

# Predictive factors for local recurrence in osteosarcoma

## 540 patients with extremity tumors followed for minimum 2.5 years after neoadjuvant chemotherapy

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We investigated predictive factors for local recurrence in 540 patients with non-metastatic osteosarcoma of the extremity treated with surgery and neoadjuvant chemotherapy, between March 1983 and October 1994. The median follow-up was 7.5 (2.5–15) years. Local recurrences developed in 31 (6%) patients after a median time of 2 (0.5–7) years. Local recurrence did not correlate with patients' age and sex, histologic subtype, site and tumor volume, presence of pathologic fracture, chemotherapy regimen and type of surgery. Local recurrence-free survival (LRFS) correlated with the quality of surgical margins and response to chemotherapy: the 7-year LRFS was 97% after adequate surgical margins and 71% after inadequate surgical margins ( $p < 0.0001$ ), and was 95% in good responders and 90% in poor

responders ( $p = 0.001$ ). Only 1 of 31 patients with local recurrence was free of disease 15 months after the last treatment, 3 were alive with uncontrolled disease and 27 died. This post-relapse outcome is significantly worse than in patients who relapsed with metastases only (25% free of disease, 0.5–9 years after the last treatment). We conclude that, in osteosarcoma of the extremity, limb-salvage procedures should be planned only when the preoperative staging indicates that it is possible to achieve adequate surgical margins. If the pathologic examination of the surgical specimen shows inadequate surgical margins, an immediate amputation should be considered, especially if the histologic response to preoperative chemotherapy was poor.

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High-grade osteosarcoma of the extremity has a natural history of rapid growth and early metastases. When treated with surgery alone, usually with amputation, the cure rate was poor: approximately 10% (Campanacci et al. 1981). The use of adjuvant chemotherapy increased the cure rate to 56% (Link et al. 1986, Eilber et al. 1987). However, most of the patients still underwent amputation. In more recent years, neoadjuvant chemotherapy has been introduced. (Rosen et al. 1982, Saeter et al. 1991, Bramwell et al. 1992, Bacci et al. 1993). Preoperative chemotherapy may reduce the tumor volume facilitating limb-salvage.

Limb-salvage may increase the risk of inadequate surgical margins, which predisposes to local recurrence (Enneking and Kagan 1975, Price et al. 1975, Campanacci and Laus 1980).

Few authors (Delepine et al. 1996, Kempf-Bielack et al. 1996) have studied the type of surgical margins

and their importance as risk factors for local recurrences in patients with osteosarcoma of the extremity receiving neoadjuvant chemotherapy and limb-salvage surgery. We have previously (Picci et al. 1994, 1997) analyzed factors influencing the local recurrence in patients with osteosarcoma (Table 1). These studies, however, comprised a heterogeneous group of patients that included, besides patients with osteosarcoma of the extremity who entered the first 3 Rizzoli Neoadjuvant Studies, patients with metastatic osteosarcoma at presentation, patients with tumor not confined to the extremity, patients aged 40 or older, who received a chemotherapy regimen without methotrexate, and patients who refused chemotherapy.

In our current study, we analyzed factors prognostic for local recurrence in a larger (540 cases) and homogeneous group of patients aged 40 or younger, with non-metastatic osteosarcoma of the extremity, treated with no major violations of the first 5 Rizzoli

**Table 1.** Number of patients with osteosarcoma treated at Rizzoli Institute between March 1983 and October 1994 and reported in the 2 previous and present studies on predictive factors for local recurrence

	Picci et al. 1994	Picci et al. 1997	Present study
Period	3/83–12/88	3/83–8/91	3/83–10/94
Patients with non-metastatic osteosarcoma of the extremity	219	376 (219+157)	579 (376+203)
Patients with metastases at presentation	32	42 (32+10)	0
Other than extremity location	9	0	0
Osteosarcoma varieties	8	6	0
Patients who refused chemotherapy	19	0	0
Patients who received only postoperative chemotherapy	27	29 (27+2)	0
Patients aged >40 years who received a modified chemotherapy treatment	41	61 (41+20)	0
Total	355	514	579

