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Soft tissue sarcomas of the extremities, the yield of preoperative pathology examinations

P. Verheijen[1], h. Witjes[2], A. Hennipman[2], T. van Dalen[1].
[1]*Diakonessenhuis, Surgery, Utrecht, The Netherlands;* [2]*University Medical Center, Surgery, Utrecht, The Netherlands*

Background: In the work-up of extremity soft tissue sarcomas (STS) a correct histopathological diagnosis is essential before surgical treatment. While open incisional biopsies (IB) have been the golden standard for long, large core needle biopsies (CNB) and even fine needle aspiration (FNA) are increasingly being used to establish a diagnosis. In a nation-wide study in patients that were operated for extremity STS, the preoperative use of IB, CNB and FNA was evaluated and their sensitivity assessed.
Patients and methods: All patients that were operated in the Netherlands between November 2000 untill December 2003 for a newly diagnosed extremity STS were retrieved from the national automated pathological database: PALGA. Biopsies were considered affirmative when it concluded the presence of a mesenchymal malignancy.
Results: In this period, 505 patients in the Netherlands underwent resection of an extremity soft tissue sarcoma in. Definitive surgery was done in 158 patients (31%) without preoperative pathological examination. Of the remaining 347 patients (69%), 319 patients (63% of all patients) had a histological biopsy and/or 99 patients (20% of all patients) a FNA. In patients who were biopsied (n = 319), IB was done more often than CNB (147 vs. 100 patients), while in 72 patients information about the nature of the histopathologic biopsy (CNB or IB) was unclear. An affirmative diagnosis of "mesenchymal malignancy" could be established in 140/147 patients (95%) after IB, in 80/100 patients (80%) after CNB and in 39/99 patients (39%) after FNA. The correct histomorphological tumour type was diagnosed in 80%, 53% and 19% respectively.
Conclusion: In this nationwide study in patients that were recently treated for extremity STS, one third of the patients was operated without preoperative pathological analysis. Although the sensitivity of core needle biopsies is high, open biopsies still have a higher sensitivity and when it comes to a correct histomorphological diagnosis this difference increases. An open incisional biopsy should still be considered the golden standard in the preoperative work-up of extremity STS.

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Intraoperative electron beam radiotherapy combined with dose-reduced external beam radiotherapy is highly effective in limb-sparing treatment of extremity soft tissue sarcomas

S. Oertel[1], R. Krempien[1], F. Roeder[1], A. Funk[1], L. Bernd[2], M. Büchler[3], P. Huber[4], S. Eichin[1], J. Debus[1], M. Treiber[1]. [1]*University Clinic Heidelberg, Radiooncology, Heidelberg, Germany;* [2]*University Clinic, Orthopedics, Heidelberg, Germany;* [3]*University Clinic, Surgery, Heidelberg, Germany;* [4]*German Cancer Research Center, Radiooncology, Heidelberg, Germany*

