Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 5, pp. 1480–1487, 2008
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0360-3016/08/$–see front matter

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doi:10.1016/j.ijrobp.2008.03.008

CLINICAL INVESTIGATION **Sarcoma**

EFFECTIVENESS OF RADIOTHERAPY IN MYXOID SARCOMAS IS ASSOCIATED WITH A DENSE VASCULAR PATTERN

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Purpose: **Surgery and adjuvant radiotherapy (RT) have long been the standard treatment for most deep-seated sarcomas; however, since the randomized trial from the National Cancer Institute of Canada, which described similar local control for pre- vs. postoperative RT, both modalities are now widely accepted. As a group, sarcomas are classified as radiation resistant. The subgroup of myxoid liposarcoma (MLS), a sarcoma with a typical vascular crow's feet pattern, is highly radiosensitive, but a mechanism for this phenomenon is unknown. Here we describe our results with preoperative RT and propose a mechanism explaining the high sensitivity based on the distinctive vascularization pattern of MLS.**

Methods and Materials: **Between 2002 and 2006, 31 sarcoma patients, including 10 with MLS, underwent preoperative RT at our institute. Resected specimens were histologically evaluated, focusing on classification, grade, and vascularization patterns.**

Results: **Twenty sarcomas showed more than 80% pathologic response after preoperative RT. A pathologic complete response was found in all "pure" MLS specimens after preoperative RT (n = 8). There were no pathologic complete responses in the remaining sarcoma patients (n = 23), although 12 showed 80% to 90% pathologic response. In contrast to the remaining RT-resistant sarcomas, the highly responding specimens contained branching vasculature, partial thrombus formation and inflammation of medium sized arterioles, similar to the vascular changes in MLS.**

Conclusions: **Both MLS and sarcomas with MLS-like vasculature are highly radiosensitive. Radiation sensitivity may be explained by changes in medium-sized arterioles, obstructing the specific crow's feet vascularization and inducing hypoxia with secondary tumor cell death.** **© 2008 Elsevier Inc.**

Sarcoma, Preoperative radiotherapy, Myxoid liposarcoma, Vascular.

INTRODUCTION

Surgery is the standard therapy for sarcoma, including liposarcoma. At our institute neoadjuvant radiotherapy (RT) is considered for all intermediate- and high-grade sarcomas with a tumor-free margin of less than 10 mm in the absence of an intact fascial layer and for all patients with recurrence who have not undergone RT at primary presentation. The aim of combination treatment is to achieve maximum local control while preserving functional outcome.

As a group, sarcomas are classified as radiation resistant. Although myxoid liposarcoma (MLS) is reported to be responsive to RT, with high rates of regression and even complete clinical response (1–5). The literature indicating high radiosensitivity remains, however, anecdotal (6). Moreover, older studies are difficult to interpret since different subtypes of (lipo)sarcomas have not been distinguished clearly and diagnostic criteria have changed over the years.

Until 2002, surgery followed by RT was the standard treatment for most deep-seated sarcomas. Because of the results of the randomized trial from the National Cancer Institute of Canada, which described a comparable local control for pre- and postoperative RT, both modalities are now widely accepted (7). High radiosensitivity of MLS was subsequently found in two retrospective reviews in which MLS specimens showed significant reduction in size after preoperative RT (8, 9). The mechanism responsible for this specific high radiosensitivity is, however, unknown. Preoperative RT creates the opportunity to investigate the specific effect RT has on

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Conflict of interest: none.

Acknowledgments—This manuscript is dedicated to the memory of J.L. (Hans) Peterse M.D., who tragically died suddenly during the project.

Received Jan 18, 2008, and in revised form March 3, 2008. Accepted for publication March 3, 2008.

specific sarcoma subtypes, which can lead to refinement of indications for RT in sarcoma management. As MLS is characterized by a very distinctive vascularization pattern, this feature may be related to its high radiation sensitivity.

Of all liposarcomas, MLS comprise 40% to 50%. Clinically, MLS are initially slow to progress and are predominantly located on the extremities, especially the thigh. Histologically MLS is characterized by the presence of a mucoid or gelatinous matrix and a delicate plexiform capillary pattern (Fig. 1a). The diagnosis is usually based on clinical, histologic, and immunohistochemical information; however, in cases of uncertain diagnosis, translocation analysis can reveal the genetic basis. In more than 95% of cases, MLS have shown a classic t(12–16) or a t(12–22) translocation similar to the more aggressive variant, round cell liposarcoma, resulting in a TLS-CHOP or a EWS-CHOP fusion oncogene, respectively. These translocations are therefore implicated in both oncogenic transformation and inhibition of adipogenesis (10).

