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Invited review

Selected aspects of soft tissue sarcoma

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This is a review of selected aspects of management of adult patients with soft tissue sarcoma and a consideration of several recent developments. Mention is made of the evidence that there are unique gene clusters for at least several of the pathological types of soft tissue sarcoma. This is judged to be a precursor of coming advances in genetic-based diagnosis and the potential for prediction of biological behavior and response to the diverse treatment strategies. There has been remarkably rapid development of clinically valuable imaging techniques (CT, MRI, dynamic MRI, MRS, and PET) separately or using image fusion techniques which not only provide superior delineation of limits of extension of tumor but also their physiological status. These techniques are likely to be integrated into the treatment delivery system to provide four-dimensional treatment planning and delivery. One new method for determination of the involvement of lymph nodes by metastatic tumor is presented which has high accuracy for nodes ≥6 mm in size. The rationale for employing radiation prior to or following resection is considered and then the results at three years of the Canadian Phase III Trial of pre vs post operative radiation therapy for patients with soft tissue sarcoma are presented. Similar local control but higher overall survival rates were found for the pre-operative arm; however, there was a significantly higher rate of wound healing problems. Then the potential for major gains in the effectiveness of radiation based on improving technologies against these tumors is considered. An anti-angiogenic agent (the antibody to Vascular Endothelial Growth Factor 2, DC 101) has been shown to reduce significantly the radiation dose to inactivate two human tumor xenografts. Further, studies on C3H mice bearing spontaneous autochthonous fibrosarcoma have shown significant growth delay by that same antibody.

Mięsaki tkanek miękkich – wybrane zagadnienia

W pracy przedstawiamy wybrane zagadnienia dotyczące mięsaków wywodzących się z tkanek miękkich, z uwzględnieniem kilku nowości. Wspominamy o dowodach na istnienie unikalnych klasterów genów dla co najmniej kilku typów histopatologicznych mięsaków. Sądzi się, że jest to zapowiedź postępu w zakresie diagnostyki genetycznej, który może pozwolić ocenić biologię nowotworu oraz pozwolić przewidzieć odpowiedź na różne metody terapeutyczne. Omawiamy również znaczny postęp w dziedzinie technik obrazowania (CT, NMR, MRS i PET) tak osobno, jak i z zastosowaniem fuzji obrazów, umożliwiającej nie tylko dokładne ustalenie granic naciekania guza, ale również ocenę fizjologiczną. Należy sądzić, że opisane techniki zostaną wykorzystane w radioterapii, aby umożliwić czterowymiarowe planowanie leczenia i ułatwić podaż dawek. Opisujemy nową metodę oceny zajęcia węzłów chłonnych przez przerzuty. Metoda ta cechuje się bardzo dużą dokładnością w przypadku węzłów o średnicy ≥6 mm. Przedstawiamy naszą opinię na temat naświetlania przed i pooperacyjnego oraz wyniki zebrane podczas trzech lat trwania Canadian Phase III Trial, porównującego wyniki przed i pooperacyjnego naświetlania u chorych z mięsakami tkanek miękkich. U chorych naświetlanych przed operacją obserwowano dłuższe przeżycia całkowite i podobne wyniki w zakresie wznowy miejscowej, niemniej występowało u nich znamiennie więcej powikłań gojenia się ran pooperacyjnych. Następnie przechodzimy do omówienia możliwości poprawy skuteczności radioterapii w oparciu o techniki naświetlania stosowane w mięsakach tkanek miękkich, wspominając, że zastosowanie specyficznego czynnika hamującego angiogenezę (przeciwciało przeciw II czynnikowi wzrostu śródbłonka naczyniowego/Vascular Endothelial Growth Factor 2/ DC 101) przyczyniło się do znamiennego zmniejszenia dawki promieniowania, koniecznej do inaktywacji dwóch ludzkich mięsaków przeszczepionych międzygatunkowo. Co więcej, zastosowanie wspomnianego przeciwciała u myszy szczepu C3H, u których wystąpiły autochtoniczne, spontaniczne nowotwory o typie fibrosarcoma, znamiennie opóźniło wzrost guza.

