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# Long term survival in adult osteosarcoma patients treated with a two-drug regimen: Final results of the OSAD93 phase II study of the FSG-GETO

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ABSTRACT

*Rationale:* We report a phase II trial (OSAD93) testing CDDP with ifosfamide (IFO), without doxorubicin in neoadjuvant phase, in adult osteosarcoma with a 25 years follow-up.
*Patients and methods:* This is a multicentric phase II study of neoadjuvant chemotherapy with IFO and CDDP in localized high-grade osteosarcoma of patients. Patients received 4 pre-operative courses of IFO 9 g/m$^2$ and CDDP 100 mg/m$^2$ on day 4 (SHOC regimen), followed by local treatment. Doxorubicin was added post-operatively (HOCA regimen) in patients with > 10 % residual tumor cells. A Good Histological Response (GHR), ie ≤ 10 % residual tumor cells in > 30 % of patients, was the primary objective. Disease-free survival (DFS), overall survival (OS) and toxicity were secondary objectives.
*Results:* From Jan 1994 to Jun 1998, 60 patients were included. Median age was 27 (range: 16–63). Primary tumor sites were limbs (76 %), trunk, head or neck (24 %). After neoadjuvant SHOC, grade 3–4 and febrile neutropenia, thrombopenia, and re-hospitalization occurred in 58 %, 17 %, 17 % and 22 % of SHOC courses and in 76 %, 28 %, 47 %, 47 % of HOCA courses, respectively. GHR was obtained in 16/60 (27.5 %) patients. With a median follow-up of 322 months, the DFS and OS were 51.8 % and 64.4 % at 5 years. At 10 years, DFS and OS were 49.9 % and 64.4 %. At 25 years, DFS and OS were 47.8 % and 55.9 %. No long-term cardiac toxicity was observed. Three patients developed a second malignancy (one fatal) after 300 months.
*Conclusion:* Though the primary endpoint of OSAD93 was not met, this pre-operative doxorubicin-free regimen led to excellent long-term survival with limited toxicity in localized osteosarcoma.

## 1. Introduction

High-grade osteogenic sarcoma of the bone is a rare malignant primary tumor, affecting 6/1000,000 people annually [1,2]. Osteosarcoma often occur in children and adolescents, albeit > 25 % are diagnosed in adult patients [1–3]. The latter have a different clinical presentation, natural history and a worse prognosis in particular in patients over 40 [4–7].

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The treatment of osteosarcoma requires a multidisciplinary management. It combines neoadjuvant and/or adjuvant chemotherapy and surgical resection of the tumor [3,8–11]. The most frequently chosen therapeutic strategy is neoadjuvant chemotherapy [8–33], which enables the identification of patients with a poor histological response, to whom a change in post-operative chemotherapy may be proposed [3,30,31]. However, the recent EURAMOS randomized study failed to confirm the benefit of post-operative adaptation of chemotherapy with ifosfamide and VP16 in case of poor histological response [25,26]. The chemotherapeutic regimens used in osteosarcoma are based on different combinations of the following cytotoxic molecules: HDMTX, doxorubicin, cisplatin, ifosfamide, and VP16 [8–33]. The most commonly used, namely the MAP regimen, the AP regimen, T10B, the M-IE, API-AI were reported in very large series, with few randomized studies comparing these protocols directly [16–20,22,23,25,26].

Less intensive and complex regimens, lacking HDMTX or anthracycline have been investigated with the aim of minimizing the toxicity of these agents in cured patients, in children or adults [34–36]. Long-term cardiac toxicity, e.g., heart failure, occurs in up to 5 % of cured patients and is associated with a dismal prognosis. In addition, secondary leukemia is a frequent fatal complication of these treatments.

Few prospective studies have investigated specific regimens for adult high-grade osteosarcoma [4,7,28,34]. Our previous studies on neoadjuvant treatment of adult patients with osteosarcoma showed that an ifosfamide-CDDP based chemotherapy resulted in a good histological response rate with a 5-year disease-free and overall survival over 60 % [32,33,38].

This supported the launching in 1993 of the OSAD93 phase II study evaluating a combination of CDDP and ifosfamide in adult patients with high-grade osteosarcoma. We report here the long-term results of this study with a median follow-up of over 25 years.

## 2. Patients, material and methods

### 2.1. Patients

This prospective phase II study was conducted between January 1994 and June 1998 (Registration number, French Ministry of Health 94–0031). Inclusion criteria were as follows: age $\geq$ 16, high-grade osteogenic sarcoma, from the limb, trunk or head and neck, and without metastasis on a diagnostic work-up including CT scan and bone scan. Patients had to have had no previous treatment or previous malignancy, with normal renal, cardiac and hepatic functions. No concurrent therapy was allowed and patients were required to give a written informed consent prior to inclusion, according to French laws at that time. A description of patients is presented in Table 1.

Biological data at baseline and during treatment were obtained from local laboratories, including blood cell counts, platelets, alkaline phosphatase (ALP) levels, and lactate dehydrogenase (LDH) levels. For alkaline phosphatases and LDH, the normal range for the patient was added to the case report form. For prognostic analyses, we selected a threshold level of ALP and LDH levels of 120 % of the upper normal limit of the report to define the group with increased values. MRI and CT scans were conducted at baseline and during treatment at the hospital site.

