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.

1193 ORAL

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

to be significant for LR-RFS (5-year LR-RFS 79% with adjuvant RT versus 59% without RT; p = 0.009). When the different histologies were analysed separately, results suggested significance for LMS (all stage p = 0.05, stage I and II: p = 0.03) and MMMT (p = 0.04), but not for ESS. In the multivariate analysis stage, age and histology were significant prognostic factors for OS; stage, grading, histology, and tumor size were significant for CSS, and finally, RT was the only factor with a statistically significant impact on LR-RFS. Acute toxicity was mild; 2 cases of G3–4 late toxicity were observed concerning the lower gastrointestinal tract.
Conclusions: our series confirms that RT has a major role as adjuvant treatment in uterine sarcomas, by increasing the disease control in the pelvis. This is statistically significant for LMS and MMMT. The lack of impact on CSS and RFS and the relevance of distant failure call for systemic adjuvant treatments.

1196 POSTER

The combination of liposomal anthracyclines and ifosfamide in the treatment of advanced soft tissue sarcomas – first clinical results

J.M. Siehl, U. Keilholz, A. Schmittel, G. Hütter, H. Szelenyi, E. Thiel. *Charité – Campus Benjamin Franklin, Medizinische Klinik III, Berlin, Germany*

Background: Actually the standard chemotherapy for advanced soft-tissue sarcomas is a combination of doxorubicin and ifosfamide. For both drugs there is a dose-response relationship. The main problem, however, is a high rate of toxicities.
Liposomal encapsulation of anti-cancer drugs is a strategy pursued to reduce toxicity and improve tumour uptake. Liposomal anthracyclines are far less cardiotoxic than the conventional formulations and they might accumulate at the site of the tumour. So far there are little data on the efficacy of liposomal anthracyclines in advanced soft-tissue sarcomas when used as single agents. The role of liposomal anthracyclines in combination with ifosfamide is yet to be determined. Our first recently reported data [1] are now extended.
Patient and methods: In a phase II study we combined liposomal daunorubicine (L-Dauno; DaunoXome®) with ifosfamide in the treatment of advanced soft tissue sarcoma. 40 patients were enrolled, 35 of them were treated first line. In another 10 patients we combined liposomal doxorubicine (L-Doxo; Myocet®) with ifosfamide.
Results: For both combinations toxicity was tolerable. The response rate was 31% with a median overall survival of 14 months in the L-Dauno/ifosfamide group. The response rate of the L-Doxo/ifosfamide group will be presented at the meeting.
Conclusions: The combination of liposomal anthracyclines and ifosfamide turned out to be a safe and effective regimen in the treatment of advanced soft tissue sarcoma. Further evaluation in randomized trials should be performed.

References

[1] Siehl JM et al Cancer 2005 in press.

1197 POSTER

Dermatoscopic pictures of malignant melanoma

V. Karanikolic, M. Stanojevic, T. Kozomara. *Dermatologic Clinic, Oncology, Nis, Yugoslavia*

Background: Dermatoscopy is non invasive diagnostic technique for early detection of melanoma. The aim of the study was to explore clearly atypical dermatoscopic melanoma pictures.
Methods: Retrospectively were followed data of 677 patients for whom the dermatoscopy results were obtained during the two years period. Total dermatoscopy score (TDS) was assessed according to the ABCD rule of Stolz. The result was considered clearly false positive when TDS was six or more and histopathology showed no characteristics of malignant melanoma. The result was considered clearly false negative when TDS was four or less and histopathology was characteristics of malignant melanoma.
Results: Our results showed that in 3(0.44%) patients with dermatoscopy score (6.4; 6.7; 6.9) a doubtless dermatoscopy picture characteristic of malignant melanoma did not correspond to the histopathology result. Histopathology confirmed dermal nevus in two cases and junctional-pigmented nevus in one case. Patient with TDS 2.6 had false negative result, in whom histopathology confirmed amelanotic-melanoma (Clark IV).
Conclusion: Dermatoscopy can be use as routine non invasive diagnostic procedure for malignant melanoma with high percentage of sensitivity.

