

Intraarterial Cisplatin and Intravenous Adriamycin in Nonmetastatic Osteosarcoma of the Extremities: A Single Institution Experience in Taiwan

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Background: For nonmetastatic osteosarcoma of the extremities, the optimal treatment now consists of multiagent neoadjuvant and adjuvant chemotherapy and limb-sparing surgical procedures. The degree of tumor necrosis after neoadjuvant chemotherapy is one of the most important prognostic indicators. Intraarterial cisplatin and intravenous adriamycin could achieve a good initial tumor response and convert the response to an ultimate cure.

Methods: Between January 1989 and July 2004, 16 patients with nonmetastatic osteosarcoma of the extremities received intravenous adriamycin and intraarterial cisplatin monthly for 2-5 courses, based on achievement of a maximized angiographic response, followed by limb salvage surgery and then adjuvant intravenous chemotherapy with adriamycin and cisplatin. After resection, if patients had a good response (the extent of tumor necrosis was $\geq 90\%$), the same regimen was administered intravenously every three weeks for a total of six courses of chemotherapy. Poor responders (tumor necrosis $< 90\%$) were treated with a regimen of high-dose methotrexate with leucovorin rescue (HD-MTX) or ifosfamide, cisplatin, and etoposide (ICE).

Results: Patients received an average of four cycles of neoadjuvant intraarterial chemotherapy. Sixteen patients underwent limb-preservation surgery and 12 had $> 90\%$ tumor necrosis. With an average follow-up of 93.5 months, 8 patients were continuously disease-free, 6 died of disease and 2 had no evidence of disease 112 and 182 months respectively after relapse. The 5-year overall survival rate was 61%. No patient developed clinically detectable cardiac toxicity or ototoxicity after adriamycin and cisplatin administration. Febrile neutropenia occurred infrequently.

Conclusion: This study shows the effectiveness of treating nonmetastatic osteosarcoma of the extremities with intraarterial cisplatin and intravenous adriamycin infusion in Taiwan. However, the number of patients evaluated and treated in a single hospital was obviously too few to be considered statistically robust and this regimen deserves further testing in a multi-institutional fashion.
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Key words: osteosarcoma, nonmetastatic, chemotherapy, tumor necrosis

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Osteosarcoma is a rare malignant tumor of bone that comprises less than 1% of all newly diagnosed cancers.⁽¹⁾ However, it is the most common primary sarcoma of bone. According to data from the Taiwan Cancer Registry from 1998 to 2001, the incidence rate of osteosarcoma in Taiwan was between 0.12% and 0.89%.⁽²⁾ When osteosarcoma was treated by surgery alone, usually amputation, its cure rate was approximately 10%.⁽³⁾ With the introduction of multiagent neoadjuvant chemotherapeutic regimens e.g. Memorial Sloan-Kettering Cancer Center (MSKCC) T10,⁽⁴⁾ Cooperative German-Austrian-Swiss Osteosarcoma Study Group (COSS) 86,⁽⁵⁾ M.D. Anderson treatment and investigation of osteosarcoma (TIOS) 3,⁽⁶⁾ Scandinavian Sarcoma Group,⁽⁷⁾ and Osaka C,⁽⁸⁾ adjuvant chemotherapeutic regimens such as University of California, Los Angeles (UCLA)⁽⁹⁾ and Multi-Institution Osteosarcoma Study (MIOS),⁽¹⁰⁾ and limb salvage surgery over the last 25 years, survival has improved, with long-term relapse-free survival rates of 55-76%.⁽¹¹⁻¹³⁾

For over two decades, the T-10 protocol and its variants with high dose methotrexate, doxorubicin, cisplatin and a combination of bleomycin, cyclophosphamide, and dactinomycin have been the basic treatments of nonmetastatic osteosarcoma. One major finding was that the histologic response to neoadjuvant chemotherapy is the most important prognostic factor. Several studies reported that prognosis is strictly related to chemotherapy-induced tumor necrosis.^(5,12,14-18) One hypothesis is that exposure of tumor cells to suboptimal cytotoxic therapy may result in the development of chemoresistance and an increase in the propensity for metastatic spread.

