

tained record of the period between July 1990 and December 2002. Aiming confirmation, a thorough histopathologic re-review was undertaken of the well preserved pathologic material available of 45 cases. With specialised techniques like immunohistochemistry and electron microscopy using unanimously agreed, defined and strict criteria for pathologic diagnosis, out of 51 cases, only 26 were classed as conventional HPC. These patients were further analysed with respect to clinical variables (site, age at diagnosis, gender), operation variables (gross or microscopic margins), tumor variables like size (<5; 5-10 and >10 cms), recurrence and metastasis. Kaplan-Meier survival statistics were used for disease free and disease specific survival.

**Results:** Of 51 patients at initial presentation, pulmonary (34.6%) and extremity (36.4%) sites were the most common, followed by trunk (30.7%) of total cases. 19 (73%) patients were in the <50 year age group and 7 (27%) had age >50 years. Primary tumors comprised of 18 (69%) cases. 5 (19%) had locally recurrent tumors and 3 (11.5%) had metastatic disease. Median follow up (n=26) was 39 months (range: 5-72 months). Overall survival rates at two and five years were 87% and 78% respectively. At last follow up disease specific survival was 76%. 88% mean survival at 48 months was noted in patients undergoing complete resection (n=13).

**Conclusions:** Currently, the recommended approach is complete resection of the tumors. Unlike a majority of studies this analysis emphasizes a more favourable survival outcome. Hence, outright major surgical intervention is cautioned against and a more conservative approach is advocated, especially for pathologically well confirmed conventional hemangiopericytomas.

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POSTER

# **Post-operative radiotherapy for soft tissue sarcoma of the anterior compartment of the thigh: should the sartorius muscle be included?**

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**Background:** The clinical target volume (CTV) of post-operative radiotherapy for soft tissue sarcoma of the limbs conventionally includes the whole of the transverse cross section of the affected anatomical compartment. In the anterior thigh, sartorius appears to lie within its own fascial compartment, and could be safely excluded. We investigated the potential impact of omitting sartorius from the anterior muscle compartment on patients with soft tissue sarcoma of the thigh.

**Materials and Methods:** Using CT data, the anterior compartments of six patients were outlined twice, initially including and then excluding the sartorius muscle. The length of the CTV was set to be the same as the original plan. Full conformal radiotherapy plans were prepared. The volume of the anterior compartment, both with and without sartorius, and the corresponding planning target volume (PTV) were calculated. For both volumes, the unirradiated normal tissue corridor was outlined on each CT slice, in order to calculate its circumference at each level and its total volume. The corridor was defined as the volume of normal tissue outside the projections of the treatment beams or conformal blocks, which should therefore receive less than 50% of the prescribed dose. The corridor circumference at each level was expressed as a percentage of the total leg circumference and the mean of these values was calculated.

**Results:** For the six patients, the mean reduction in volume of the anterior compartment when sartorius was excluded was 10% (95% confidence interval 8 to 12%), whilst the mean decrease in PTV was 11% (95% CI 7 to 14%). There was a substantial increase in the volume of the unirradiated normal tissue corridor with a mean value of 77% (95% CI 41 to 114%) when sartorius was excluded. In addition, the increase in the means of the normal tissue corridor expressed as a percentage of the whole leg circumference was considerable.

**Conclusions:** It is essential to know the anatomy of the sartorius muscle to be able to exclude it from the anterior compartment. The increase in the size of the normal tissue corridor when sartorius is excluded should deliver clinical advantage by decreasing the normal tissue adverse effects.

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POSTER

# **Ifosfamide, carboplatin, etoposide induces a 50% overall response rate and 1 year overall survival rate in patients with recurrent/refractory soft tissue and bone sarcoma: Embryonal rhabdomyosarcoma histology and complete response to ICE are independent factors significantly associated with improved survival**

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**Background:** Survival after relapse in patients with soft tissue sarcoma (STS), especially rhabdomyosarcoma (RMS), Ewing's sarcoma (ES) and osteosarcoma (OTS) has historically been poor (Pappo et al JCO, 1999; Ward et al JCO, 1994). Ifosfamide (I), carboplatin (C) and etoposide (E) (ICE) each have single agent activity against STS and bone sarcoma (Pinkerton et al Can Clin Pharm, 1985; Ettinger et al Cancer, 1999 and Kung et al Invest New Drugs, 1998).

**Material and Methods:** We evaluated the overall response rate (ORR) and overall survival (OS) in patients with recurrent/refractory sarcoma treated with ICE chemotherapy in 3 successive CCG trials (CCG 0894, CCG 0924, CCG 0931). I (1800 mg/m<sup>2</sup>/d, days 0-4), C (400 mg/m<sup>2</sup>/d, days 0-1) and E (100 mg/m<sup>2</sup>/d, days 0-4) were administered to 104 patients. Each ICE cycle was repeated every 21 days following recovery of ANC \* 1000/mm<sup>3</sup> and platelet \* 100k/mm<sup>3</sup>. Post ICE TX was investigator choice and included either additional chemotherapy, radiotherapy and/or Auto/SCT.