**Table 2.** Limb-salvage (LS) and local recurrences (LR) according to the 5 chemotherapy protocols investigated

Protocol period	Preoperative chemotherapy	Postoperative chemotherapy	n	LS	LR	necr. $\geq 90\%$	Adeq. SM	30 mo DFS
1° (1983–86)	MTX-CDP	GR: MTX-CDP-ADM PR: ADM-BCD	126	71%	4.8%	48%	89%	54%
2° (1986–89)	MTX-CDP-ADM	GR: MTX-CDP-ADM PR: MTX-CDP-VP16-IFO-ADM	142	85%	2.8%	77%	82%	82%
3° (1990–91)	MTX-CDP-ADM	GR: MTX-CDP-ADM PR: MTX-CDP-ADM-IFO	96	80%	8.3%	54%	88%	61%
4° (1991–92)	MTX-CDP-ADM	MTX-CDP-ADM-IFO	59	88%	5.1%	78%	86%	71%
5° (1993–94)	MTX-CDP-IFO-ADM	MTX-CDP-IFO-ADM	117	95%	8.5%	78%	81%	77%
Total			540	84%	5.7%	66%	85%	70%

CDP was delivered intra-arterially. Only in the 3° protocol were patients randomized to receive CDP i.a. or i.v. M methotrexate, P cisplatin, given intrarterially but, in the 3rd protocol, patients were randomized to receive P intraarterially or intravenously, A doxorubicin, BCD bleomycin cyclophosphamide dactinomycin, E etoposide, I ifosfamide, GR good responder patients ( $\geq 90\%$  tumor necrosis), PR poor responder patients ( $< 90\%$  tumor necrosis), SM surgical margins, 30 months DFS disease-free survival at a real follow-up of 30 months.

Neoadjuvant Protocols for chemotherapy. Our series adds 203 patients with non-metastatic osteosarcoma of the extremity, not included in the previous studies.

## Patients and methods

### Patient selection

579 patients with non-metastatic osteosarcoma of the extremity, younger than 40 years, entered the first 5 Rizzoli neoadjuvant studies, carried out between March 1983 and October 1994. 33 patients were excluded for major protocol violations, 5 because of death caused by chemotherapy toxicity and 1 because of death unrelated to disease; the remaining 540 patients were included in this study.

### Preoperative evaluation and chemotherapy

The diagnosis of osteosarcoma was always made by histologic examination of specimens, taken from an

open biopsy. The primary tumor was evaluated by plain roentgenograms, technetium bone scintigraphy, angiography, and CT and MRI in recent years. Metastatic disease was investigated, using bone scintigraphy and CT of the lungs. All examinations were repeated after primary chemotherapy, before definitive surgery.

Chemotherapy was given according to 5 regimens (Table 2).

### Surgery

The type of surgery (amputation, limb-salvage or rotationplasty) as well as the type of reconstruction for patients treated with limb-salvage (prosthesis, allograft, vascularized graft) were chosen according to location and extension of the tumor, the patient's age and the desired life style. Limb-preserving surgery was only performed if preoperative staging showed that it was possible to achieve adequate surgical margins.

**Table 3. Local recurrences according to the surgical margins and histologic response variables**

	Patients	Local recurrences	CP of LR% <sup>a</sup>	P-value <sup>b</sup>
Sex				
Men	307	21	8.5	0.2
Women	233	10	4.8	
Age				
<14 years	228	16	8.2	0.3
≥14 years	312	15	5.9	
Site				
Femur	292	23	9.1	0.1
Tibia	146	6	5.5	
Humerus	65	2	3.4	
Other	37	0	0	
Histology				
Osteoblastic	370	22	7	0.9
Chondroblastic	70	3	4.6	
Fibroblastic	43	3	4.8	
Other	57	4	9.9	
Volume <sup>c</sup>				
< 150 mL	155	9	6.5	0.5
≥ 150 mL	203	8	4.7	
Fracture				
Yes	71	5	7.5	0.6
No	469	27	6.7	
Surgery				
Amputation	61	2	3.5	0.7
Rotation plasty	27	2	7.4	
Limb-salvage	452	28	7.2	

<sup>a</sup> CP Cumulative probability: 7-year local recurrence probability, according to Kaplan-Meier analysis.

<sup>b</sup> Log rank test.

<sup>c</sup> Tumor volume measured in 358 patients

61 (11%) of the 540 patients underwent amputation, 27 (5%) patients had a rotationplasty and 452 (84%) patients had a limb-salvage (Table 3).

