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

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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 unrefined 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 antitumoral activity in the PEComas.
The molecular characterization of sarcomas allowed to develop effciently 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 is soft tissue sarcoma (SST) 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.
SST 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 pentoxyphilline and a-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 fist 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.

1. It has become clear that labels such as MFH and HPC no longer represent distinctive tumour entities, to the extent that their use may represent source of diagnostic confusion.
2. New entities has been reported showing distinctive morphological, genetic and clinical features. Important examples are represented by “pseudomyogenic hemangioendothelioma” and “myoepithelioma of bone and soft tissue”.
3. New genetic data have been reported in benign, borderline and malignant lesions. Among them nodular fasciitis, angiomatoid “malignant” histiocytoma and epithelioid hemangioendothelioma.
4. Recent data have shown that the prognostic value of translocation in sarcoma (Ewing’s sarcoma, synovial sarcoma and alveolar rhabdomyosarcoma) is less robust than initially hoped.
5. A prognostic signature based on array CGH (CINSARC) has been developed that may significantly improve our capacity to discriminate among thoe patients belonging to the somewhat “grey” G2 category.
6. Following the success of imatinib therapy in GIST other molecular targets has been investigated: ALK in inflammatory myofibroblastic tumour, mTOR in malignant PEComa and MDM2 in dedifferentiated liposarcoma all represents important example underscoring the necessity to define robust predictive biomarkers.

These only represent examples of recent advances in the field of soft tissue tumours that certainly support the opportunity to update the currently available classification scheme.

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Treatment of Dyspnea − What Does the Evidence Support?

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Inhaled Furosemide − Yes or No?

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Breathlessness is a prevalent symptom in patients with cancer, and can be difficult to treat. Furosemide is a safe and relatively cheap drug, with few adverse effects. Evidence from two case series and a case report has suggested that nebulised furosemide may relieve dyspnoea in patients with advanced cancer. However, two small, randomised controlled trials evaluating furosemide in patients with cancer have failed to show benefit. Inhaled furosemide cannot, therefore, be recommended for the palliation of dyspnoea on the basis of current evidence.

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The Role of Opioids in Alleviating Cancer-Related Dyspnea

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Up to 50% to 70% of terminally ill cancer patients experience dyspnea in the last 6 weeks of life, and the symptom is aggravated with disease progression. Dyspnea causes suffering and severely hampers the patients’ quality of life. Despite a paucity of prospective randomized trials, the literature review lends support to the use of opioids for the alleviation of dyspnea in cancer patients. There is evidence that subcutaneous morphine is effective in treating dyspnea in advanced cancer patients. The role of nebulized morphine remains less certain because it has been found to be equally effective to subcutaneous morphine, yet its superiority compared with placebo had been documented only partially. Most studies assess the short-term effect of opioids on dyspnea. Future studies are needed to evaluate the effects of opioids in alleviation of dyspnea for longer periods of time.

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The Efficacy of Benzodiazepines for Palliating Dyspnoea: a Systematic Review

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Background: Breathlessness is a common devastating symptom of advanced cancer reaching prevalences of 90% in patients with lung cancer. It has a profound effect on patients and families and current palliative strategies are ineffective. Benzodiazepines are commonly used for this symptom.

Materials and Methods: A Cochrane Review of benzodiazepines in breathlessness was carried out using standard protocol. Papers were checked independently by two reviewers.

Selection criteria: Randomised controlled trials (RCTs) and controlled trials (CTs). *Participants*: Adult patient with breathlessness from malignant/advanced non-malignant diseases.

Intervention: Benzodiazepines compared with either placebo or other drugs.

Outcomes: Subjective measures of breathlessness as primary outcome. Study quality assessed using Jadad scale, Edwards score.

Results: Meta-analysis was conducted where appropriate; 7 studies were identified including 200 analysed participants with advanced cancer and COPD. Analysis of all seven studies (including meta-analysis of 6 out of 7) did not show beneficial effect of benzodiazepines on breathlessness severity in this group. Furthermore no significant effect was observed in the prevention of breakthrough dyspnoea in cancer patients. Sensitivity analysis demonstrated no significant differences regarding type of benzodiazepine, dose, route, frequency of delivery, duration of treatment or type of control.

Conclusions: There is no evidence to support the use of benzodiazepines in breathlessness in patients with advanced cancer. Benzodiazepines anecdotally are consistently observed to be helpful but should be used as a second or third line treatment within an individual therapeutic trial when opioids and non-pharmacological treatments have first been used to maximum effectiveness. There is a need for further well-conducted and adequately powered studies in those differentiating between end of life (last few days) and the last few months of life.

References

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Pleural Effusion Management

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Malignant pleural effusions are defined by the presence of malignant cells within the pleural space. They are a frequent clinical problem in oncology, present in about 20% of patients who die from cancer. Metastatic breast and lung cancers represent 50−65% of the causes of malignant pleural effusions.

The diagnosis may be made on pleural fluid obtained through thoracocentesis in about 60% of cases, but may necessitate a thoracoscopy, the only procedure with a nearly 100% sensitivity. About 20% of pleural effusions in patients with known cancer are unrelated to the underlying malignancy. The overall prognosis of patients with malignant pleural effusion is poor, with median survivals ranging from 3 to 12 months, depending mainly on the stage and type of the underlying malignancy and the patients’ performance status.

Besides treating the cause (i.e., the underlying malignancy), treatment options include (a) observation in patients with asymptomatic effusions if the diagnosis is known, (b) iterative therapeutic pleural aspirations, mainly in patients with slow recurring effusions or a short life expectancy, (c) small-bore (10−14F) intercostal tube drainage followed by pleurodesis, (d) thoracoscopic pleurodesis and (e) long-term ambulatory indwelling pleural catheter drainage.

Thoracoscopic talc pleurodesis remains the therapeutic reference, but it can be performed only in patients with a performance status $\leqslant 2$ and a satisfactory lung re-expansion following pleural evacuation. Talc pleurodesis appears equally effective when administered as a slurry through a chest tube or by insufflation under thoracoscopic control.

Long-term ambulatory indwelling pleural catheter drainage is indicated in case of pleurodesis failure (i.e., recurrence of a symptomatic effusion) or contraindication (trapped lung). This technique is increasingly used as a first line treatment when the diagnosis is known, and it achieves a rate of spontaneous pleurodesis nearing 50%.

Ideally, dedicated respiratory multidisciplinary teams should make therapeutic decisions in patients with malignant pleural effusion, and quality of life concerns should have a major place in these decisions.