### 2.2. Treatment

#### 2.2.1. Chemotherapeutic regimen before interim analysis

In the first part of the study (until June 1994), two distinct regimens were given according to the age of the patients:

**- 1) Patients under 25:** received a regimen combining high-dose methotrexate 8 g/m$^2$ at days 1, 8, 15, 43, 50, 68 and 75 and a combination of ifosfamide 3 g/m$^2$/day with MESNA on days 1–3, and CDDP 100 mg/m$^2$ on day 4 (the SHOC regimen) and on day 22, 57. Post-operative treatment was scheduled to be similar in patients with less than 10 % viable cells upon histological examination of the primary tumor, while 3 courses of the HOCA regimen (ifosfamide 3 g/m$^2$/day on days 1–2, doxorubicin 60 mg/m$^2$/day on day 1, CDDP 100 mg/m$^2$/day on day 3) at 21 days intervals were given to patients with a higher percentage of viable cells.

Only 3 patients were treated with this regimen pre-operatively, due to the occurrence of two grade 4 toxicity events among the 3 patients, leading to regimen discontinuation. They are not included in the analysis of the results of the SHOC regimen presented in the Results section.

**- 2) Patients aged 25 or over:** received 4 courses of SHOC at 21 days interval prior to surgical resection. After surgery, patients with less than 10 % viable cells upon histological examination of the primary tumor received two post-operative courses of SHOC, while 3 courses of the HOCA regimen at 21 days intervals were given to patients with a higher percentage of residual cells.

**Table 1**
Clinical description of the 63 patients.

| | | N (%) |
|---|---|---|
| **Age:** | median (range) | 27 (16–63) |
| **Age** | 16-24: | 26 (41 %) |
| | 25-40 | 23 (35 %) |
| | > 40: | 14 (23 %) |
| **Gender** | | |
| | M: | 49 (77 %) |
| | F: | 14 (22 %) |
| **Tumor site** | | |
| ***Limb*** | | |
| Femur: | Lower extremity | 16 (23 %) |
| | Upper | 4 (6 %) |
| | Diaphysis | 6 (10) |
| Tibia: | | 12 (12 %) |
| Humerus: | | 6 (10 %) |
| Others | | 3 (5 %) |
| ***Trunk/head &neck*** | | |
| Iliac | | 4 (6 %) |
| Mandible | | 4 (6 %) |
| Maxilla | | 3 (5 %) |
| Others | | 5 (13 %) |
| **Histological subtype** | | |
| Osteogenic sarcoma | | 43 (68 %) |
| Fibroblastic | | 4 (6 %) |
| Anaplastic: | | 2 (3 %) |
| Chondroblastic: | | 5 (8 %) |
| Others | | 4 (6 %) |
| Not specified | | 5 (8 %) |
| **Tumor size** | median (range) | 87 (20-220) |
| **on MRI (mm):** | | |
| not specified | | 7 (11 %) |
| **Alkaline phosphatases** | | |
| Ratio: Patient value/UNL | | |
| median (range) | | 1.2 (0.2-43) |

The three patients treated with HDMTX before the amendment were men, aged 19,23,24, with primary tumors of femur, tibia, and maxilla

#### 2.3. Chemotherapeutic regimen after interim analysis

In the second part of the study, after the amendment of June 1994 (see Results section first paragraph), patients aged under 25 received a similar pre-operative regimen as older patients, i.e., 4 courses of SHOC pre-operatively. As for older patients, the post-operative treatment was 2 courses of SHOC in patients with 10 % or fewer residual cells upon histological examination of the primary tumor, and 3 course of HOCA in patients with > 10 % residual tumor cells. In patients under 25 with more than 10 % residual cells upon histological examination of the primary tumor, post-operative treatment included anthracyclins, with HDMTX 8 g/m$^2$ day 1, 8, 15, 41, 48, 55, doxorubicin (80 mg/m$^2$) day 22 and 62 or HOCA left at investigators discretion.

### 2.4. Administration of chemotherapy

HDMTX was administered in 1.0 litre of 5 % dextrose in water with 1 mEq/kg of sodium bicarbonate administered as a 4-h infusion. Oral rescue with leucovorin began 20 h after each methotrexate infusion at a dose of 15 mg up to a total of 11 doses given every 6 h. Hydration and alkalinization were performed orally or intravenously (i.v.) to achieve urine output of 1600 L/$m^2$ for the first 24 h and 2000 L/$m^2$ for the next 48 h with urine pH in excess of 7.0. Serum methotrexate levels and renal function were monitored daily. HDMTX was administered on weeks 1, 2, 3, 6, 7, 10 and 11. Ifosfamide was administered over 3 h in 250–500 mL saline serum given daily. Mesna (3.6 g/$m^2$ /day) was given as a continuous infusion for 3 days, with hydration up to 2.0 L/day. CDDP was administered as a short i.v. infusion over 1 h in 3 % hypertonic saline. Doxorubicin was administered as a bolus i.v. infusion. Chemotherapy courses were given when an absolute neutrophil count above $1.5 \times 10^9$/L and platelets above $100 \times 10^9$/L were reached.

### 2.5. Local treatment

Surgical resection of the primary tumor was scheduled between 21 and 35 days after the fourth pre-operative course of SHOC, or 8–21 days after the last HDMTX course (for patients aged $< 25$ prior to interim analysis). Local treatment was conservative surgery or amputation for tumors of the limbs. For osteosarcomas of the trunk or head and neck, complete surgery was recommended if feasible. If not feasible or refused by the patient, external beam radiotherapy with photon (40 Grays) with daily fractions of 2 Grays followed by neutron therapy (equivalent to 20 Grays) was recommended, in particular for tumors of the pelvis and the trunk.

### 2.6. Follow-up

After the treatment phase, patients were followed for progression and survival according to the clinical practice guidelines at that time, usually 3–4 times monthly in the first 3 years, 6-monthly until 5 years, yearly until 10 years, and beyond 10 years, most often every 2 to 3 years, depending on the choice made by the investigators and patients. In addition, for the purpose of this report, each viable patient was contacted in 2023 by the team in charge to collect information on long-term adverse events or medical history.