Objective: Management of extremity soft tissue sarcomas has changed dramatically during the past 25 years towards a multimodal approach combining limb-sparing surgery with adjuvant radiotherapy. However, severe side effects resulting in clinically significant limb-function impairment are observed in up to 36% of patients after adequately dosed conventional radiotherapy. We review the results of a treatment strategy combining dose-reduced external beam radiotherapy (EBRT) with intraoperative electron beam radiotherapy (IEORT), which has been implemented in Heidelberg 10 years ago, focussing on local control and the incidence of side-effects.
Patients/Methods: We analyzed the outcome in 153 adult patients treated for extremity soft tissue sarcomas in Heidelberg from June 1991 to June 2004. Median follow up was 48 months. 38% of patients suffered from recurrent, 62% from primary soft tissue sarcomas. Most patients suffered from malign fibrous histiocytomas (35%), liposarcomas (30%) or leiomyosarcomas (10%). Grading distribution was as follows: 57% G3, 35% G2, 8% G1. In 34% of patients the tumors were resected with wide clear margins, 20% with margins below 1 cm (R0); 34% showed microscopic (R1), 12% macroscopic tumor residues (R2). 37% of the treated tumors had a size <5 cm (maximal diameter), 33% of 5–10 cm and 30% were >10 cm. IOERT was delivered via linear accelerator in the operating theater. Electron energies ranged from 8 to 15 MeV. IEORT doses ranged from 10–20 Gy (90% isodose, median 15 Gy) covering the complete tumor bed. Healthy normal tissue was either displaced or covered with appropriately sized lead shields. EBRT was delivered by linear accelerators with 6–23 MV photon energies. 29% of patients had received EBRT preoperatively, 71% received EBRT 2–8 weeks postoperatively. Doses of 39.6–54 Gy (mean 43 Gy) in daily fractions of 1.8–2 Gy were prescribed. CT-based 3D conformal treatment planning was used in all cases. The volume treated included the tumor bed (with surgical clips marking the IOERT-field), plus a wide margin of 5 cm whenever possible.
Results: Our results show an overall 5-year survival rate of 70%. Local control rate after 5 years was 78% and 73% after 10 years, respectively. 5-year distant failure free survival was 53%. 5-year survival rates after R0-resection was 76%, after R1/R2 resection 55% (not statistically significant with p = 0.1). The overall survival rates did not significantly depend on the resection status either. Primary versus recurrent tumor as well as tumor size did not result in essential differences concerning local control rates. Grading, however proved to be of significant prognostic impact on overall survival, but not on local control rates. Overall 5-year survival was better in patients after R0 or R1-resection versus R2 resection though (78% versus 45%, p = 0.01). The applied IEORT dose resulted in a statistically significant difference: 5-year local control after IEORT dose below 15 Gy was 62%, above 15 Gy was 75% (p = 0.008). Acute complications were observed in 28% of patients (89% CTC 1 or 2, 11% CTC3), mainly including wound-healing disturbances, skin damage and seromas. 5 patients had to undergo resurgery. Late effects were scored according to LENT-SOMA scale and were observed in 19% of patients (95% grade 1 or 2), with lymphedema, nerve lesions and contractures due to fibrosis being prevalent. Overall 90% of patients alive 5 years after IEORT showed no significant impairment of limb function in daily life activities.
Conclusions: IEORT represents an excellent method to reduce EBRT in multimodal limb-sparing treatment of extremity soft tissue sarcomas. Radiation induced side effects are low, while an excellent local control rate is preserved.

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The Rotterdam Experience of 217 TNF-based Isolated Limb Perfusions (ILP) for advanced Soft Tissue Sarcomas (STS): long-term follow up, prognostic factors and subgroup analysis

D. Grünhagen, J. de Wilt, C. Verhoef, A. van Geel, A. Eggermont.
Erasmus MC – Daniel den Hoed Cancer Center, Surgical Oncology, Rotterdam, The Netherlands

Background: Extensive and mutilating surgery is often required for locally advanced Soft Tissue Sarcoma (STS) of the limb. As it has become apparent that amputation for STS does not improve survival rates, the interest in limb-preserving approaches has increased. Isolated Limb Perfusion (ILP) with TNF and Melphalan is successful in providing local tumour control and enables limb-preserving surgery in a majority of cases. Here we report on the mature largest single-institution experience with 217 consecutive ILPs for STS of the extremity.
Methods: Prospectively maintained database at a tertiary referral centre. From July 1991 – July 2003, 217 ILPs were performed in 197 patients with locally advanced STS of the extremity. ILPs were performed at mild hyperthermic conditions with 1–4 mg of TNF and 10–13 mg/L limb-volume Melphalan (M) for leg and arm perfusions respectively. We studied the outcome of the patients and performed an analysis to identify prognostic factors for response, disease control and survival after ILP.
Results: Overall response rate was 75%. Limb salvage was achieved in 87% of the perfused limbs and local control could be obtained in 74%. Median survival post-ILP was 57 months and prognostic factors for survival were Trojani grade of the tumour and ILP for single vs. multiple STS. The procedure could be performed safely with a peri-operative mortality of 0.5% in all patients with no age-limit (median age 54 years, range 12–91). Systemic and locoregional toxicity were modest and easily manageable. Limb salvage percentages in subgroups of patients with systemic metastases, multiple sarcomas in the limb and recurrences in previously irradiated areas were all highly positive (97%, 82% and 65% respectively).
Conclusion: TNF+M-based ILP can provide limb salvage in a significant percentage of patients with locally advanced STS and has therefore gained a permanent place in the multimodality treatment of STS.