1198 POSTER

Evaluation of risk during preoperative chemotherapy in osteosarcoma

G. Machak. *N.N. Blokhin Cancer Center, General Oncology, Moscow, Russian Federation*

Purpose: The purpose of this study was to analyze the correlation between clinical and imaging responses to preopera-tive chemotherapy and outcome in non-metastatic osteosarcoma.
Patients and methods: Two hundred ninety-three IIB osteosarcoma patients were treated according to two neoadjuvant protocols. Between 1986 and 1999 preoperative chemotherapy consisted of 3–5 cycles of IA doxorubicin 90 mg/m^2 or cisplatin 120 mg/m^2. Since 1999, 3–4 cycles of doxorubicin and cisplatin are administered in the similar doses. The clinical status, standard two-plane X-ray, CT, MRI pictures and angiography were assessed at diagnosis, after two cycles of chemotherapy and before local treatment. Median follow-up was 36 months. Multivariate analysis was performed by means of Cox regression.
Results: During follow-up, 139 (47%) patients died of disease, 4 (1%) because of chemotherapy complication. At last examination, 150 patients were alive. In univariate analysis, the following features, assessed after two cycles of chemo-therapy, significantly correlated with disease-free survival: clinical response, (p = 0.0004), absolute tumor volume (ATV) with threshold value at 300 ml, (p = 0.00001), relative degree of tumor regression, (p = 0.0001), intra-osseal part structure, (p = 0.0003), degree of periosteal reaction assimilation, (p = 0.0004), margination of extra-bone masses, (p = 0.0001), an-giographic response (p = 0.005). After chemotherapy, the predictive value of these features increased and two additional characteristics became related to outcome: healing of cortical bone (p = 0. 001) and disappearance of extra-bone masses (p = 0.0001). After two chemotherapy cycles ATV at cut-off value 300 ml remained informative in multivariate analysis, (p = 0.0001). The presence of two or more radiographic features (intra-osseal part healing, periosteal reaction assimila-tion, and margination of extra-bone masses), defined as radiographic response, was related to more favorable DFS at 5 yrs (64±11% versus 15±3%, d = 0.00001). In patients with ATV less than 300 ml and radiographic response after two cycles, the predicted 5 yrs DFS was 66%, compared with 9% in alternative group. After completion of chemotherapy, the best outcome can be expected if tumor decreases in volume more than 20% and achieves the value less than 300 ml, (p = 0.0002). In patients with such tumor regression and radiographic response the predicted 5 yrs DFS was 74%, com-pared with 10% among non-responders.
Conclusions: This study demonstrates that in osteosarcoma patients treated with neoadjuvant protocols, the risk of disease progression can be evaluated before histological examination of removed tumor. Assessment of clinical and imag-ing response during induction chemotherapy could be useful when individualized treatment before surgery is intended.

1199 POSTER

Patterns of progression in gastrointestinal stromal tumor treated with imatinib mesylate

M.H. Ryu, J.L. Lee, H.M. Chang, T.W. Kim, H.J. Kang, H.J. Sohn, J.S. Lee, Y.K. Kang. *Asan Medical Center, Internal Medicine, Seoul, Korea*

Background: Although most patients with gastrointestinal stromal tumor (GIST) treated with imatinib mesylate achieve remission or disease stabilization, a significant proportion show progressive disease (PD) with or without initial favorable responses. We evaluated and categorized the patterns of progression of metastatic or unresectable GIST treated with imatinib to identify the prognostic significance and contribution to further treatment decision-making.
Methods: We prospectively gathered clinical data from 62 GIST patients treated with imatinib mesylate (400 mg/day) over a period of median 26 months. Twenty-one of these patients showed evidence of PD based on RECIST criteria.
Results: Four patterns of PD were defined: focal progression (FP, N = 4), general progression (GP, N = 6), new cystic lesion (NCL, N = 6) and new solid lesion (NSL, N = 5). The groups were found to differ in terms of time to progression and prior response to imatinib. The proportion of patients who responded to escalated doses of imatinib (600–800 mg/day) was significantly higher in NCL patients (P = 0.04). Overall survival and survival from the confirmation of PD were significantly better in NCL or FP patients compared with NSL or GP patients ($P = 0.0157$, $P = 0.0023$)
Conclusions: We identified four patterns of disease progression with different clinical characteristics and impact on survival. Knowledge of these patterns was relevant for early detection and may be helpful in further treatment decision-making.