### 2.7. Statistical analysis

#### 2.7.1. Endpoints

The main objective of this phase II regimen was to reach a good histological response rate to preoperative chemotherapy, as determined by the local pathologists of the reference/ participating center. Good histological response was defined here as a percentage of residual cells on histological samples equal to or under 10 % [32,39]. Secondary objectives were good disease-free, progression-free, and overall survival, and low toxicity. The minimal acceptable histological response to preoperative chemotherapy was set at 30 %. The expected histological response rate was 60 %.

#### 2.7.2. Experimental design

The trial was conducted in two stages, using the optimal two-stage design described by Simon [23]. The hypothesis was that a histological response rate of 30 % does not warrant further investigation of the regimen, and a response rate of 60 % would lead to the conclusion that the regimen deserved further investigation. α was the accepted probability of recommending the protocol for further trials, with a true response rate equal to or lower than 30 %: in the present trial, α was set at 0.05. β was the accepted probability of rejecting the drug from further trials with a true response rate of 60 %; in the present trial, β was set at 0.10. Given this hypothesis, the minimal sample size to be reached for the current trial was 53 patients.

### 2.8. First step

In this step, the trial could be discontinued after integrating 24 patients if and only if $\leq 7$ responses were observed, in which case the protocol would be deemed not sufficiently efficient. Otherwise, patients would be added to the trial until a minimum of 53 patients were evaluable for response.

### 2.9. Second step

In this step, if the trial was not discontinued in the first step, the study would be continued until 53 evaluable patients were included. It could then be discontinued if and only if $\leq 21$ responses were observed, in which case the protocol would be deemed to yield a histological response rate under 60 %. However, if $> 21$ good histological responses were observed, the trial would be stopped with the conclusion that the protocol induced a histological response rate above 30 %.

## 3. Discontinuation rules in the event of toxicity

A study of the feasibility of the protocol was scheduled. The maximal acceptable rate of non feasibility of the protocol was defined as 10 %. With an alpha risk of 5 % and a power of 95 %, the protocol would be stopped if either 2 of the first 3 patients, 3 of the first 8 patients, 4 of the first 14, or 5 of the first 20 could not complete the protocol and/or experienced grade 4 non-hematological toxicity or death.

## 4. Survival

Survival curves were plotted according to the Kaplan-Meier method, and compared using the logrank test. Multivariate analysis of prognostic factors for survival were performed using the Cox model. Statistical analyses were performed using the SPSS 23.0 software.

## 5. Results

### 5.1. Discontinuation due to toxicity for the first 3 patients aged under 25

Two of the first 3 patients aged under 25 experienced grade 4 non-hematological toxicity during the first 3 courses of HDMTX, and could not complete the following part of the protocol. These side effects occurred before the first preoperative course of SHOC. One patient experienced grade 4 liver cytolysis, one experienced grade 4 acute leucoencephalopathy both following HDMTX administration. Both patients received an adapted chemotherapy regimen and underwent tumor resection. Both subsequently relapsed and died of tumor progression. Because the discontinuation rule for toxicity was met, a study amendment was submitted in June 1994, and all subsequent patients regardless of age received 4 courses of SHOC as a preoperative regimen. This article reports these 60 patients.

### 5.2. Clinical description of the 60 patients

Sixty patients were included after the amendment. Description of all patients is provided in Table 1. Five (7 %) patients were aged between 16 and 18, and 14 (22 %) were above 40. Sixteen (28 %) patients had tumors in the trunk or head and neck.

### 5.3. Toxicity of pre- and postoperative regimens

#### 5.3.1. Preoperative chemotherapy

The side effects of 231 courses of preoperative SHOC given to 60 patients are reported in Table 2. Febrile neutropenia was reported after 40 of the 231 courses (17 %). Platelets and red blood cell transfusion

**Table 2**
Toxicity of SHOC & HOCA regimens.

| | Grade | | | | |
|---|---|---|---|---|---|
| | **0** | **1** | **2** | **3** | **4** |
| **SHOC** | | | | | |
| **Nausea/Vom.** | 48 (21 %) | 47 (21 %) | 72 (31 %) | **45 (26 %)** | **5 (2 %)** |
| **Mucositis** | 199 (86 %) | 18 (8 %) | 8 (3 %) | **0** | **0** |
| **Renal** | 219 (97 %) | 1 (0.5 %) | 0 | **0** | **1 (0.5 %)** |
| **Cardiac** | 218 (97 %) | 2 (1 %) | 0 | **1 (0.5 %)** | **0** |
| **Neurological** | | | | | |
| - Central | 228 (100 %) | 0 | 0 | **0** | **0** |
| - Peripheral | 218 (97 %) | 4 (2 %) | 2 (1 %) | **0** | **0** |
| **Fever** | 178 (77 %) | 2 (1 %) | 25 (11 %) | **20 (9 %)** | **0** |
| **Neutropenia** | 44 (19 %) | 12 (5 %) | 18 (8 %) | **42 (18 %)** | **89 (40 %)** |
| **Thrombopenia** | 138 (66 %) | 17 (8 %) | 18 (8 %) | **25 (12 %)** | **11 (5 %)** |
| **Anemia** | 101 (49 %) | 46 (22 %) | 31 (15 %) | **21 (10 %)** | **7 (3 %)** |
| **Infection** | 193 (87 %) | 4 (2 %) | 13 (6 %) | **11 (5 %)** | **0** |
| **HOCA** | | | | | |
| **Nausea/Vom.** | 20 (25 %) | 21 (25 %) | 25 (31 %) | **15 (19 %)** | **0** |
| **Mucositis** | 67 (85 %) | 9 (11 %) | 3 (4 %) | **1 (1 %)** | **0** |
| **Renal** | 81 (100 %) | 0 | 0 | **0** | **0** |
| **Cardiac** | 80 (97 %) | 0 | 0 | **0** | **1 (1 %)** |
| **Neurological** | | | | | |
| - Central | 78 (100 %) | 1 (1 %) | 0 | **0** | **0** |
| - Peripheral | 68 (97 %) | 9 (2 %) | 3 (1 %) | **0** | **0** |
| **Fever** | 63 (79 %) | 2 (3 %) | 10 (14 %) | **4 (5 %)** | **0** |
| **Neutropenia** | 10 (13 %) | 1 (1 %) | 6 (8 %) | **10 (13 %)** | **47 (63 %)** |
| **Thrombopenia** | 23 (31 %) | 6 (8 %) | 10 (13 %) | **11 (15 %)** | **24 (32 %)** |
| **Anemia** | 20 (27 %) | 19 (26 %) | 24 (32 %) | **5 (6 %)** | **5 (6 %)** |
| **Infection** | 70 (87 %) | 3 (4 %) | 2 (3 %) | **5 (6 %)** | **1 (1 %)** |