### **Pathological evaluation of the surgical margins and of the response to chemotherapy**

After surgery, the entire specimen was evaluated in detail and any suspicious margin was marked with Indian ink.

Surgical margins were defined according to Enneking et al. (1980). The least adequate margin, microscopically, in the entire specimen was taken as the definitive margin. Radical surgical margins were achieved in 31 patients (6%), wide in 426 (79%), marginal in 55 (10%), intralesional in 18 (3%) and contaminated in 10 (2%) patients, thus 15% had inadequate surgical margins (marginal, intralesional, contaminated).

A larger percentage of inadequate surgical margins was seen in resected patients than in patients who underwent amputation (18% vs 3%;  $p = 0.001$ ). The adequacy of surgical margins did not correlate with tumor size (adequate surgical margins: 86% for tumor

< 150 mL vs. 84% for tumor ≥ 150 mL;  $p = 0.6$ ) and the site of the tumor (adequate surgical margins: femur 85%, tibia 87%, humerus 75%, others 89%;  $p = 0.2$ ).

The histologic evaluation of the response of the primary tumor was performed by Picci et al.'s method (1985): the resected specimen was sectioned in the longitudinal plane, photographed, divided into sections and numbered. From 5 to 28 blocks per specimen were histopathologically reviewed, to determine the amount of tumor necrosis. The histologic response was graded as total (no viable tumor cells), good (≥ 90% tumor necrosis) or poor (< 90% tumor necrosis). A good response was achieved among 359 (66%) patients with total necrosis in 97 (18%) cases. The rate of good histologic response was lower in the chondroblastic subtype (50%) than in osteoblastic (66%), fibroblastic (70%) and other (74%) histotypes ( $p < 0.001$ ).

### **Follow-up**

No patients were lost to follow-up. During the post-operative chemotherapy, radiographs were taken of the operated limb and of the chest at 2-month intervals. After completion of chemotherapy, all patients were followed in the outpatient clinic in our institution at 2-month intervals for the first 3 years and then every 6 months by roentgenograms of the primary site and the chest. Additional investigations were made, when clinically indicated. Local recurrences, suspected from clinical and radiologic findings, were always confirmed by histologic examination of an open biopsy or of surgical specimens.

In May 1997, with a median follow-up of 90 (30–177) months, 329 (61%) patients remained continuously free of disease and 211 patients had relapsed: 31 (6%) with local recurrence (all also had metastases) and 180 (33%) with distant metastases. The median time to local recurrence was 21 (5–76) months.

Local recurrence was always associated with metastases: to the lungs in 20 patients and to other bones in 11 patients. In 18 patients, metastases developed 6 (2–14) months after local recurrence, in 10 patients local recurrence and metastases occurred simultaneously and in 3 patients, local recurrence was diagnosed 4, 12 and 18 months after metastases.

Only 1 patient, who relapsed with local recurrence and simultaneous lung metastases 76 months after the beginning of primary treatment, is presently alive and free of disease, 21 months after a new limb salvage together with a simultaneous resection of lung metastases and chemotherapy with high-dose ifosfamide (15 g/m<sup>2</sup>, by continuous infusion for 5 days). 3 patients are alive with uncontrolled disease 10, 11 and

16 months after relapse and 27 patients died of their tumor, median 12 (3–45) months after relapse.

A better post-relapse outcome was observed in the 180 patients who relapsed with distant metastases. 46 of these patients (26%), treated with thoracotomy and chemotherapy, are alive and free of disease, median 24 (4–110) months after the last treatment, 8 (4%) are alive with uncontrolled disease and 126 (70%) died of their tumor, median 11 (3–55) months after recurrence. In these patients, a different pattern of relapse was observed: the first sites of metastases were the lung in 160 (89%) cases, other bones in 18 (10%) and other sites in 2 (1%) cases.

The rate of bone metastases as a first site of the metastatic spread was higher in patients with local recurrence than in the patients who relapsed without local recurrence (35% vs 10%;  $p = 0.009$ ).

### Statistics

Local recurrence-free survival (LRFS) curves were calculated, according to Kaplan-Meier and compared by means of the log-rank test. LRFS was calculated from the first day of chemotherapy until local recurrence or until tumor-related death or until the date of the most recent follow-up examination. Cox multivariate analysis was used to identify factors predictive of local recurrence. The distribution of clinical features between the group of patients was compared by means of the chi-square test.

