1071 POSTER DISCUSSION

## The aggressiveness of hypoxic soft tissue sarcomas cannot be explained by mutations in the TP53 gene

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**Purpose:** Tumor hypoxia and TP53 mutations are two parameters suggested to have a negative impact on survival probability in human tumors. Also, In-vitro studies have shown that hypoxia induce apoptosis in p53 −/− cells tumor cells. The present study was performed to evaluate the relationship between TP53 mutations and tumor hypoxia in human soft tissue sarcomas (STS).

**Methods:** Pretreatment tumor oxygenation was measured using polarographic oxygen electrodes (Eppendorf, Germany) in 26 conscious patients with primary STS. Oxygenation parameters was tumor median pO2 and the percentage of pO2 values 2.5 mmHg (HF2.5). Gene mutations (in exons 2–11) were studied in material deriving from either fresh frozen tumor biopsies or paraffin-embedded tissue sections and using Denaturing Gradient Gel Electrophoresis (DGGE) as the initial scanning procedure and characterized by sequencing.

**Results:** TP53 mutations were identified in 6 tumors. The oxygenation status of these 6 tumors was high as the grand median of the tumor median pO2 was 24 mmHg (range 14–32) and a median HF2.5 of 2% (range 0–6). Five tumors with TP53 mutations were histopathologically grade IIIa–IIIb and the last grade III not otherwise specified.

**Conclusion:** These preliminary results show that in soft tissue sarcomas the aggressiveness of hypoxic tumors was not explained by TP53 mutations.

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## The comparison of 2 protocols for treatment of osteosarcoma (OS) with or without escalation of HDMTX enhances the high value of MTX individual adaptation

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**Purpose:** To demonstrate the role of HDMX adaptation in long term survival of patients (p.) with high grade OS, we compared our results in 2 successive OS protocols.

**Methods:** From 85 to 95, 90 p. with primary high grade OS fulfilled the classical criteria: non metastatic, resectable tumor, previously untreated. **Group 1** (G1): 45 p. received a fixed dose of MTX adapted only to age. **Group 2** (G2): 45 p. received escalating doses of MTX with PK and clinical monitoring.

**Results:** In G2, a dose escalation was necessary in nearly 70% of cases (32/45) due to low serum concentration (15), or lack of clinical response (9) or both (8). G1 p. received a mean dose of 10.5 g/m$^2$/course and G2 p. a mean dose of 13.5 g/m$^2$/course (mean seric concentration of respectively 850 $\mu$mol/l and 1175 $\mu$mol/l). No significant difference in toxicity was observed **Outcome** the overall survival and DFS at 5 (and 10) y. are respectively **71% (69%) for G1** (fixed dose of MTX), **93% (91%) for G2. The differences are statistically significant.**

**Conclusion: The serum peak and AUC are correlated with the rate of GR. The seric intensity is correlated with the late DFS.** Individual PK of MTX, supplemented by careful examination of the tumoral limb before each course of MTX led to increase the dose of MTX in 70% of p., resulting in more GR and more late survivors without significant increase of toxicity.

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## Advanced soft tissue sarcoma (ASTS): Neoadjuvant chemotherapy may allow more conservative surgery

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**Purpose:** The II trial. Evaluation of functionnal improvement of surgery and outcome.

**Medhod:** 48 patients have been included in this ongoing study since April 1996. Median age 44 years. 33 pts had a locally ASTS and 15 had metastasis, primary tumors were located to the trunc and limbs. An intensive neoadjuvant regimen (API-AI) consisting in two cycles (4 courses) of chemotherapy was designed. Doxorubicine 60 mg/m$^2$ (D1, D15), Cisplatinum 100 mg/m$^2$ (D1), Ifosfamide 5 g/m$^2$ (D2, D15) with an equivalent dose of mesna. G-CSF was added after each course for 6 days (D6–11 and D19–24).