1: n = 1 non-evaluable because treated with RT only-these 2 patients (one aged <25, the other >25) did not receive postoperative chemotherapy.
2: including 2 patients who progressed during preoperative chemotherapy
3: including 4 patients who progressed under preoperative chemotherapy

were given after 24 (10 %) and 51 (22 %) courses, respectively. Rehospitalization occurred after 43 (19 %) SHOC courses.

### 5.3.2. Postoperative chemotherapy

Postoperative treatment is described in Figure 1. Ten patients did not receive postoperative chemotherapy, because of progression under preoperative chemotherapy (n = 5), refusal (n = 2) death before surgery (n = 1), doctor's decision (n = 2).

Fifty of the 60 patients included received postoperative chemotherapy: the SHOC regimen (n = 12), the HOCA regimen (n = 28), HDMTX/doxorubicin (n = 8), or doxorubicin alone (n = 2). Three patients with good histological response and aged above 25 received HOCA (n = 2) or doxorubicin (n = 1) as protocol violation. One patient aged above 25 with poor histological response received doxorubicin as a single agent.

Eight patients aged under 25 received HDMTX and doxorubicin because of a poor histological response to preoperative chemotherapy: 2 (25 %) and 6 (75 %) experienced grade 3–4 thrombopenia and neutropenia, respectively, and 2 experienced febrile neutropenia (25 %).

The side effects of the 76 courses of HOCA are reported in Table 2. 6 of 28 patients received less than 3 courses because of toxicity or refusal. Febrile neutropenia was observed after 28 of 76 courses (29 %). Platelets and red blood cell transfusion were given after 12 (15 %) and 11 (26 %) courses, respectively. Rehospitalization was needed after 21 (27 %) of the HOCA courses. The toxicity of the postoperative courses of

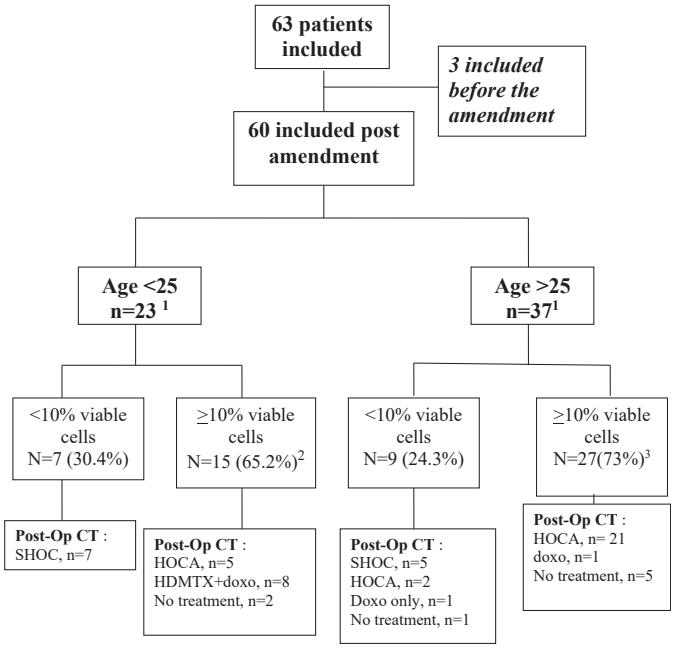


**Fig. 1. Description of the responses and post operative treatment**. 1: n = 2 patients non evaluable for histological response (because treated with RT only)-these patients did not receive postoperative chemotherapy. 2: including 2 patients who experienced clinical and radiological progression during preoperative chemotherapy. 3: including 4 patients who experienced clinical and radiological progression during preoperative chemotherapy.

SHOC and HDMTX/doxorubicin are described in supplementary Tables. The HOCA regimen was associated with more frequent and severe adverse events compared to SHOC and HDMTX/doxorubicin.

### 5.3.3. Long-term events

Two (6.1 %) of the 33 long-term survivors presented chronic renal failure. Another patient (n = 1, 3 %) was reported to present infertility with azoospermia, and another (n = 1, 3 %) reported persistent hypoacousia. Three (9.1 %) patients were reported to have a diagnosis of secondary cancer, 303, 312 and 326 months after inclusion, one low grade osteosarcoma in a different site, one glioblastoma close to the irradiated field of the sarcoma of maxillary bone, one with an epidermoid carcinoma of the skin. The three patients had no documented genetic predisposition.