### Results

There were no statistically significant differences in the 7-year cumulative probability of local recurrence related to tumor location or type of surgery, age, sex, histologic subtype, tumor volume, presence or not of pathologic fracture (Table 3). As regards the chemotherapy regimen, the incidences of local recurrence were not different among the 5 protocols used (local recurrence: first protocol 5%, second protocol 3%, third protocol 8%, fourth protocol 5%, fifth protocol 9%;  $p = 0.2$ ).

The local recurrence-free survival correlated with the quality of surgical margins and histologic response to chemotherapy. Local recurrence developed in 11 of 457 patients with adequate surgical margins and in 20 of 83 patients with inadequate surgical margins, having a 7-year LRFS of 97% (95% CI 96%–99%) for patients with adequate margins and 71% (95% CI 62%–79%) for patients with inadequate margins ( $p < 0.0001$ ) (Figure 1). No local recurrences were observed in the 31 amputated patients who had radical margins, whereas among the 426 patients with

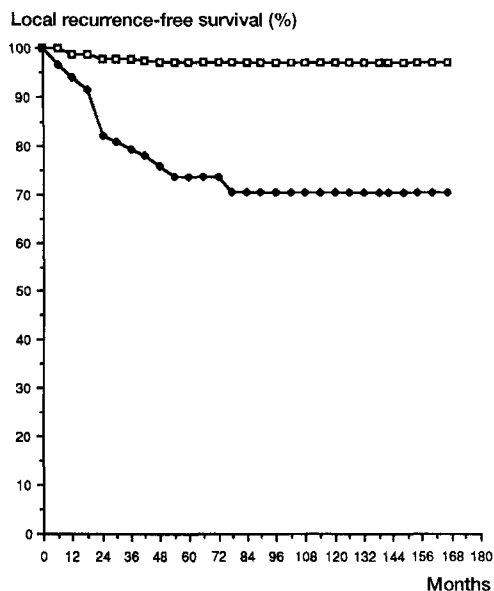


Figure 1. Kaplan-Meier analysis for local recurrence-free survival, according to the quality of surgical margins (log rank  $p < 0.0001$ ). □ Adequate radical or wide margins. ● Inadequate marginal, intralesional or contaminated margins.

wide surgical margins, 11 (2.6%) developed local recurrence ( $p = 0.8$ ).

In the group of patients with inadequate surgical margins, 11 of 55 patients with marginal margins, 6 of 18 with intralesional margins and 3 of 10 with contaminated margins had a local recurrence ( $p = 0.01$ ).

According to the histologic response to chemotherapy (Figure 2), 13 of 359 (4%) patients with a tumor necrosis  $\geq 90\%$  and 18 of 181 (10%) patients with a tumor necrosis  $< 90\%$  had a local recurrence, giving a 7-year LRFS of 95% (95% CI 93%–98%) for good responder patients and 90% (95% CI 85%–94%) for poor responders, respectively ( $p = 0.001$ ). 5 of 97 patients who had complete tumor necrosis and 8 of 262 patients with a tumor necrosis, ranging between 90% and 99% had a local recurrence ( $p = 0.5$ ).

The best LRFS was observed in the 309 patients with adequate surgical margins and good histologic response (7-year LRFS of 99%) (95% CI 97%–100%) followed by the 148 patients with adequate surgical margins and poor histologic response (7-year LRFS of 94%) (95% CI 91%–98%), the 50 patients with inadequate surgical margins and good histologic response (7-year LRFS of 71%) (95% CI 59%–83%) and the 33 patients with inadequate surgical margins and poor histologic response (7-year LRFS of 69%) (95% CI 58%–80%) ( $p < 0.0001$ ) (Figure 3).