Since 2002, preoperative RT has gained a prominent position in the management of sarcoma patients at our institution. The choice of preoperative RT is based on the expected narrow surgical margins near important neurovascular structures and on the histologic type and grade of the sarcoma. Here, we describe our experiences with preoperative radiation of 31 sarcoma patients and describe the histologic features and in particular the distinctive microvasculature. As part of this

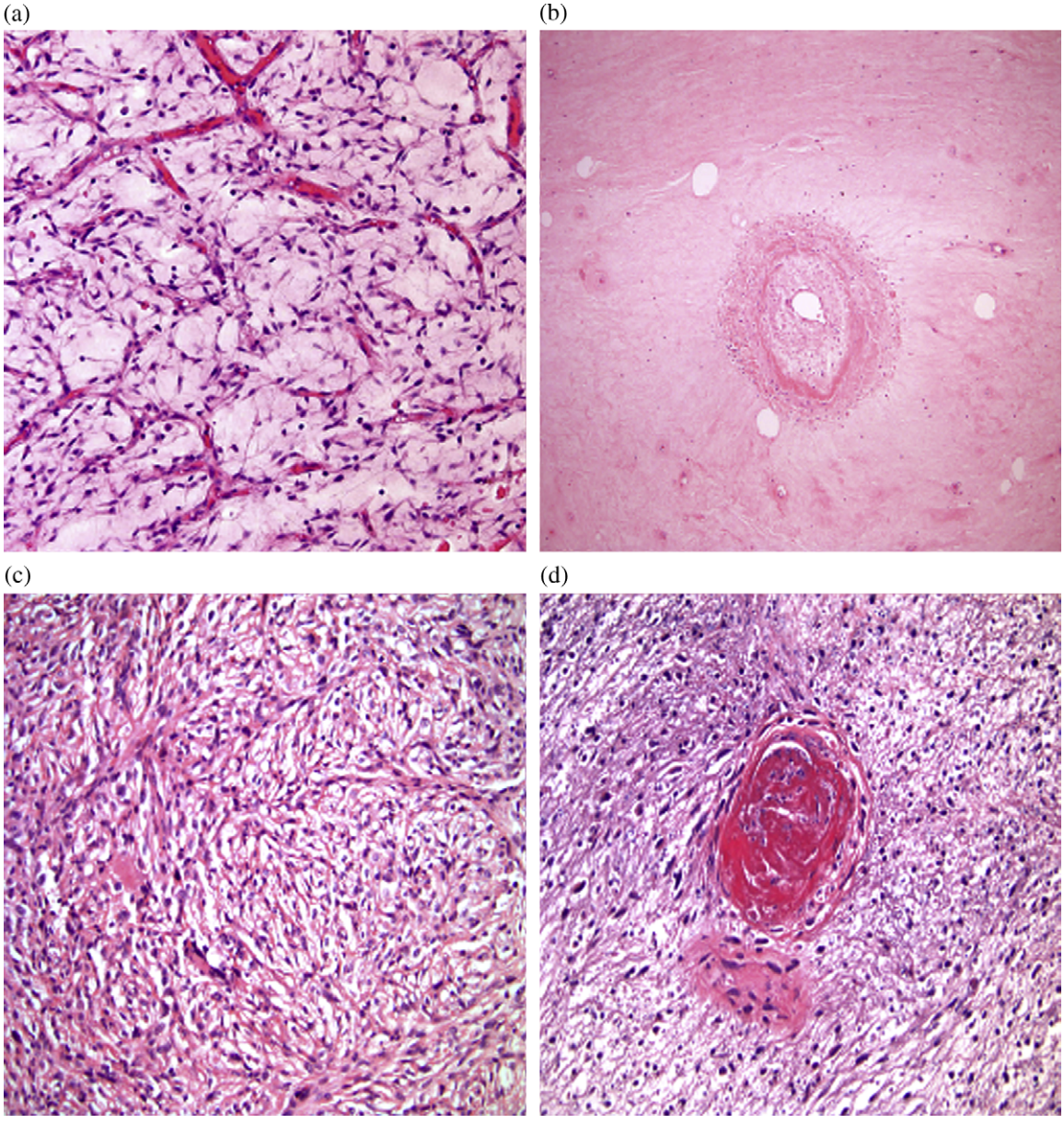

Fig. 1. (a, upper left) Myxoid liposarcoma (MLS) before radiotherapy (RT). Histology MLS with primitive mesenchymal cells and small lipoblasts in a prominent myxoid stoma with a specific crow's feet vascular pattern. (b, upper right) Arteriole MLS after RT showing a medium-sized arteriole with intima and basal membrane hypertrophy, surrounded by nonviable MLS tissue. (c, d) Sarcoma with MLS-like vasculature, showing near complete pathologic response, with typical arteriolar damage similar to MLS damage.

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