### 5.4. Primary endpoint: good histological response

Among the 60 patients included post-amendment, 6 (10 %) underwent amputation as local treatment, 2 (3.3 %) underwent radiotherapy only and 52 (86.7 %) had conservative surgery. The 2 patients who received radiotherapy only without evidence of progression (1 osteosarcoma of the maxilla, one of the base of the skull) were considered as non-evaluable for the primary endpoint. Six of the 60 patients (10 %) had complete histological response to preoperative SHOC (grade 4). Ten (16.7 %) had 1–10 % residual cells on the primary tumor (grade 3), 16 (26.7 %) had 11–50 % residual viable cells on the primary tumor (grade 2), and 20 (33.3 %) had more than 50 % residual tumor cells in the primary tumor. Six had no report on the percentage of residual tumor cells but were reported as poor responders. Taken together, 16 of 60 (26.7 %) of all patients and 16 of 58 (27.5 %) operated patients were qualified as good responders to preoperative chemotherapy with SHOC.

### 5.5. Survival

The median follow-up of the whole series was 322 months (26 years

and 10 months).

At 60 months, disease-free survival (DFS) and overall survival (OS) of the 60 patients were 51.8 % and 64.4 %, respectively (Fig. 2). At 120 and 300 months, the DFS of the 60 patients was 49.9 % and 47.8 %, while OS was 64.4 % and 55.9 % (Fig. 2).

There was no death from osteosarcoma after 93 months, and only one relapse after 67 months (local relapse resected at 157 months, alive and progression-free 72 months after).

No significant difference of DFS or OS were observed in patients with primary site on the limbs vs trunk/head and neck, flat bone vs long bones, male vs female sex, size of the tumor > 100 mm on MRI or X-Ray/CT scan (not shown).

No significant survival difference was observed across the 4 groups of histological responders (Figure 3 A, p = 0.13), but patients with grade 4 complete histological response had a better survival than the 3 other groups combined (logrank, p = 0.01). Long-term survival was similar