**Results:** 44 patients are evaluable for response.

Table 1:

| Clinical Response | Locally ASTS (29) | Metastasis (15) |
|---|---|---|
| C.R. | 0 | 1 |
| P.R. | 10 | 7 |
| O.R. | 10 (35%) | 8 (53%) |
| S.D. | 16 (55%) | 4 (27%) |
| P.D. | 3 (10%) | 3 (20%) |

Among the 29 operated patients, 10 (35%) had more conservative surgery and avoided abdomino perineal or limb amputations.

**Conclusion:** Neoadjuvant chemotherapy allows to modify surgery in a more conservative way in 35% of ASTS. It seems very interesting if mutilating surgery is considered at first. There is no parralelism between clinical and histological response. Survival impact must be evaluated by further study.

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## Retroperitoneal soft tissue sarcoma: A difficult diagnosis

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**Purpose:** Succesfull surgery of retroperitoneal soft tissue sarcoma (RSTS) is dependent on preoperative planning, only possible when the diagnosis is established before definitive treatment. In a population based study, the share of patients was determined in whom the diagnosis was established only after definitive treatment. Factors contributing to an erroneous diagnosis were analysed and the influence on outcome of treatment evaluated.

**Method:** In a nation-wide study eligible data were collected on 126 patients with RSTS between 1989–1993. Mean age was 56 yrs., M/F ratio was 57/69. Patients were categorised as diagnosed correctly (group 1) or erroneously (group 2) before definitive treatment.

**Results:** Forty percent of all patients (51/126) were initially treated for assumed other disease. The clinical presentation was similar in both groups, although 8 of 10 patients with an acute presentation were in group 2. Tumour histology, malignancy grade and localisation were the same. The tumours of patients in group 2 were smaller (median diameter 12 cm. vs. 20 cm.; $p < 0.05$). Clinical work-up in group 2 contained less frequently CT-imaging (62% vs. 89%; $p < 0.001$) and biopsy (64% vs. 20%; $p < 0.001$). Treatment of the 75 patients in group 1 led to abandonment of surgical treatment in 12 and complete resection in 47 of the 63 remaining patients (75%). Surgery in 49 patients in group 2 resulted in complete resection in 27 patients (55%).

**Conclusion:** Forty percent of patients with RSTS were treated for assumed other diagnoses. Incomplete work-up was a contributory factor in a minority of these patients. Despite smaller tumours, treatment of preoperative erroneously diagnosed patients resulted in less complete resections.

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## Significant improvement of relapse free survival as well as time to distant failure for adult grade 3 soft tissue sarcoma after adjuvant augmented chemotherapy plus adjuvant hyperfractionated accelerated radiotherapy: A prospective randomized trial of the Austrian cooperative soft tissue sarcoma study group

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The present prospective randomized trial was carried out to compare the efficacy and toxicity of adjuvant augmented chemotherapy (ACT) added to adjuvant hyperfractionated accelerated radiotherapy (HA-RT) after wide or marginal resection of soft tissue sarcoma (STS). 59 patients underwent primary surgery by wide or marginal excision and were subsequently randomized to receive either adjuvant HA-RT alone or under the addition of six courses of an adjuvant ACT containing ifosfamide (1500 mg/m$^2$, days

1–4), DTIC (200 mg/m$^2$, days 1–4) and doxorubicin (25 mg/m$^2$, days 1–2) augmented in time and administered in 14-day-intervals made possible by subcutaneous administration of G-CSF (30 × 10$^6$ IU/d) on days 5–13. According to the randomization protocol, 28 patients received adjuvant HA-RT only, whereas 31 patients were treated with additional adjuvant ACT. After a mean observation period of 41 ± 19.7 (range: 8.1–84) months, 16 patients (57%) after adjuvant HA-RT vs. 24 patients (77%) after adjuvant HA-RT + ACT were free of disease ($p > 0.05$). Within the HA-RT group, tumor relapses occurred in 12 patients (43%; 6 patients with distant metastases, 2 with local relapse, 4 with both) vs. 7 patients (23%; 5 patients with distant metastases, 1 with local recurrence, 1 with both) from the HA-RT + ACT group. Mean relapse-free survival ($p = 0.1$), time to local failure ($p = 0.09$), time to distant failure ($p = 0.17$) as well as overall survival ($p = 0.4$) did not differ significantly between the two treatment group. However, subgroup analysis of grade 3 soft tissue sarcoma revealed a significant advantage of both relapse-free survival ($p = 0.03$) and time to distant failure ($p = 0.03$) in patients receiving HA-RT + ACT ($n = 25$) as compared to patients treated with HA-RT only ($n = 16$).