In the 5 patients who had a local recurrence, in spite of total tumor necrosis, surgical margins were wide in

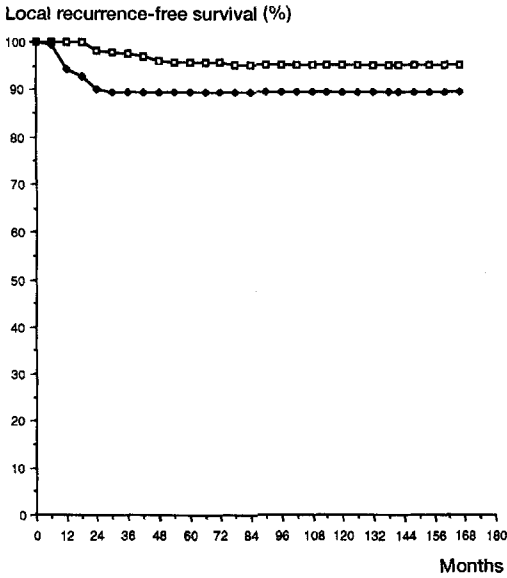


Figure 2. Kaplan-Meier analysis for local recurrence-free survival according to the histologic response to primary chemotherapy (log rank  $p = 0.008$ ). □ good responder patients ( $\geq 90\%$  tumor necrosis). ● poor responder patients ( $< 90\%$  tumor necrosis).

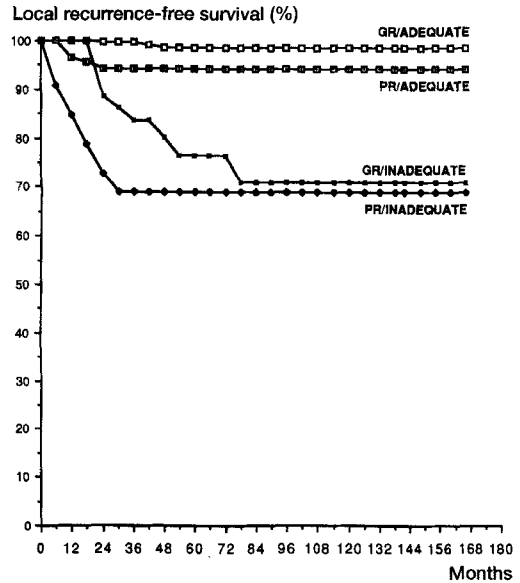


Figure 3. Kaplan-Meier analysis for local recurrence-free survival, according to the histologic response to primary chemotherapy and surgical margins (log rank  $p < 0.0001$ ). GR/ADEQUATE good responder patients with adequate surgical margins. GR/INADEQUATE good responder patients with inadequate surgical margins. PR/ADEQUATE poor responder patients with adequate surgical margins. PR/INADEQUATE good responder patients with inadequate surgical margins.

1 case, marginal in 2, intralesional in 1 and contaminated in the remaining patient.

The multivariate analysis, including factors such as type of surgery (amputation, rotationplasty, limb-salvage), site (femur, tibia, humerus) and tumor size ( $\geq 150$  mL vs  $< 150$  mL), histologic subtype (osteoblastic vs chondroblastic vs fibroblastic vs other), histologic response ( $\geq 90\%$  vs  $< 90\%$  tumor necrosis), surgical margins (adequate vs inadequate) showed that the main factor for local recurrence was the quality of surgical margins: inadequate surgical margins (relative risk 3.2; CI 95% 2.2-4.6;  $p < 0.0001$ ) followed by the histologic response to primary chemotherapy ( $< 90\%$  tumor necrosis: RR 1.6; CI 95% 1.1-2.3;  $p = 0.008$ ).

## Discussion

Since the introduction of effective neoadjuvant chemotherapy regimens and more accurate clinical staging of the tumor, more than 80% of patients with osteosarcoma of the extremity have been considered treatable with limb-salvage surgery (Bacci et al. 1993). Limb-salvage is associated with a risk of inadequate surgical margins, that has been clearly shown to be very important for local recurrence in osteosar-

coma patients treated with surgery alone: 30% when adequate surgical margins were achieved and 80% with inadequate surgical margins (Enneking and Kagan 1975).

In the 540 patients we analyzed, a limb-salvage procedure was performed in 84% of cases and the percentage (6%) of local recurrences was low. This compares favorably to other studies (Saeter et al. 1991, Winkler et al. 1991, Bramwell et al. 1992).

Rougraff et al. (1994) evaluated 227 patients with non-metastatic osteosarcoma of the distal femur, who were treated in 26 institutions. They reported 8 local recurrences in 73 (11%) patients who had a limb-salvage procedure and 9 local recurrences in 115 (8%) patients who had an above-the-knee amputation, and no local recurrences in 39 patients who had a disarticulation at the hip.