Key words: imaging techniques, soft tissue sarcoma, radiotherapy
Słowa kluczowe: techniki obrazowania, mięsaki tkanek miękkich, radioterapia

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Introduction

The progressive growth of medical sub-specialization has resulted in several medical centers with teams of physicians, scientists and support staff who concentrate their professional careers to improving the management of patients with soft tissue sarcoma. These teams are comprised of sarcoma specialists in orthopedic and general surgery, adult and pediatric medical oncology, radiation oncology, pathology, diagnostic radiology, tumor biology, biostatistics, nursing, data and protocol management. The expectation is that such concentration of talent does result in a higher standard of patient care and an acceleration of advances in this field. Such commitment of time and effort to this one category of tumors has, to this date, had a clearly positive impact.

In this paper, consideration is to be given to a several selected aspects of the present and potential future care of patients with soft tissue sarcoma.

Diagnosis

Diagnostic Radiology

Current imaging studies employed in nearly all patients suspected of having a soft tissue sarcoma are plain films, CT and MRI (with contrast) and increasingly PET. Dynamic MRI and MRS imaging are being evaluated and with promising results. Changes in tumor volume following radiation have not been established as useful predictors of the radiation effect in terms of the critical end-point, viz clonogen cell kill.

Presently available imaging methods do provide clinically useful information as to the sarcoma size, exact anatomic site, local pattern of extension and distribution of necrosis. In the not distant future, the character of metabolic activity throughout the tumor should become available.

Here, mention is made of a potentially important advance in assessment of the nodal status. Soft tissue sarcoma infrequently has metastatic disease in regional lymph nodes. However, the frequency is clinically important for grade III sarcomas >5 cm and all epithelioid sarcomas and rhabdomyosarcomas [1]. A new technique for imaging of the regional nodes is briefly described which will be tested on sarcoma patients in the near future. Harisinghani et al at MGH employ an iron oxide compound which is administered systemically and is taken-up nearly uniformly by lymph nodes throughout the body [2]. On post-injection MRI, the normal nodes are uniformly black. Any portion of the node involved by tumor does not take up iron and is, accordingly, visualized as white due to the absence of iron. An example of this new imaging method is presented in Figures 1a and b from a study of the axillary nodes in a patient with carcinoma of breast. As shown in Fig. 1 a, only size and number of the nodes can be determined from the MRI prior to injection of the contrast agent. Following injection of the iron oxide, the normal nodes are black, Fig. 1 b. In one node, there is a white region, viz the portion of the node, which did not collect the iron oxide. This node was proven to be a site of metastatic tumor. Harisinghani and team have had a >95% accuracy in studies of patients with pelvic cancers in the identification of nodes of ≥6 mm which have metastatic tumor.

Pathology

Histopathologic diagnosis is a critical component of the patient management. The biopsy needs to be planned by an experienced member of the team in order that there is no negative impact on the definitive treatment due to improper placement of the core needle track or scar for an incisional biopsy. That is, these have to be sited so as to be included in the surgical specimen or in the radiation treatment volume. Regrettably, there is not a rare patient