Treatment-associated toxicity in patients receiving HA-RT + ACT included alopecia of WHO grade 3 in all cases, leukopenia of WHO grades 1 and 2 in 19 patients (61%), grade 3 in 4 (13%) and grade 4 in 4 patients (13%), thrombocytopenia grades 1 and 2 in 7 patients (23%), grade 3 in 1 patient (3%) and grade 4 in 1 patient (3%). Non-hematologic toxicity consisted of stomatitis WHO grade 3 in 1 patient (3%). In 2 patients (6%), ACT was discontinued after 2 cycles due to impairment of wound healing. Acute local toxicity was mild (2 versus 3 moist desquamations in the HA-RT and HA-RT + ACT groups, respectively). Severe late local toxicity consisted of two infected endoprostheses (one in either group), one fracture of an irradiated thigh (HA-RT + ACT), and one case of severe fistulation with bone necrosis leading to amputation without evidence of local relapse (HA-RT + ACT).

We conclude that the addition of adjuvant ACT to adjuvant HA-RT in patients with surgically adequately removed grade 3 STS significantly improved relapse-free survival as well as time to distant failure. Furthermore, the inclusion of ACT should be considered in the treatment of grade 3 adult STS.

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## Prognostic factors in completely resected liposarcomas (LPS)

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**Purpose:** The aim of this study was to identify prognostic factors regarding recurrence and survival after complete resection of LPS.

**Patients and Methods:** All consecutive LPS (reviewed diagnosis), treated with curative intent at the G.U.H. from 1977–1997, were analyzed.

**Results:** 66 pts (35, 31; median age: 53 (range 11–80) years) were reviewed. 49 primary LPS, 17 recurrent LPS. Histology: myxoid n = 31, well-differentiated n = 22, dedifferentiated n = 7, pleomorphic n = 3, nos n = 3. Grade I: n = 48, grade II: n = 10, grade III: n = 6, nos: n = 2. During a median follow-up of 58 (range: 5–210) months, 20 pts developed a local recurrence (30%), and 11 pts distant metastases (17%). At analysis, histologic subtype and anatomic site were the only independent prognostic factors regarding local recurrence, tumor grade regarding distant metastases, and histologic subtype and tumor grade regarding disease-free and overall survival. Retroperitoneal localization, dedifferentiation and grade II–III were negative prognostic factors. Size, primary/recurrent LPS, and type of resection were not independent prognostic factors.

**Conclusion:** LPS have a relatively mild biologic behavior, with exception of dedifferentiated LPS and grade II–III tumors. Independent prognostic factors regarding recurrence, metastasis and survival are anatomic site, histologic subtype, and grade.

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## OSAD93: A multicentric pilot study of high dose ifosfamide (HDI) and CDDP in adult patients (PTS) with non metastatic osteosarcoma

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**Purpose:** Based on previous results in adults (Proc. ASCO 1993, abst. 1646), a multicentric pilot study of neoadjuvant chemotherapy with HDI and CDDP was initiated in pts > 16 years (ys) with osteosarcoma, in 1993.

**Methods:** 4 preoperative courses (crs) of SHOC (Ifosfamide: 3 g/m$^2$ d1 to d3 CDDP: 100 mg/m$^2$ d4) were given, followed by local treatment. Post operative chemotherapy was: *1)* 3 crs of SHOC in pts with ≤10% viable tumor cells, *2)* 3 crs of HOCA (Adriblastin: 60 mg/m$^2$, d1 to d2; Ifosfamide: 3 g/m$^2$ d1 to d2, CDDP: 100 mg/m$^2$ d3) in pts with >10% of viable tumor cells.