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Prognostic indicators of locoregional and systemic recurrences after sentinel lymph node biopsy in patients with cutaneous melanomas

A.C.J. van Akkooi[1], J.H.W. de Wilt[1], C. Verhoef[1], W.J. Graveland[2], A.N. van Geel[1], M. Kliffen[3], A.M.M. Eggermont[1]. [1]*Erasmus Medical Center – Daniel den Hoed Cancer Center, Surgical Oncology, Rotterdam, The Netherlands;* [2]*Erasmus Medical Center – Daniel den Hoed Cancer Center, Statistics, Rotterdam, The Netherlands;* [3]*Erasmus Medical Center – Daniel den Hoed Cancer Center, Pathology, Rotterdam, The Netherlands*

Summary/Objective: Although the sentinel node (SN) technique is widely used, there is no evidence that the SN procedure in melanoma patients influences survival. The objective of this study was to investigate the prognostic value of the SN status, especially in terms of disease-free survival (DFS) and overall survival (OS) and to evaluate locoregional control after the SN procedure.

Methods: Prospective database study of 262 consecutive sentinel node procedures in primary melanoma patients, (primary: Breslow thickness >1 mm and/or ulceration, and/or Clarke level IV) treated between 1997 and 2004. Histopahologic work up of the SN according to the EORTC Melanoma Group protocol (Cook MG et al, J Pathol. 2003 Jul; 200(3): 314–9). Analysis of DFS and OS was performed using the Kaplan-Meier approach. Multivariate and univariate analysis using the Cox's proportional hazard regression model were performed to assess the prognostic value of covariates with respect to DFS and OS.
Results: At least one SN was harvested in each patient. Median follow-up was 23.3 months. In 77 patients the SN contained metastatic melanoma cells (29%). The established false-negative rate during follow-up was 9.4%. Patient factors that determined SN status were Breslow thickness and ulceration. Patient factors that influenced disease-free survival were SN status, location and ulceration of the primary tumor. Overall survival was influenced by SN status and ulceration of the primary tumor. Locoregional recurrence was 6.5% in SN negative patients versus 22.1% in SN positive patients ($P < 0.001$). The distant recurrence rate was 3.8% in SN negative patients versus 27.3% in SN positive patients ($P < 0.001$). The in-transit metastasis rate correlated with SN-positivity, Breslow thickness and ulceration. Actuarial 5-year overall survival rate in SN negative patients was 93% and in SN positive patients 51% ($P < 0.001$).
Conclusions: The SN procedure is a reliable and accurate procedure and SN status is the most important predictive factor for DFS and OS. Our findings confirm that the EORTC Melanoma Group SN work up protocol detects SN positivity in about 30%, which is substantially higher than most procedures reported in the literature (average of 18%). Breslow thickness and ulceration are both factors influencing SN status. SN positive patients have a significantly increased risk to develop any form of locoregional or distant recurrence compared to SN negative patients.