**Results:** There were 97 evaluable patients for tumor response: median age 14.1 yrs (2.8-22.5), 56% male and 46% female. Histological categories included OTS (n=34), RMS (n=27), ES (n=21), other sarcomas (n=15). Response rates in all patients included 27% CR, 24% PR (ORR=51%), 33% SD and 16% PD. The ORR by histological groupings were RMS: 66%, ES: 48%, OTS 36%, other sarcomas 60%. Grade III/IV hematological toxicity occurred in all patients. There was a 7% incidence of grade IV non-hematological toxicity. The 1 and 2 yr OS rates were 50% and 29%, respectively. Patients obtaining a CR after ICE had an 81% and 54% 1 and 2 yr OS rate, respectively (P<0.001). Patients with RMS with embryonal histology had a 1 and 2 yr OS rate of 86% and 46% vs in other histologies of rhabdomyosarcoma 40% and 20%, respectively (p<0.014).

**Conclusion:** In summary, ICE chemotherapy has an excellent induction ORR in patients with refractory/recurrent sarcoma. Patients with recurrent/refractory sarcoma who attain a CR, RMS histology or RMS embryonal histology have a significantly improved survival following ICE reinduction therapy.

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POSTER

# **Pterin-dependent tyrosine hydroxylase mRNA is not expressed in human melanoma cells**

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**Background:** Tyrosinase (EC 1.14.18) is a key enzyme in pigment formation. It acts by hydroxylation of L-tyrosine to L-dopa and then by oxidation of L-dopa to dopaquinone, which is then further processed to pigment. With mammalian tyrosinase the hydroxylation step is characterized by a lag period, which is eliminated by the addition of L-dopa. In addition to tyrosinase the enzyme tyrosine hydroxylase (EC 1.14.16.2) has occasionally been described to occur in melanocytes side by side with tyrosinase and suggested to produce L-dopa as the co-substrate for tyrosinase. It is therefore important to quantify the amount of the transcript of this enzyme in pigment cells and melanoma cells to understand whether this enzyme could possibly take part of pigment formation.

**Material and methods:** Twelve different melanoma cell lines and 8 neuroblastoma cell lines were investigated. The melanoma cells were characterized as pigmented or non-pigmented according to the results from pigment degradation studies. Total RNA was extracted from 10<sup>6</sup> cells by the QIAamp RNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) and eluted in 40 µl of RNase-free water. First strand cDNA was synthesized from 10 µl RNA. A real-time reverse transcription-polymerase chain reaction method was used to quantify tyrosine hydroxylase mRNA. The calibrator used was obtained by amplification of a segment of cDNA from tyrosine hydroxylase mRNA, which included the target and allowed estimation of the number of transcripts per cell.

**Results:** The median tyrosine hydroxylase mRNA in 12 of 12 melanoma cell lines was 0.000383 transcripts/cell (range 0.000012-0.005340 transcripts/cell). In neuroblastoma cells the median tyrosine hydroxylase mRNA number was 0.4 transcripts/cell (range 0.02-25 transcripts/cell). The results should also be compared with earlier found median transcript concentrations of four melanocyte-specific proteins, which varied between 116 and 435 transcripts/cell in the pigmented melanoma cell lines, and between 0.7 and 11 transcripts/cell non-pigmented melanoma cell lines.

**Conclusions:** Less than 1 of 1000 melanoma cells contains any tyrosine hydroxylase mRNA. This is so low a number that the enzyme can not be produced effectively. Thus, pterin-dependent tyrosine hydroxylase can not be present in melanoma cells and does not contribute to pigment formation by producing any priming amounts of L-dopa for proper function of tyrosinase in human melanoma cells.

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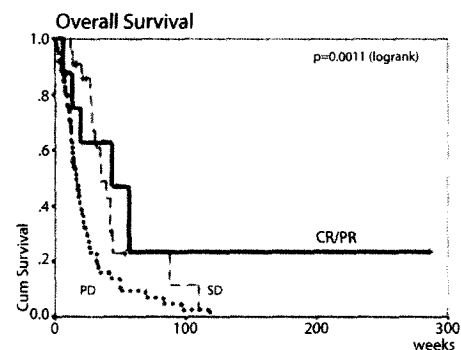
POSTER

### Second-line treatment of disseminated malignant melanoma with Fotemustine

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In a retrospective analysis, the role of the nitrosourea Fotemustine in the second-line treatment of disseminated malignant melanoma was evaluated. The multicentric study included a thorough review of patient's charts treated with Fotemustine during the period 1992-2002 in 11 melanoma centers in Germany.

A total of 91 patients (43m, 48f) aged 29-87 years (median 65y) could be identified who were treated for melanoma metastasis with intravenous Fotemustine after relapse in first-line therapy. First line therapy often consisted of single agent DTIC (37%), temozolomide (13%), or combined DTIC/immunotherapy (18%). Eight patients had received polychemotherapy containing nitrosoureas. 38 patients (42%) had progressed with brain metastasis. Fotemustine was applied 100mg/sqm i.v. weekly for 3 weeks, and evaluation usually took place at day 50. In stable or responding patients a maintenance treatment was initiated. Seven of the patients with brain metastasis received a simultaneous total brain irradiation



In 8.8% of the patients an objective response could be achieved. Responses lasted from 4 to 285 weeks (median 23.5 weeks) and responding patients showed prolonged overall survival (Fig.1). The extent of metastatic disease appeared as a major prognostic factor, specifically when only 1 or 2 organs were affected. The presence of brain metastasis had limited prognostic impact in this group of patients (Table 1).