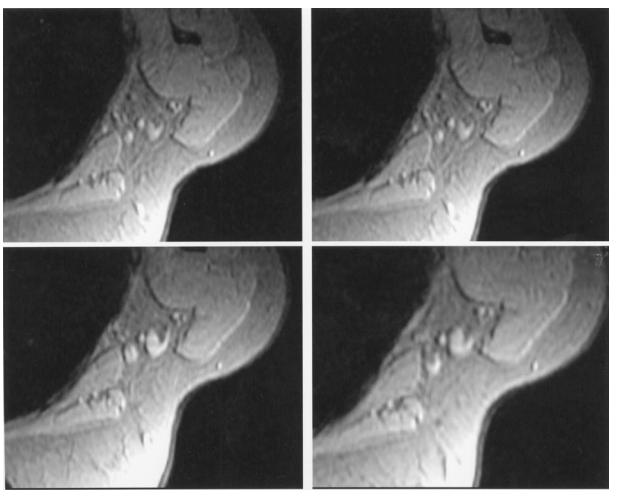

Figure 1a

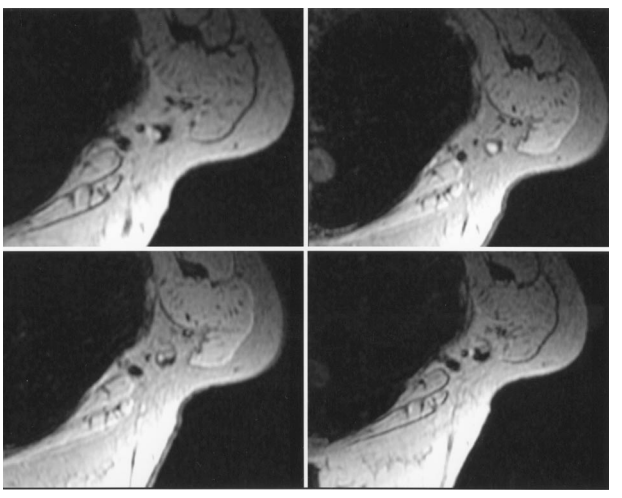

Figure 1b

Figure 1. MRI images of the axilla after injection of an iron oxide contrast agent into a patient with carcinoma of the breast. **Figure 1a** is prior to injection and clearly demonstrates normal appearing nodes. In **Figure 1b**, the normal nodes are black except for a portion of one node that is devoid of contrast, the site of a focus of metastatic tumor

whose biopsy site forces a less than optimal definitive treatment.

Pathological diagnosis is becoming progressively more objective with the use of immunohistochemical staining, karyotyping and cDNA array genetic characterization. From the latter, the expectation is not only more accurate diagnosis of tumor type, but also reliable information for prediction of the biological behavior and quantitation of response to the planned treatment (radiation, drug, biological agent, immunologic, genetic, etc.). There appears to have been substantial achievement by genetic techniques in the definition of the type for several categories of tumors. The Vancouver and Stanford groups have reported in Lancet [3] their analysis of the expression of 5520 genes in a series of 41 soft tissue sarcomas by cDNA array technology. Quite impressively their data indicate that there are distinctive clusters of genes for monophasic synovial sarcomas (104 genes, including synovial sarcoma X (SXX), retinoic acid pathway genes and epidermal growth factor receptor gene) and gastrointestinal stromal tumors (125 genes}. Of special interest was the finding that of 11 leiomyosarcomas, 6 expressed a cluster of 24 genes associated with muscle structure and function while most of the other 5 did not exhibit expression of any of these genes, but were, however, Desmin positive. Within a short time, there will almost certainly be accrual of substantial additional data which will provide the basis for increasingly objective criteria for designation of the pathological type of sarcoma. Not as rapid in the realization will be the availability of new genetic information on the tumor cells and the cells from several relevant normal tissues which will prove to be of enormous value in planning the management strategy of the sarcoma patient.

Management of the primary soft tissue sarcoma (non rhabdomyosarcoma), stage M0

There are two general goals for the management of patients with soft tissue sarcoma: 1) eradication of all local, regional and distant disease and 2) the production of no complications and minimal functional and cosmetic deficit. At present all treatment methods have some associated short and long term morbidity. Defining the management strategy which realizes the best available balance between cure probability vs overall functional/cosmetic outcome will rely on an increasingly complex data base for each patient.

Surgical resection is recommended for virtually all Stage M0 patients. To decrease the extent of resection of grossly uninvolved normal tissues, surgery is combined with radiation in a large proportion of patients. The rationale is the high frequency of microscopic extension of sarcoma beyond the limits of the gross lesion (imaging and clinical examination). According to present understanding, permanent local control requires the removal or eradication of 100.0% of tumor clonogens. Thus, surgical margins must be wide of the grossly evident disease to include all of the sub-clinical disease. These wider margins mean further reduction in the functional and cosmetic outcome. That radiation in moderate dose levels is effective in killing all of the cells in the microextensions has been established. Hence, a combination of less than radical resection with moderate radiation doses is an effective approach for control of the local disease. Two immediate questions are 1) what is the evidence that radiation is a useful modality against soft tissue sarcomas; and 2) if effective, what is the most effective sequence of the two modalities?

