

Scientific Symposium (Mon, 26 Sep, 14:45–16:45) New Avenues in Soft Tissue Sarcoma

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INVITED

Unplanned Excisions of Soft Tissue Sarcoma Results in Increased Rates of Local Recurrence Despite Full Further Oncological Treatment (Clinical, Biopsy, Surgery, Imaging)

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Background: Unplanned excision of soft tissue sarcoma (STS) accounts for up to 40% of all initial operations for STS and are undertaken when the mass is presumed to be benign. The effect this has on outcome has never been fully established.

Methods: Patients with extremity or trunk STS between 2001 and 2005 who were treated by an initial inadvertent operation and then referred immediately to our Unit were identified. Outcomes were compared to a control group of patients with STS who were Stage matched, and had been treated conventionally by core biopsy and definitive surgery. Endpoints were local recurrence, distant metastases and sarcoma-specific survival.

Results: 134 patients who had undergone an unplanned excision of a STS were identified. 121 underwent a further re-excision and 51 (48%) of these patients had residual tumour identified after surgical re-excision. 209 Stage matched controls were identified who were treated conventionally. Median follow-up was 51.6 months.

Local recurrence rates were considerably higher in the study group (23.8% vs. 11%, $p=0.0016$), despite the control group having more Stage 3 tumours. When the tumours were matched by Stage, an increase in local recurrence was seen across all Stages but was most pronounced for Stage 3 tumours (37.5 vs. 14.2%, $p=0.005$). Metastasis-free and sarcoma-specific survival was also significantly increased for Stage 3 tumours.

Stage	Cohort	Recurrence, n (%)	P
Stage 1	Study ($n=60$)	11 (18.3%)	0.023
	Control ($n=74$)	5 (6.7%)	
Stage 2	Study ($n=58$)	15 (25.8%)	0.1274
	Control ($n=37$)	4 (10.8%)	
Stage 3	Study ($n=16$)	6 (37.5%)	0.0051
	Control ($n=98$)	14 (14.2%)	

Conclusion: Unplanned initial excisions of extremity soft tissue sarcomas may compromise long-term local control of extremity STS despite full further oncological management.

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Soft Tissue Sarcoma as a Model for Targeted Treatment and Drug Development

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The recent progress of the biology of the locally aggressive sarcomas of soft tissues and related connective tissue tumours enabled to reclassify molecular and histological entities of the disease. Five subgroups of sarcomas and connective tissue tumours may be identified with specific types of driving molecular alterations: 1) sarcomas with specific translocations with fusion oncogenes (e.g. Ewing sarcomas), 2) sarcomas with tyrosine kinase mutations (KIT in GIST); 3) tumours with deletion of tumour suppressor genes (TSC in the PEComas, NF1 in MPNST of type 1 neurofibromatosis), 4) sarcomas with MDM2/CDK4 amplification in the 12q13–15 amplicon (e.g. well differentiated or dedifferentiated liposarcomas); 5) sarcomas with complex genetics present more refined genetic changes (leiomyosarcomas, osteosarcomas). In addition to these 5 groups, locally aggressive tumours, e.g. desmoids tumours are also characterized by alterations of the Wnt, beta catenin, APC, while giant cell tumours of the bone (GCTB), are characterized by RANK/RANKL activation through a complex interaction between the cellular stroma and giant tumour cells.

The identification of these abnormal pathways has been shown to guide efficiently the development of effective targeted therapeutic agents against sarcomas in particular GIST and DFSP (imatinib), GCTB (denosumab), and to a more limited extent PEComas, endometrial stromal sarcomas, Ewing sarcomas, ... Among the recent examples, imatinib has been shown efficient for the treatment of DFSP, characterized by a translocation of the gene PDGF, or in pigmented villonodular synovitis (PVNS), a tumour of soft

part also locally aggressive, caused by an abnormality of the gene coding for the M-CSF. Several clinical trials of phase I and II trials demonstrated the antitumour activity of anti-IGF1R antibodies in Ewing, whose fusion gene downregulates IGFBP3. Inhibitors of MDM2 have been reported to exert biological antitumour activity in liposarcomas with MDM2 amplification. Inhibitors of mTOR (sirolimus, temsirolimus) demonstrated an antitumoural activity in the PEComas.

The molecular characterization of sarcomas allowed to develop efficiently novel targeted therapeutics in these rare subsets of tumours. Because of the knowledge of driving molecular alterations, sarcomas represent optimal models for the development of targeted treatments. Translational research is and will be an essential tool for the development of new treatments and the identification of the mechanisms of response and resistance set up by these tumours.

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Innovative Radiotherapy Approaches in Soft Tissue Sarcoma

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The role of radiotherapy in soft tissue sarcoma (STS) has recently evolved with the development of conservative surgery, particularly in the progressive generalisation of a limb preservation combined strategy. Not unlike in breast cancer, 30 years ago.

STS are rare tumours, with more than 50% in limbs (especially lower limb). The low frequency explains the lack of firm, level 1 evidence for the current combined strategy. Still, the preservation of limbs is a goal sufficiently desirable for the combined approach to have gained general acceptance, if, and only if, the prospect of preservation implies a sufficient functional result (motility). Sometimes, unfortunately, a well conducted amputation remains preferable, but this is in a minority of case today.

Current indications include: high grade tumours (high local relapse rate), tumours larger than 5 cm, deep-seated (in muscle compartments), with a high probability of marginal excision or positive margins (contact with bone, with neuro-vascular bundles).

The role of radiotherapy is to help surgery to provide for a high local control rate while conserving the function. Radiotherapy side-effects and complications must be minimised to achieve this goal.

1. Skin is one limiting tissue, with a high risk of sclerosis after irradiation, especially of the resection path. There is currently little that can be done to limit sclerosis. Specific drugs have been used like pentoxifylline and α -tocopherol with limited success. Research is on-going in the field of radiation sclerosis to limit its severity. Preoperative irradiation is also more skin-sparing compared to postoperative RT.
2. Bone preservation: constraints have been developed for the prevention of radiation-induced bone fracture ($V40 < 64\%$), Dmean < 37 Gy, Dmax < 59 Gy.
3. A preoperative approach, in addition to sparing the skin, has also the advantage of reducing the overall irradiated volume (the CTV is easily identified and the tissues undisturbed by surgery), reducing the total radiation dose (50 Gy instead of 60–66 Gy). It has the disadvantage to increase wound healing problems, especially in lower limbs.

A preoperative approach is thus appealing, as the total dose and the total irradiated volume are two main contributors to the risk of long-term functional damage after irradiation. Wound healing is certainly an issue of importance, but it is a more temporary problem than functional damage.

Last but not least, the irradiation technique contributes to a better functional outcome by implementing image-guided procedures that help for a better day-to-day repositioning and a reduced PTV margin for set-up errors. Indeed, limbs are particularly difficult to immobilise and irradiate reproducibly, partly due to the lack of good bony landmarks (long, straight bones do not offer optimal information for repositioning).

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Who Needs a (new) Histopathological And/or Molecular Classification?

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The last WHO classification dates back to 2002. The main strength of the new scheme was represented by the integration of classic morphology, immunophenotype and genetics. On that occasion a precise definition of benign, borderline and malignant soft tissue tumours was provided. Many new entities were introduced for the first time and classic labels such as "malignant fibrous histiocytoma (MFH)", hemangiopericytoma (HPC), and fibrosarcoma were deeply reshaped. In addition the use of the FNCLCC grading system was endorsed. The 2002 WHO classification has certainly gained broad acceptance however, during the last 10 years substantial new data has been generated that fully justifies a revision.