Side effects were moderate and mainly affected the haematologic system with grade III/IV thrombopenia in 28 (30.8%), neutropenia in 19 (20.9%), and anemia in 11 (12.1%) of the patients. Further side effects included mild to moderate liver toxicity, and in some cases nausea.

In conclusion, Fotemustine can safely be administered as second-line therapy with some degree of antitumour activity in patients with metastatic malignant melanoma.

Abstract 834: Table 1: 2nd-line Fotemustine - single agent - iv

	n	OS (95% CI) [weeks]	CR (%)	PR (%)	OR (%)
Total	91	21.7 (14.9; 28.6)	2 (2.2%)	6 (6.6%)	8 (8.8%)
Tumor load					
Limited disease	19	31.9 (19.1; 44.7)	1 (5.3%)	2 (10.5%)	3 (16.8%)
Extensive disease	72	20.1 (16.0; 24.3)	1 (1.4%)	4 (5.6%)	8 (7.0%)
Metastatic sites					
1	21	31.9 (6.88; 56.8)	2 (9.5%)	4 (19%)	6 (28.5%)
2	27	35.4 (8.76; 62.1)	-	2 (7.4%)	2 (7.4%)
3	20	18.4 (8.19; 28.7)	-	-	-
4+	23	18.0 (9.93; 26.1)	-	-	-
Brain mets w/w TBI	38	22.0 (13.1; 30.9)	1 (2.6%)	1 (2.6%)	2 (5.2%)
With radiation	7	34.4 (0; 71.8)	-	1 (14.3%)	1 (14.3%)
without radiation	31	22.0 (1; 26.4)	1 (3.2%)	-	1 (3.2%)

OS: overall survival; CI: confidence interval; CR: complete remission; PR: partial remission; OR: objective response; TBI: total brain irradiation

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POSTER

### Primary mucosal malignant melanoma - a retrospective single centre study

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**Background:** Primary mucosal melanomas (MM) are rare, far fewer in number than melanomas of the skin. They manifest a more aggressive biologic course and such behaviour attends melanomas at any mucosal site. The authors study population characteristics, prognostic factors, and survival.

**Material and methods:** This study was performed retrospectively to include all cases of MM seen at the Portuguese Institute of Oncology, Oporto, Portugal, between 1984 and 2002. A total of 52 patients were reviewed. Clinical data was extracted from each patient's records. After excluding patients on who most clinical information was unavailable (n=5), 47 patients remained for analysis. Primary anatomic site of MM, the symptoms and signs that brought him/her to the doctor, the clinical stage at presentation, the treatment modality and the outcome, were analyzed. The data related to the macroscopic and microscopic characteristics of the lesion were obtained from the pathologist original report. Overall and disease-specific survival, were calculated using the Kaplan-Meier method, and univariate survival analysis was performed using the log-rank test.

**Results:** Forty-seven cases of Caucasian MM form the basis of this study. There were 13 men (27.7%) and 34 women (72.3%), with a median age of 66 years (33-86). Seventeen patients (36.1%) had MM of the head and neck (MMHN), 20 patients had MM of the genitalia (42.6%) and 10 patients had primary anorectal melanoma (21.3%). Regarding the patients with MMHN, the primary tumour arose in the oral cavity in 9 (53%) and the nasal cavity in 8 (47%). Within the oral cavity, 43% lesions involved the palate. The origin of the MM of the genital tract was: vulva, 13 patients (65%) vagina, 7 (35%). The anorectal melanoma patients were distributed by anal, 7 patients (70%) and rectum, 3 patients (30%). Among the 17 patients with MMHN, 13 patients (76.4%) had Stage I or localized disease, 4 (23.5%) had Stage II or locoregional disease and none had Stage III or distant disease at presentation. Clinical stages at presentation for genital tract melanoma were assigned as follows: Stage I, local disease only, 13 patients (65%); and Stage II, regional disease, 7 patients (35%). The 10 patients with anorectal melanoma comprehended 3 patients (30%) with localized disease, 4 (40%) with regional lymph node metastases and 3 (30%) with distant metastases at presentation. After developing symptoms, the median time to diagnosis was 11 months (1-84). The median follow-up time was 24 months (0.3-125), with an overall survival (OS) of 27 months (12-42). Attending the mucosal site OS analysis revealed 59 months (±15) for MMHN, 56 months (±13) for MM of the genitalia, and 10 months (±5) for anorectal MM. Univariate survival analysis were performed within each of the former groups, and for none of the tested risk factors we achieved a significant value.

**Conclusions:** The outcome is poor, with 5-year OS well below 50% (35% in our study). Among prognostic factors, only the anatomic site of origin showed significant influence in survival (p=0.02).