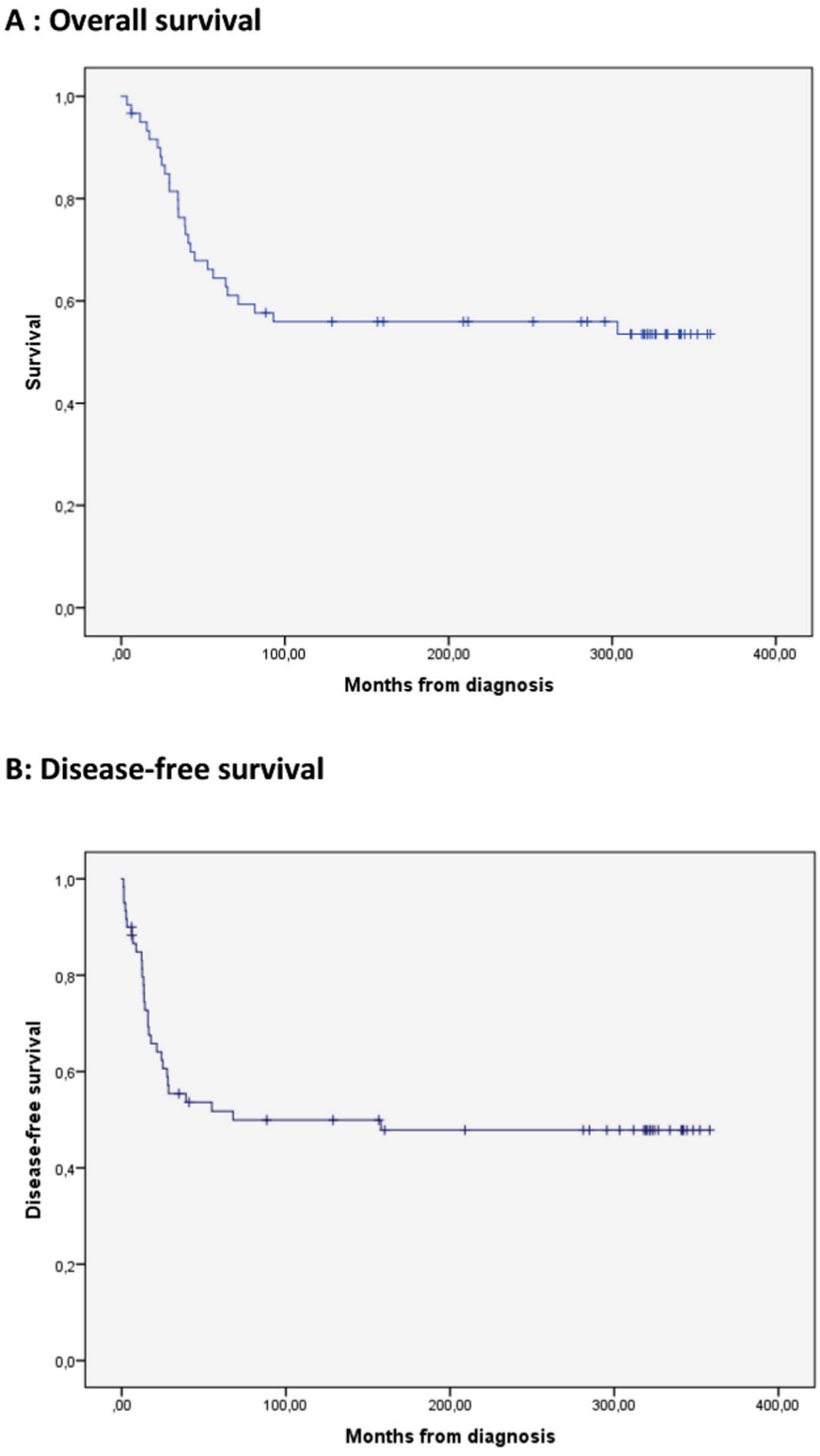


**Fig. 2.** A & 2B: Disease-free and overall survival of the OSAD93 series.

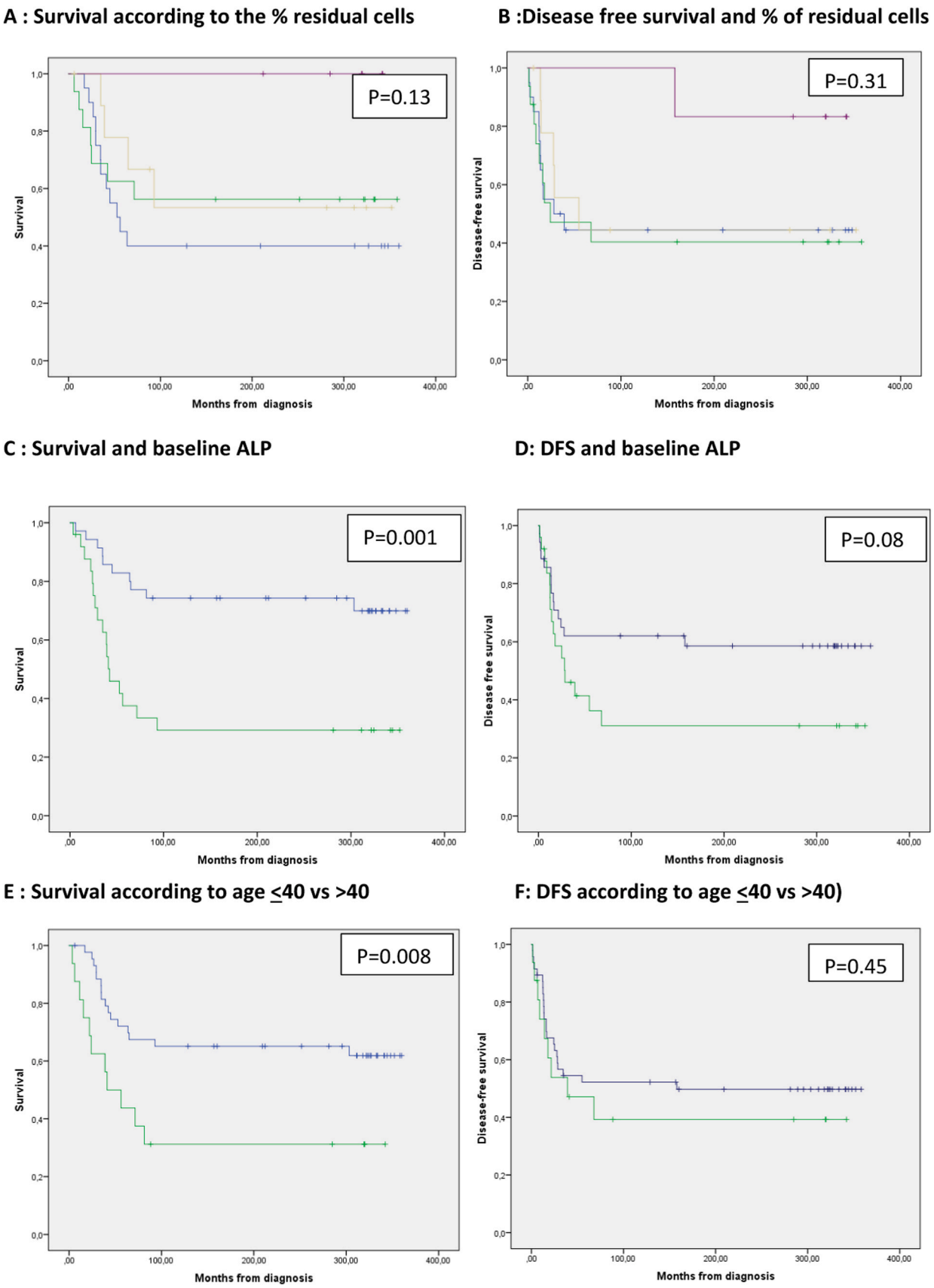


**Fig. 3. Survival and disease-free survival of the whole cohort.** A: OS according to the percent of viable tumor cells: purple 0 %, brown 1–10 %, green: 11–50 %, blue > 50 %. B: DFS according to the percent of viable tumor cells purple 0 %, brown 1–10 %, green: 11–50 %, blue > 50 %. C: OS according to baseline alkaline phosphatase levels (≤1.2 in blue vs >1.2 ULN in green). D: DFS according to baseline alkaline phosphatase levels (≤1.2 in blue vs >1.2 ULN in green). E: OS in patients age≤ 40 in blue vs > 40 in green. F: DFS in patients age≤ 40 in blue vs > 40 in green.

for patients with 1–10 % vs 11–50 % vs > 50 % residual cells for OS or DFS (Figure 3).

Patients aged above 40 had a significantly lower OS, but a similar DFS (Figure 3).

Alkaline phosphatase levels determined before treatment were correlated with tumor size on X ray or CT-scan (Pearson's correlation test: 0.651, $p < 0.0001$) but not on MRI (Pearson's correlation test: 0.089, $p = 0.55$). Survival was significantly worse in patients with increased alkaline phosphatase levels (>1.2 UNL, see Material and Methods) at diagnosis, while the difference was not statistically significant for DFS (Figure 3). Alkaline phosphatase levels after neoadjuvant chemotherapy, at the time of local treatment had no prognostic value for survival, nor did the normalization of ALP levels in patients with increased baseline (not shown).

Finally, we explored prognostic factors for DFS and OS in univariate and multivariate analysis using a Cox model. Age, sex, pre-treatment alkaline phosphatase levels, limb sites vs other sites, and good histological response (≤10 % vs others) were tested. No significant ($p < 0.05$) prognostic factors for DFS were identified in univariate. In multivariate analysis, increased ALP was the only parameter retained in the model (Table 3).