**Results:** 59 pts were included: 14 females/45 males; median age: 28 (range: 16–64). Tumor sites were: femur (25), tibia (10), humerus (6), flat bones (15), others (3). The toxicity of pre-operative SHOC was evaluated in 213 crs. Grade 3 and 4 neutropenia, and febrile neutropenia occurred after 19%, 40% and 10% of crs respectively; growth factors were administered in 20% of crs; grade 3 and 4 thrombopenia in 11% and 5% of crs respectively; grade 3 and 4 anaemia in 9% and 4% of crs respectively; grade 3–4 vomiting occurred after 21% of crs; grade 3 infections occurred after 5% of crs; 2/3 of patients underwent grade 3 alopecia after the 4th course; hospitalisation for toxicity occurred after 20% of crs. 53 pts underwent surgery after pre-operative SHOC (45 conservative; 8 radical). The pts who had progressed before surgery were considered as poor responders. Therefore, the histological response was: 16 (29%) good responders (Huvos 3–4), 40 (71%) bad responders (Huvos 1–2). With a 33 months median follow-up, overall and progression-free survival at 4 ys are 56% and 43% respectively.

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## Neoadjuvant radiochemotherapy (RCT) in soft tissue sarcoma

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**Purpose:** To evaluate response, long-term control, functional outcome and toxicity following neoadjuvant RCT in advanced and recurrent soft tissue sacoma.

**Methods:** Between 1992 and 1998, a total of 23 patients in whom primary curative limb sparing surgery seemed impossible entered the study. Sixteen patients (pts) had primary and 7 pts recurrent sarcoma. The stages (UICC 1997) were: rIA (2), rIIA (5), IIA (4), IIB (2), III (7), IV (3). RCT consisted of an accelerated split-course radiation (1.5–1.6 Gy twice daily, median total dose 60 Gy, range 60–64 Gy, break of 1 week after 30 Gy) with concomitant chemotherapy using adriamycin (50 mg/m$^2$/d on days 2 and 30) and ifosfamide (1.5 mg/m$^2$/d on days 1–5, 29–33). Median follow-up was 26 months (range 2–92 months).

**Results:** 22 pts underwent surgery with a curative (R0) resection being achieved in 20/22 (91%) pts and gross residual (R2) tumor or unclear tumor margins (RX) in 1 pt, respectively. Effective tumor-downstagigng was documented in 4/22 (18%) pts (ypT0: 3 pts, ypT1: 1 pt). Long-term local tumor control after R0/X resection remained 100%. Delayed wound healing was only noted in 1/22 (5%) patient. Four pts developed distant metastases. Overall-, NED- and distant-metastases-free survival rates were 83%, 64% and 68%, respectively, at 3 years. Grade 3/4 neutropenia (WHO) was seen after 21/46 (46%) cycles of chemotherapy with one pt dying of sepicemia. The functional results were good to excellent in 18/22 (82%) pts.

**Conclusion:** Accelerated split-course radiation with 60–64 Gy and concomitant chemotherapy using adriamycin/ifosfamide is a safe and effective treatment for soft tissue sarcoma. This regimen may be considered in all cases with recurrent and advanced disease not amenable to primary curative or limb sparing surgery.

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## Surgical management of gastrointestinal stromal tumors (GIST)

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**Purpose:** Clarify the surgical treatment of GIST.

**Methods:** 56 patients were identified from a single institution database. Local (L) or metastatic (M) first recurrence (R) were studied according to the type of surgery: wedge resection (WR) or organ resection (OR). When stomach or rectum were resected, total (T) and partial (P) resection were compared (total/partial gastrectomy; anterior resection/rectum abdomino perineal resection)

**Results:** Median age was 55 years. Location: stomach (Stom) 25, duodenum (Duod) 6, small intestine (Small int.) 19, rectum (Rect) 6. 7 patients