT, complete gross resection and postoperative BT for RPS [15]. In patients who received XRT and BT, postoperative mortality and grade IV morbidity rates within 3 months of surgery were 10% and 21%, respectively, leading us to amend the trial protocol and eliminate BT to the upper abdomen. The purpose of the present study is to describe the long-term survival rate in patients managed with preoperative XRT and resection, and to determine whether addition of BT provided any survival advantage.

Methods

Patients

From June 1, 1996 to May 10, 2000, all patients with RPS referred to the Sarcoma team at Princess Margaret (PMH) and Mount Sinai Hospitals (MSH), in Toronto, Ontario, were considered for enrolment in a phase II trial of preoperative XRT, combined with dose escalation with postoperative BT. Of 83 referred patients, 28 were excluded, and 55 were enrolled after informed consent [15]. The trial protocol was reviewed and approved by the REBs of PMH and MSH.

Inclusion criteria

All patients had biopsy proven soft tissue sarcoma arising from any retroperitoneal location and confirmed by pathology review at our institution. For consistency, we have maintained the original classification of malignant fibrous histiocytoma (MFH) when assigned. Patients had primary or recurrent RPS of any grade. Consensus on potential for complete gross resection and patient performance status suitable for multimodal therapy was required for entry.

Exclusion criteria

Patients were excluded if they (i) had recently undergone resection at another institution, (complete or incomplete) ($n = 14$); (ii) had evidence of metastatic disease or unresectable abdominal disease ($n = 12$); or (iii) did not consent to enrollment ($n = 2$) [15].

Multimodal treatment

Of 55 patients entered on study, nine experienced tumour progression and/or decline in performance status during XRT obviating resection. Median survival in this group was 2 months, and all 9 patients were dead within 6 months. Of the remaining 46 patients, all underwent grossly complete curative intent resection; 2 had undergone prior XRT and received BT only, while 4 received postoperative XRT with or without BT. This report focuses on the group of 40 patients who were radionaive, completed preoperative XRT and underwent curative intent resection.

Preoperative XRT technique

Radiation treatment planning conventions for this trial predate the 1999 ICRU-62 recommended conventions on radiotherapy contouring and nomenclature. The tumour volume was identified on the planning CT. A non-uniform normal tissue margin of no less than 1.0 cm and up to 2.0 cm was established about the tumour volume, comprising what is presently considered as CTV and PTV. The planning goal was to obtain coverage of this normal tissue volume with the 95% isodose line. Beam orientation and shielding was established to minimize dose to small bowel, liver and contralateral kidney. All patients underwent a standardized preoperative conformal external beam treatment protocol with 45 Gy fractionated over 5 weeks. A dose of 50 Gy over 5 weeks was allowed if the total dose to critical structures permitted. In this case the brachytherapy dose was reduced from 25 Gy to 20 Gy.

Surgical technique

Resection was undertaken 4–10 weeks following completion of XRT allowing maximal effect of radiotherapy and recovery from any short term toxicity. Major neurovascular structures were preserved where possible, but included in *en bloc* resection if technically necessary.

Brachytherapy technique

A single plane of afterloading BT catheters was placed on the resection bed intra-operatively (Fig. 1). Three to eight catheters were placed to create a planar implant, with orientation maintained by securing them with chromic catgut sutures to a polyglactin 910 mesh secured to the field at risk. The field at risk was designated as areas in close proximity to the tumour, which despite maximal resection were judged to have a high risk of residual microscopic disease, or where dissection was intimate to vital, unresectable structures. Initiation of BT was commenced with observable return of gastrointestinal function (postoperative days 7–14). Suitability of the implant was confirmed using dummy wires, and then radiation was commenced using afterloaded Iridium-192 seeds. In later years an Iridium-192 pulsed dose rate afterloading unit was employed. BT was given at a dose rate of 0.5 Gy/h and at a depth of 0.5 cm. The intent in all cases was to deliver 20–25 Gy via BT depending on the total preoperative external beam dose given. The typical reason for premature termination of brachytherapy was unacceptable displacement of the catheters during treatment.

Follow-up

Following discharge, patients were assessed with history and physical exam plus CT-AP and CXR every 4 months for 2 years, every 6 months until year 5, then annually. Recurrence was defined as a new or progressing mass on serial imaging, with or without biopsy confirmation. Recurrence was categorized as abdominal and/or distant.

Data collection

Clinicopathologic, treatment, and outcome data were collected in a prospective database from time of referral. Treatment related toxicities were evaluated and recorded prospectively [15]. Acute radiation toxicity during and after preoperative XRT were scored according to the contemporaneous RTOG scoring system.