For OS, in univariate analysis, good histological response, age > 40 and baseline alkaline phosphatase level were the only parameters correlated with OS. High baseline alkaline phosphatase levels (Hazard ratio 5,33 [95 % CI:3.39.–8.38], $p < 0.001$) and good histological response (Hazard ratio 0,24 [95 % CI:0.12.–0.42], $p = 0.0001$) were retained in the Cox model (Table 3).

## 6. Discussion

Although 30 % of osteosarcoma are diagnosed in adult patients [1–3], only a limited number of clinical trials have specifically investigated osteogenic sarcoma in adult patients [4,7,28,34]. Osteogenic sarcomas occurring in adults have distinct natural history and clinical presentations than in children, and a higher risk of toxicity with HDMTX and doxorubicin in the short-, mid- and long-term [34–36].

OSAD93 was a multicentric prospective phase II trial exploring an age-adapted neoadjuvant and adjuvant chemotherapy for adult osteosarcomas, using a neoadjuvant regimen of CDDP and ifosfamide only, without preoperative doxorubicin or HDMTX, with a follow-up over 25 years. This study had previously been reported as an abstract format over a decade ago.

To our knowledge, together with the long-term follow-up of the Bernthal et al study [10], this is the series with the longest median follow-up reported in osteosarcoma.

### 6.1. Rationale for the selection of the regimen

The preoperative regimen combined high-dose ifosfamide and CDDP, without doxorubicin, based on a previous trial [32,38]. While HDMTX was initially kept for patients aged < 25 in the pre-amendment version of the protocol, a discontinuation rule for toxicity was met after 2 patients experienced grade 4 toxicity with HDMTX. All 60 patients presented herein therefore received ifosfamide and CDDP (SHOC regimen) as neoadjuvant treatment. The postoperative regimen was modified in case of poor histological response, with the addition of doxorubicin, and with the possibility, as used in 8 patients, to add HDMTX for patients aged < 25. However, this postoperative program was not applied in 10 (17 % of patients) patients following their decision or that of their physician. This is one of the limitations of this study. In 1993, the rationale to investigate this SHOC regimen in adult osteosarcoma stemmed from different considerations: 1) the distinct clinical presentations and natural history of adult patients with osteosarcoma as well as their worse prognosis compared to children when pediatric protocols were used; 2) the poor tolerance to regimens used in osteosarcoma of children in particular HDMTX, and 3) the high cumulated dose of doxorubicin that may result in late cardiac complications and substantial morbidity for cured adult patients [35,36]. The encouraging results observed with ifosfamide and without HDMTX, in both phase II trials led to the selection of these protocols [32,33,38].

### 6.2. Characteristics of the patients

The population of patients included was notably different from that of most large multicentric series of trials on osteosarcoma. In OSAD93, there was a greater proportion of trunk tumors (24 % vs 4 % in the EURAMOS study and 6 % in the COSS series, 0 % in the OS94, 8 % in OS2006) [5,23,27,39]. This parameter is associated with a worse prognosis in children [40].

Not unexpectedly, there were 54 (3.2 %) patients aged> 40 in the compiled series of the COSS including 1702 patients, 12 %> 25 years in OS2006, 0 % in OS94 vs 14/60 (22 %) in the present series [40,41]. All these characteristics have been reported to be negatively correlated with prognosis [4,39,40]. In the present study, increased ALP levels (>1.2UNL) were a prognostic factor for survival. This level (20 % in OSAD93) was similar to a series in children (23 % in OS94) [23].

### 6.3. Primary endpoint

The primary endpoint of the present phase II study was the rate of histological response (0–10 % residual tumor cells). The results obtained in the 58 evaluable patients showed that the SHOC regimen yielded a good histological response in 26.7 % of patients, and failed to reach the 30 % good histological response rate selected as the threshold level. Of note, 6 patients progressed before the date of surgery. Two patients were aged> 40; one (aged 63) was not operated because of a worsening clinical condition, and 1 had no documented histological response. Both died before 20 months. The remaining 4 patients (aged<40) had a grade 1 or 2 histological response and were alive progression free in 2023. With the AP or HDMTX plus AP regimens for limb sarcomas, response rates ranged from 34 % (OS94), 52 % (EURAMOS) 55 % (COSS), 65 % (OS2006) [5,23,27,39,40]. In series of adult patients, response rates were 34 % for API-AI [7], 41 % and 60 % for API-AI and MEI in the 18–25 year-old population [28], while no consolidated numbers are reported in the EUROBOSS study [6]. The histological response rate observed in the OSAD93 study was therefore low but close to that of patients in the same age group in the literature.

**Table 3**
Prognostic factors.

| | | **Disease-free survival** | | | **Overall survival** | | |
|---|---|---|---|---|---|---|---|
| | | Univariate (logrank p) | Cox | | Univariate (logrank p) | Cox | |
| | | | RR (95 % CI) | P | | RR (95 % CI) | p |
| **Age (years)** | ≤ 40 vs > 40 | 0.65 | - | | **0048** | **-** | |
| **Site (bone)** | Limb vs trunk | 0.64 | - | | 0699 | | |
| **Sex** | Female vs male | 0,51 | - | | 0,09 | | |
| **ALP** | ≤ vs > 1.2 UNL | 0.07 | **2.22 [1.49-3.95]** | **0.044** | **0.003** | **5.33 [3.39-8.38]** | **< 0.001** |
| **Histol. Response** | ≤ 10 % vs > 10 % | 0.08 | - | | **0.012** | **0.24 [0.12-0.42]** | **0.011** |

#### 6.3.1. DFS & OS

Disease-free survival was 51.8 % and 49.9 % at 5 and 10 years, respectively, in the OSAD93.