We had a statistically significantly higher percentage of inadequate surgical margins in limb-salvage patients than in those who underwent amputation, but the incidence of local recurrence was not significantly influenced by the type of limb-salvage procedure performed. The main risk factor for local recurrence was the adequacy of the surgical margins, local recurrence being 2.2 times commoner in those who had inadequate margins than in patients with adequate surgical margins.

The histologic response to neoadjuvant chemotherapy significantly influenced the incidence of local recurrence also, but to a lesser degree. In fact, those patients who had a poor histologic response to chemotherapy and adequate surgical margins showed a high LRFS probability (94%). On the contrary, patients with inadequate surgical margins and a good histologic response to chemotherapy had a low LRFS probability (71%). Moreover, it is important to underline that 5 local recurrences developed in patients who had a histologically complete tumor necrosis.

A correlation between local recurrence and histologic response to chemotherapy has been reported by Kempf-Bielak et al. (1996), who retrospectively evaluated 504 patients treated over 10 years in three multicentric studies with 63 participant institutions: the rate of local recurrence was 8% for the patients with poor histologic response and 3% for those who had a good histologic response. Unfortunately, the quality of surgical margins was not analyzed in this large study. Delepine et al. (1996) evaluated 112 patients treated with limb-salvage and neoadjuvant chemotherapy; a similar rate of local recurrence (15%) was found in patients with adequate surgical margins or good histologic response to chemotherapy. After multivariate analysis, the quality of the biopsy and length and effectiveness of primary chemotherapy were reported as the main risk factors for local recurrence.

The results of the present study in part modify those we have earlier reported (Picci et al. 1994, 1997). Those studies were based on a heterogeneous group of patients with osteosarcoma treated at our institution and we found that neoadjuvant chemotherapy-induced tumor necrosis was the main predictive factor for local recurrence. The present study confirmed the importance of the histologic response to primary chemotherapy in relation to the incidence of LR, but it clearly demonstrated that the quality of surgical margins was the primary risk factor for local recurrence in non-metastatic osteosarcoma of the extremity and that a good histologic response did not compensate for inadequate surgical margins.

The outcomes of the 31 patients who had a local recurrence were poor. In all cases, local recurrences were accompanied by metastases and, in spite of treatment, only 1 patient is presently alive and free of disease. The postrelapse outcome in patients with local recurrence was worse than that observed in 180 contemporary patients who relapsed with metastases alone, while 26% of patients are alive and free of disease.

The reason for this worse prognosis could be the different patterns of distant recurrence observed in patients who relapsed locally or with metastases. In

fact, bone metastases, as a first sign of systemic spread of the tumor, were observed in 3 times more patients with local recurrence than in patients who relapsed without local recurrence. This different behavior in spreading suggests that tumors which locally recur may have a different biology and aggressiveness than tumors which do not.

Patients should be informed about the high risk of local recurrence in case of inadequate surgical margins and, particularly in case of poor histologic response to primary chemotherapy, a secondary amputation should be recommended. For this reason, an accurate pathologic examination of surgical margins and histologic response to chemotherapy must be performed in every patient with osteosarcoma, after surgical resection of the tumor.

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## References

- Bacci G, Picci P, Ferrari S, Ruggieri P, Casadei R, Tienghi A, Brach del Prever A, Gherlinzoni F, Mercuri M, Monti C. Primary chemotherapy and delayed surgery for non-metastatic osteosarcoma of the extremity. Results in 164 patients preoperatively treated with high-dose methotrexate (iv) followed by cisplatin and doxorubicin. *Cancer* 1993; 72: 3227-38.
- Bramwell V H C, Burgers M, Sneath R, Souhami R, Van Oosterom A T, Voute P A, Rouesse J, Spooner D, Craft A W, Somers R, Pringle J, Malcom A J, Van der Eijken J, Thomas D, Uscinska B, Machin D, van Glabbeke M. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: The first study by the European Osteosarcoma Intergroup. *J Clin Oncol* 1992; 10: 1579-91.
- Campanacci M, Laus M. Local recurrence after amputation for osteosarcoma. *J Bone and Joint Surg (Br)* 1980; 62: 201-7.
- Campanacci M, Bacci G, Bertoni F, Picci P, Minutillo A, Franceschi C. The treatment of osteosarcoma of the extremity: twenty years' experience at the Istituto Ortopedico Rizzoli. *Cancer* 1981; 48: 1456-61.
- Delepine N, Delepine G, Alkallaf S, Voisin M C, Desbois J C, Debré R. Local relapses following limb-sparing salvage surgery for osteosarcoma. Prognostic factors and influence of chemotherapy. *ASCO Proceedings* 1996; 15: 526.
- Eilber F, Giuliano A, Eckardt J, Patterson K, Moseley S, Goodnight J. Adjuvant chemotherapy for osteosarcoma: A randomized prospective trial. *J Clin Oncol* 1987; 5: 21-6.
- Enneking W F, Kagan A. The implications of skip metastases in osteosarcoma. *Clin Orthop* 1975; 111: 33-41.