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Quantitative RT-PCR (qRT) based analysis of tyrosinase, MART-1 and MAGE-A3 in Sentinel Lymph Nodes (SLNs) from Malignant Melanoma (MM) patients

M. Gonzalez Cao[1], J. Puig[2], C. Badenas[2], J. Malvehy[3], M. Bes Rastrollo[4], C. Conil[5], R. Rull[6], S. Martin Algarra[1], S. Vidal[7], S. Puig[3].
[1]Clinica Universitaria de Navarra, Medical Oncology, Pamplona, Spain; [2]Hospital Clinic, Laboratory of Genetic, Barcelona, Spain; [3]Hospital Clinic, Dermatology, Barcelona, Spain; [4]Clinica Universitaria de Navarra, Preventive Medicine and Public Health, Pamplona, Spain; [5]Hospital Clinic, Radiotherapy, Barcelona, Spain; [6]Hospital Clinic, Surgery, Barcelona, Spain; [7]Hospital Clinic, Nuclear Medicine, Barcelona, Spain

Background: Detection of micrometastases in SLNs is critical for staging of melanoma. When SLNs are involved, survival is reduced in 40%, nevertheless, prediction of outcome is imprecise with conventional techniques. We and others have found that detection of a higher number of tumor-specific molecular markers in melanoma SLNs may identify patients with an increased risk of recurrence. We have compared the results of this analysis using different criteria: the classical numerical criterium and the presence of specific combinations of markers.
Material and methods: 157 pts with cutaneous melanoma 0.75 mm Breslow thickness underwent SLN biopsy. A portion of each SLN was stored frozen at −80ºC and assessed by qRT for mRNA of three genes: MART-1 (antigen recognized by T cells-1), MAGE-A3 (melanoma antigen gene-A3 family) and tyrosinase.
Results: Twenty-five (15.9%) pts had histologically positive (HISTOL+) SLN. Marker expression for Tyrosinase, MART-1 and MAGE-A3 in HISTOL+ and HISTOL− pts were as follows: 92%, 72%, 36% and 77%, 35%, 11%. All individual markers and their combinations had prognostic significance for DFS in the crude analysis. Nevertheless, in the multivariate analysis no single marker had prognostic significance, only the criteria of "two or more positive markers" ($HR = 2.37$, $p = 0.036$), as well as the "simultaneous positivity of tyrosinase and MART-1" ($HR = 2.35$, $p = 0.038$) were independent prognostic factors. Pearson correlation test found a significant correlation between these two criteria ($r = 0.919$; $p < 0.001$). Numerical criteria using "two or more positive markers" and the criteria of "simultaneous positive tyrosinase and MART-1" identified 66 pts (42%) and 60 pts (38%), respectively. Risk scores for each individual could be calculated by a risk equation derived from the regression model with a sensibility of 63% and a specificity of 68% (area under the ROC curve of 0.836).
Conclusions: Multimarker qRT is an useful molecular staging test that may more precisely identify patients with higher risk of recurrence. Patients with positive SLNs for two or more markers have a higher risk of recurrence, and these patients were mainly those who were positive simultaneously for tyrosinase and MART-1. It suggests that a more simple assay avoiding MAGE-A3 could be use with similar results.