With the limits of indirect comparisons, in the EURAMOS study, the event-free survival (EFS) was 60 % for all M0 patients at 5 years, but with an unfavorable hazard ratio of 1.53 in adult patients [40]. In the EOI study using AP, the 5-year EFS was 40 % [20], while it was 53 % with MEI in adults [29], and 50 % within the OS2006 subgroup of patients aged 18–25 [28]. Five-year EFS was reported to be 50 % for EUROBOSS with a median follow-up of 35 months [6].

In long-term studies by Bielack et al [5], Bernthal et al [10], Longhi et al [42] and Mc Tiernan et al [43] with a patient follow-up of 10 years, these series of osteosarcoma of all ages had an EFS of 49.8 %, 28 %, 42 % and 48 %, respectively, compared to 49.9 % for OSAD93 with only adult osteosarcoma. At 20 years, the EFS was 28 % and 40 % for two of these studies with long-term follow-up [10,41] vs 47.8 % for the present OSAD93. The results obtained with adult patients of our OSAD93 study are very similar to series using T10, AP, MAP regimens.

The overall survival was 64.4 % and 56 % at 5 and 10 years (and beyond), respectively, in our study. In the EURAMOS study, the OS was 76 % for M0 patients at 5 years, but was not specifically reported for adults, and once again had an unfavorable hazard ratio of 1.27 for adult patients [40]. In the EOI study using AP, the 5-year OS was 50 % [20], while it was 60 % within the OS2006 subgroup of patients aged 18–25 [28]. Of note, the 5-year OS for the EUROBOSS study was 60 % with a median follow-up of 35 months [6]. Overall, these protocols report a 5-year OS ranging from 40 % to 60 %, consistent with our OSAD93 series (53.8 %) [6].

Long-term studies with a follow-up of 10 years, which also included series of patients of all ages with osteosarcoma [5,10,41,42], reported on an OS of 59.8 %, 38 %, 53 %, and 40 %, respectively, again consistent with our 10-year OS rate of 56 %.

At 20 years, the OS was 56 % in OSAD93, 38 % for the Bernthal study [10], and 43 % in the study by Longhi et al [42]. The results obtained in our adult population are in the same range to those obtained with standard protocols for osteosarcoma of all ages.

Whether the modification in the postoperative treatment of poor responders (grade 1 and 2) contributed to the favorable outcome cannot be established from our study. The randomized EURAMOS study testing postoperative treatment adaptation was negative for the primary endpoint [26] suggesting that it should not have had a major impact.

### 6.4. Toxicity

In the present study, the initial regimen included HDMTX for patients aged < 25, but had to be amended because of 2 severe toxic events leading to discontinuation rules as scheduled in the protocol. However, HDMTX was given to 8 patients < 25 postoperatively with acceptable toxicity (suppl. Tables). The toxicity of the SHOC and HOCA regimens was acceptable, in terms of acute, mainly haematological toxicity. HOCA was associated with more severe adverse events in the postoperative setting compared to the SHOC regimen.

The long-term adverse events and medical history were collected from the different sites in 2023, by contacting patients directly. The declared long-term toxicity of the treatment was limited: no cardiac toxicity was reported in the present series for long-term survivors, with a regimen in which the total dose of doxorubicin did not exceed 240 mg/m$^2$. This contrasts with the 5–9 % rate of cardiac failure and 50 % mortality at 5 years, reported in other series with long-term follow-up [10,34–37,41,42]. In addition, the rate of secondary malignancies was limited, and occurred at a very late stage, all > 25 years after the diagnosis of osteosarcoma. The nature of the secondary malignancies, i.e., glioblastoma, close to the site of radiotherapy for one of the 2 patients who had not been operated, and a second low grade osteosarcoma for another patient, suggest a possible genetic predisposition which was not tested. The third secondary cancer was a skin carcinoma.

### 6.5. Prognostic factors

Only alkaline phosphatase levels was a prognostic factor for DFS. Prognostic factors for OS were age > 40, good histological response to neoadjuvant CT and pre-treatment alkaline phosphatase levels. Alkaline phosphatase levels are generally higher in patients under 16, not included in this study, and in women. The threshold level of ALP used here was therefore 120 % of the upper normal limit for ALP in the local biological report. The poor DFS and OS of patients with grade 1 and 2 histological responses in this series is consistent with previous studies, but it is interesting to note that in this adult series of osteosarcoma, only grade 4 (0 % residual osteosarcoma cell) had a superior long term OS. Interestingly also, among the 6 patients reported to have progressed during neoadjuvant treatment, 4 are long term survivors. The long-term survival of patients with > 50 %, 11 %– 50 %, 1–10 % residual cells after neoadjuvant therapy was actually very similar in the long term. In multivariate analysis, both good histological response and increased ALP levels (>1.2 ULN) were retained as an independent prognostic factors for OS. The survival of the 31/60 (52 %) patients with ALP under 1.2 UNL was > 70 % at 30 years, which is remarkably good.

**In conclusion,** the OSAD93 protocol failed to reach its primary endpoint 25 years ago. However, it yielded very good levels of disease-free and overall survival in this population of non-metastatic adult osteosarcoma 30 years after its initiation.

This is a simpler, less intensive protocol, with limited toxicity. Long-term survival was in the same range as that of the very few series of osteosarcoma of all ages, treated with standard protocols. Long-term toxicity was limited with no reported cases of cardiotoxicity.

This protocol represents a reasonable option for the treatment of osteosarcoma of adult patients, in particular to minimize the risk of long-term cardiac toxicity.

This analysis also shows the importance of very long-term follow-up of clinical trials. For curable diseases, such analyses should be encouraged to gain a better understanding of the efficacy of treatments in the long term.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114228.

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