The early experience with radiation in the treatment of patients with soft tissue sarcoma was interpreted by clinicians to show that radiation was of no clinical value for those tumors [4]. The basis for that opinion up to the 1960's was due to: 1) treatment of large lesions; 2) use of radiation alone; 3) due to technical factors, the radiation dose was low (<50 Gy); and 4) efficacy was judged by speed of regression. None of these factors apply today. Ruka [5] determined the *in vitro* survival fraction at 2 Gy for a series of cell lines derived from soft tissue sarcomas and a series from carcinomas of the breast. There was no difference in the radiation sensitivity between the two series of cell lines, as shown in Figure 2. There is now ample documentation that resection of small carcinomas of the breast and of soft tissue sarcomas (≤4 cm) and post-operative radiation therapy yields local control probabilities of ≥90% at 5 years [6]. Thus, the available evidence suggests that malignant epithelial and mesenchymal tumors (non-exophytic) of a specified volume require approximately the same dose to achieve a defined tumor control probability.

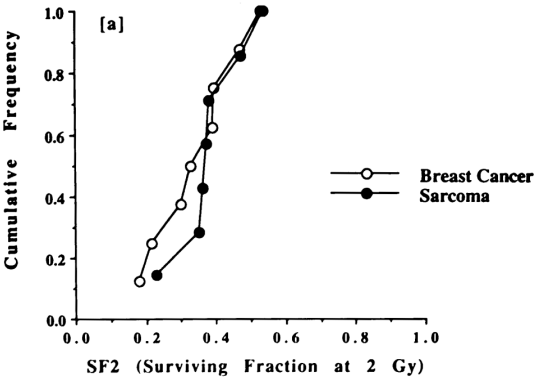

Figure 2. Cumulative frequency of survival fractions at 2 Gy of cell lines derived from carcinomas of the breast and from soft tissue sarcomas as determined *in vitro* [5]

Surgery may be recommended as the sole treatment for lesions, which can be resected with widely negative margins while retaining good function and cosmesis. Unfortunately, sarcomas which meet this requirement are uncommon, *viz*, small lesions in relatively fleshy parts. To avoid a margin which is close at some point requires loss of important anatomic structures in a high proportion of sarcomas at the elbow, wrist, hand, ankle, foot and many sites in the head and neck region. Thus, even for

small low-grade lesions at these sites, conservative surgery and radiation would be expected to yield better functional results for many such patients. Generally, satisfactory margins for surgery alone are judged to be the closest margin which is proven to be negative at ≥2 cm. Our experience has been that the narrowest margin is rarely greater than 10 mm even for lesions of the thigh and torso. A closer margin may be entirely acceptable when that margin is an intact fascial plane or bone.

For the great majority of sarcomas, the preferred management by the MGH Sarcoma team is the combination of pre-operative radiation and surgery. Our experience is that radiation administered pre-operatively has several significant advantages relative to post-operative irradiation. These include:

1. The volume of irradiated tissues is substantially less due to the fact that the treatment volume is planned entirely on the defined volume of tumor (gross and sub-clinical) and the anatomic site. No consideration is, of course, given to the tissue planes to be handled subsequently by the surgeon. In contrast post-operative treatment includes the entire surgical bed. That is, the rationale for administration of radiation post-operatively is that tumor cells had been spilled into the tumor bed and or there are microscopic foci in the tissues adjacent to the surgical margins. The latter constitutes "cut-through" of tumor. The implication is tumor cell contamination of the entire tumor bed. The difference in treatment volume has been quantitated in the study by Nielsen et al from the Ontario Cancer institute [7] and shown to be substantial. The lesser volume of irradiated tissues results in less severe and less frequent late radiation changes in normal tissues.
2. The radiation dose is significantly lower in nearly all patients. Namely, for pre-operative irradiation the dose is ~50 Gy in 5 weeks *vs* ~66 Gy for post-operative irradiation to margin negative patients.
3. The basis for the higher dose in post-operative treatment is, perhaps, that during the 2-4 weeks between surgery and the start of post-operative treatment, the residual tumor clonogens are bathed in all of the cytokines the local tissues can muster to accelerate wound healing. There is virtual certainty that those same cytokines accelerate tumor clonogen proliferation. The result is that by the start of post-operative radiation, there are a larger number of tumor cells, which must be killed than obtains for radiation administered prior to surgery.
4. There is essentially no risk of autotransplantation of tumor in the surgical bed or of distant metastasis developing from cells spilled into the tumor bed or exfoliated into the blood vascular spaces during the surgical procedure. Comparatively low doses, *e g*, ~2 Gy x 10, appear to be effective in prevention of wound seeding. This contrasts with the need for some 50 Gy to inactivate very small foci of established tumor.
5. There is no delay in the start of radiation treatment. For large tumors or in anatomic sites with poor or compromised vascular supply, there may be long delays before healing is adequate for the commencement of the post-operative radiation. We have seen gross tumor regrowth prior to the start of radiation therapy when wound healing has been slow.
6. Some inoperable lesions may become operable following the pre-operative treatment.
7. Pre-operative treatment is much more likely to involve multidisciplinary planning of overall strategy.
8. This approach does demand special care in planning the treatment so as to include the minimum of normal tissues not judged to be involved by sub-clinical extensions of tumor in the treatment volume. This decreases the probability of delay in wound healing. Further, the surgeon needs to handle the irradiated tissues with greater care than when operating on unirradiated tissues. Additionally, the wound needs to be closed in layers and to avoid tension. This latter may require use of vascularized flaps, grafts etc. Microvascular surgery is making significant contributions to the success of grafting in difficult circumstances.

There are advantages to radiation given following surgical resection. These include:

1. There is no delay to surgery. For some patients, there is anxiety to "have the tumor out".
2. The complete and untreated tumor specimen is available for pathological study.
3. Were chemotherapy given pre-operatively, an estimate of the response to the drugs may be made
4. There is no radiation impairment of wound healing.

O'Sullivan et al, have published the preliminary results from the important Canadian Phase III trial designed to assess the relative efficacy of treatment of patients with extremity soft tissue sarcoma stage M0 by pre vs post operative radiation therapy [8]. There were 94 and 96 patients for the pre and the post operative arms, respectively. Treatment was 50 Gy at 2 Gy/fraction over ~ 5 weeks pre-operatively vs 66 Gy post-operatively also at 2 Gy /fraction. At a median follow-up of 3.3 years, there was comparable local control at ~90%. Overall survival was 85% vs 72% favoring the pre-operatively treated patients. There was a significantly higher wound healing delay in the pre-operatively irradiated patients, *viz*, 35% *vs* 17%. Longer-term follow-up is required to assess the impact of the much larger treatment volumes and higher dose in patients treated post-operatively. Importantly, the available evidence from their trial is that the late fibrosis is less severe in the pre-operatively irradiated patients. This is as expected as the pre-operative group had a substantially lower dose and also a smaller treatment volume

Bujko et al, [9] analyzed the surgical wound complication frequency among 202 patients managed at Massachusetts General Hospital by pre-operative radiation and surgical resection. The incidence of complication was also 37%. This is comparable to the Canadian experience vide supra. Of these 16% required some form of surgical procedure to facilitate healing. Our conclusion

is that there must be special care with the irradiated tissue, namely avoidance of tension in closure, closure of the wound in layers, and use of flaps *etc*, to avoid tension and secure good approximation of the sides of the defect so as to minimize any seroma.