Poster presentations (Mon, 31 Oct)
Melanoma and sarcoma

1194 POSTER

Uveal melanomas treated BZ gamma knife

G. Simonova, R. Liscak, J. Novotny Jr.. *Hospital Na Homolce, Stereotactic Radioneurosurgery, Prague 5, Czech Republic*

Purpose: To analyse treatment results, complications and prognostic factors for survival of patients irradiated for uveal melanomas using the Leksell gamma knife
Material and methods: During 8 years 126 patients with uveal melanomas were irradiated using the Leksell gamma knife. The median of gross tumor volume (GTV) was 551 mm^3(33–7800 mm^3), the median of planning treated volume (PTV) was 1,300 mm^3(67–8200 mm^3), the median of tumor height was 8 mm (1–20 mm). The median of minimal single dose (Dmin) was 34 Gy (28–85 Gy). Patients were followed by an ophthalmologist at regular intervals, magnetic resonance was performed every 12 months. Tumor regression was defined as a decrease in tumor height registered by A and B ultrasonography scans and by control magnetic resonance imaging. The minimal follow up for survivors was 24 months. The SOMA LENT scoring system was used to measure radiation induced side effects.
Results: *1. Local tumor response*. The complete or partial tumor regression can be achieved in 70% of patients. The maximum local effect has been recorded after the interval of 20–30 months since the treatment (see the figure).
2. Toxicity. The most common late toxicity were: retinopathy, cataracts, secondary glaucoma and optic neuropathy. The median time to occurrence of secondary neovascular glaucoma was 18 months and we did not observe any significant influence of the minimum dose and tumor location, but a significantly lower incidence of secondary glaucoma was noticed when the volume of PTV was less than 1,000 mm^3 with an incidence 6.9%. In the analysis of late toxicity we recorded the following results: significantly lower toxicity in the optic nerve was observed when the maximum dose was less than 10 Gy (incidence of grade 3, 4 only in 2.4%), in the cornea when maximum dose did not exceed 10 Gy (incidence of toxicity 3, 4 in 3%), in the lens when the maximum dose did not exceed 7 Gy (incidence of toxicity grade 3, 4 in 7.7%) and in the iris when the maximum dose did not exceed 15 Gy (incidence of 3, 4 grade late toxicity in 4.6%).
3. Prognostic factors and survival. Patients younger than 50 years have the best prognosis, with a pre equatorial location of the tumor, when tumor height did not exceed 5 mm, GTV was not larger than 500 mm^3 and there was no other organ dissemination.
Conclusion: The acceptable incidence of late toxicity for all eye critical structures was observed when the maximum dose to these structures did not exceed 10 Gy and effective local tumor response was achieved in 70% of patients. The stereotactic irradiation can extent conservative therapeutic options for these types of tumors with visus or eye preservation.

1195 POSTER

The role of adjuvant radiation therapy in uterine sarcoma

C. Fallai[1], A. Cerrotta[1], P. Casali[2], F. Grosso[2], E. Sbicego[3], P. Olmi[3].
[1]Istituto Nazionale Tumori, Radioterapia 2, Milano, Italy; [2]Istituto Nazionale Tumori, Oncologia Medica C, Milano, Italy; [3]Istituto Nazionale Tumori, Radioterapia 1, Milano, Italy

Background: The aims of this retrospective single institution case series analysis are to investigate prognostic factors regarding overall survival (OS), cause-specific survival (CSS), relapse-free survival (RFS), and loco-regional relapse-free survival (LR-RFS), and to evaluate the role of adjuvant radiotherapy (RT) in uterine sarcomas.
Patients and methods: From 1984 to 2004, 198 patients with uterine sarcoma were treated at the Istituto Nazionale Tumori. The distribution by histology was the following: leyomiosarcoma (LMS)=95; smooth muscle tumors of unknown malignant potential (STUMP)=9; endometrial stromal sarcoma (ESS)=40; malignant mixed mullerian tumors (MMMT)=34; adenosarcoma (AS)=10; other mesenchymal types=10. Stage distribution according to FIGO (as modified by Salazar-Cancer 1978; 42:1152–60) was as follows: stage I=127; stage II=18; stage III=22; stage IVa=16; stage IVb=15. All the 167 stage I-III patients underwent surgery; 33 patients were given adjuvant chemotherapy and 45 patients were given adjuvant pelvic RT. The mean delivered dose was 54 Gy with conventional fractionation. OS, CSS, RFS and LR-RFS were calculated according to the Kaplan-Meier method. The level of significance was evaluated with the Log Rank test; the proportional hazards model of Cox was used for the multivariate analysis. Acute and late toxicity were scored according to the RTOG grading system.
Results: 5-year OS and CSS were 56% and 48.7%, respectively. RT was not a significant prognostic factor for OS, CSS or RFS, while it turned out