- Enneking W F, Spanier S S, Goodman M A. Current concepts review. The surgical staging of musculoskeletal sarcoma. *J Bone Joint Surg (Am)* 1980; 62: 1027-30.
- Kempf-Bielack B, Bielack S, Bieling P, Delling G, Fuchs N, Heise U, Kotz R, Werner M, Windhager R, Winkelmann W, Winkler K. Local failure (LF) of osteosarcoma (OS): Risk factors and prognosis. Results of the cooperative OS study group COSS. *ASCO Proceedings* 1996; 15: 520.
- Link M P, Goorin A M, Miser A W, Green A A, Pratt C B, Belasco J B, Pritchard J, Malpas J S, Baker A R, Kirkpatrick J A, Ayala A G, Shuster J J, Abelson H T, Simone J V, Vietti T J. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med* 1986; 314: 1600-6.
- Picci P, Bacci G, Campanacci M, Gasparini M, Pilotti S, Cerasoli S, Bertoni F, Guerra A, Capanna R, Albisinni U, Galletti S, Gherlinzoni F, Calderoni P, Sudanese A, Baldini N, Bernini M, Jaffe N. Histologic evaluation of necrosis in osteosarcoma induced by chemotherapy. Regional mapping of viable and nonviable tumor. *Cancer* 1985; 56: 1515-21.
- Picci P, Sangiorgi L, Rougraff B T, Neff J R, Casadei R, Campanacci M. Relationship of chemotherapy-induced necrosis and surgical margins to local recurrence in osteosarcoma. *J Clin Oncol* 1994; 12: 2699-705.
- Picci P, Sangiorgi L, Bahamonde L, Aluigi P, Bibiloni J, Zavatta M, Mercuri M, Briccoli A, Campanacci M. Risk factors for local recurrences after limb-salvage surgery for high grade osteosarcoma of the extremities. *Ann Oncol* 1997; 8: 899-903.
- Price C H G, Zhuber K, Salzer-Kuntschik M, Salzer M, Wilfert H G, Immenkamp M, Groh P, Matejovsky Z, Keyl V. Osteosarcoma in children. *J Bone Joint Surg (Br)* 1975; 57: 341-5.
- Rosen G, Caparros B, Huvos A G, Kosloff C, Nirenberg A, Cacavio A, Marcove R C, Lane J M, Mehta B, Urban C. Preoperative chemotherapy for osteogenic sarcoma: selection of postoperative adjuvant chemotherapy based on the response of primary tumor to preoperative chemotherapy. *Cancer* 1982; 49: 1221-30.
- Rougraff B T, Simon M A, Kneisl J S, Greenberg D B, Mankin H J. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur. *J Bone Joint Surg (Am)* 1994; 76: 649-55.
- Saeter G, Alvegard T A, Elomaa I, Stenwig A E, Holmstrom T, Solheim O P. Treatment of osteosarcoma of the extremities with the T-10 protocol, with emphasis on the effects of preoperative chemotherapy with single-agent high dose methotrexate: A Scandinavian Sarcoma Group Study. *J Clin Oncol* 1991; 9: 1766-75.
- Winkler K, Bieling P, Bielack S, Delling G, Dose C, Jurgens H, Kotz R, Ritter J, Salzer-Kuntschik M. Local control and survival from the Cooperative Osteosarcoma Study Group Studies of German Society of Pediatric Oncology and the Vienna Bone Tumor Registry. *Clin Orthop* 1991; 270: 79-86.