Potential for further reductions in treatment related morbidity

The incidence and grade of morbidity secondary to the radiation is almost certainly to decrease in the coming 1-2 decades due to the impressive technical advances in the planning and delivery of radiation therapy. These improvements are to be due to: 1) major advances in imaging technology, *e g*, fusion of images from diverse methods, more accurate assessment of the anatomical extent of tumor and the biological characteristics of the tumor; 2) ability to assess tumor response (other than change in size) during the progress of the treatment; 3) much wider availability of IMRT and proton radiation beams; and 4) four dimensional treatment planning and delivery, i *e*, techniques to assure that the target is correctly positioned in the treatment beam throughout each treatment session. Thus, the treatment volume will include a smaller volume of adjacent normal tissues. For example for a thigh soft tissue sarcoma, only a small proportion of the adjacent bone need be within the high dose volume, and thereby diminish the frequency of fractures through bone uninvolved by tumor (even bones which have not had periosteal stripping. Additionally, there should be vastly improved strategies for timing of the administration of drugs or agents relative to each irradiation session.

Management of occult metastatic sarcoma in the stage M0 patients

Due to the important probability of the presence of metastatic disease in patients with intermediate to high-grade sarcomas of 5 cm or larger who are staged as M0. Many centers administer intensive chemotherapy to selected categories of such patients.

The question for soft tissue sarcomas (non-rhabdomyosarcoma) is the relative gain in long-term freedom from distant metastasis in local control patients versus serious morbidity due to the systemic therapy. Unfortunately, chemotherapy has not been as effective for the soft tissue sarcoma as for osteogenic sarcoma in enhancement of disease-free survival at 10 years. Even so there does appear to be a real benefit of neo-adjuvant chemotherapy.

At MGH, our current practice for patients with intermediate to high-grade sarcomas of ≥8 cm and Stage M0 is to recommend MAID chemotherapy and radiation prior to resection. These patients have a high probability of developing distant metastasis even though local control is achieved. Accordingly, we administer both the chemotherapy and radiation pre-operatively, i.e., to tumors with unperturbed circulation. Our current protocol is 3 cycles of MAID and two cycles of radiation prior to surgery: one radiation cycle is given between MAID cycle one and two and then a second between MAID cycles 2 and 3. Each radiation cycle is 2 Gy x 11, i e, a total of 44 Gy pre-operatively. Were there to be a positive surgical margin, a post-operative boost dose of 16 Gy is given before MAID cycle 4-6. Generally, this program is with serious hematologic morbidity [10] and an increased delay in wound healing. This was of the same order as found be Bujko [9].

DeLaney et al have updated the outcome analysis in 48 patients with large high grade sarcomas of the extremities treated at Massachusetts General Hospital on the radiation – MAID pre-operative protocol. There were 48 control patients who were treated over a similar time period and matched for sarcoma grade and size. The five-year local control results were 92% and 86% (NS), while the metastasis free survival was 75% and 44% respectively ($p<0.01$), for the test and control patients (DeLaney submitted for publication 2002). These data indicate that for the patients with grade II-III sarcomas, the MAID chemotherapy given pre-operatively does effect an increment in metastasis free survival.

At present, there are substantial numbers of clinical trials of new agents or combinations of established agents by the US NCI and the EORTC. These include trials of: Antineoplastons A 10 and AS2-1; Ecteinascidin 743, Irnotecan, Rosiglitazone, Temozolimide, TNF α, hyperthermia, limb perfusion with a variety of agents and a spectrum of anti-angiogenic agents. There is a high likelihood of positive yields from, at least, a few of these diverse efforts.

Anti-angiogenic agents

Brief mention is made of two recent laboratory results from the MGH radiation oncology group. Kozin et al, [11] first demonstrated a significant reduction in the radiation dose required to inactivate two human tumor xenografts by the combination of radiation and DC 101, an anti-vascular endothelial growth receptor-2 antibody. Izumi et al, have shown a significant and marked growth delay of the spontaneous autochthonous fibrosarcoma of the C3H mouse by DC 101 (submitted for publication, August 2002}. These findings are a positive indication that some benefit can be expected at the clinical level for use of one or more anti-angiogenic agent against appropriately selected tumors.

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