In the early 1980s, Jaffe et al demonstrated that intraarterial cisplatin could deliver higher concentrations to the tumor.⁽¹⁹⁾ Intraarterial infusion of cisplatin has been widely shown to increase the histological response to chemotherapy. Several centers have reported that the use of cisplatin as a single intraarterial agent or in combination with intravenous adriamycin improved survival.^(8,20-22) However, in the COSS -86 study, intraarterial cisplatin failed to demonstrate an advantage when combined with doxorubicin, high-dose methotrexate and ifosfamide.⁽⁵⁾ However, most protocols prescribed a fixed dosage and number of courses before surgery. In this study,

we use serial arteriograms of involved vascularity to predict tumor necrosis during intraarterial chemotherapy. It would be possible to treat individual patients before surgery to a maximum response by tailoring each patient's therapy to determine the number of courses of neoadjuvant chemotherapy. Once the decrease in neovascularity was maximized, surgery can be done as soon as possible. After the operation, an adjuvant chemotherapy regimen can be determined according to the level of tumor necrosis.

The purpose of this study was to investigate if the maximal percentage of tumor necrosis by neoadjuvant intraarterial cisplatin and intravenous adriamycin improves survival in patients with nonmetastatic osteosarcoma of an extremity.

METHODS

Between January 1989 and July 2004, a total of 32 patients were initially diagnosed with osteosarcoma in the Oncology Department of Kaohsiung Chang Gung Memorial Hospital. Of 20 patients with nonmetastatic osteosarcoma of the extremities, 16 (Table 1) received preoperative chemotherapy with a continuous intravenous infusion of adriamycin (20 mg/m² on days 1 to 4) and intraarterial cisplatin (100 mg/m² on day 5) monthly for 2-5 courses, based on achievement of maximized angiographic response, followed by limb salvage surgery and then adjuvant intravenous chemotherapy with adriamycin and cisplatin. The choice of postoperative adjuvant chemotherapy regimen depended on the tumor necrosis response. If the extent of tumor necrosis was $\geq 90\%$, the same regimen was administered intravenously every three weeks for a total of six courses of chemotherapy. If it was $< 90\%$, we changed the regimen to high-dose methotrexate with leucovorin rescue (HD-MTX) or to ifosfamide, cisplatin, and etoposide (ICE).

The femoral artery was catheterized percutaneously in an angiographic suite under sterile conditions using fluoroscopic guidance. The tip of the catheter was then positioned in the affected extremity to infuse all vessels supplying the neoplasm. Cisplatin 100 mg/m² diluted in normal saline 1000 mL was administered intraarterially by intermittent bolus infusion over two to three hours (about 300 mL every 30 minutes). The patient was restricted to bed rest for 6 hours after removing the catheter.

Table 1. Patient Data

Case no.	Gender	Age (y)	Site	Diagnosis date	IA cycles	Histological response	FU (mo)	First relapse	Status
1	F	14	Left femur	1/1991	4	95%	198		CDF
2	F	19	Right femur	1/1991	2	90%	189	1/1993	NED
3	M	47	Left femur	4/1992	3	95%	180	10/1998	NED
4	F	49	Left femur	12/1993	4	50%	162		CDF
5	M	19	Right femur	4/1994	4	90%	45	3/1995	DOD
6	F	17	Left femur	6/1995	3	95%	142		CDF
7	F	37	Right femur	4/1996	4	90%	132		CDF
8	F	22	Left femur	6/1996	4	60%	30	4/1998	DOD
9	M	17	Right tibia	10/1996	4	40%	38	10/1998	DOD
10	M	26	Right femur	1/1999	4	100%	89		CDF
11	F	17	Left femur	2/2000	4	90%	41	9/2001	DOD
12	F	13	Right humerus	1/2001	4	90%	64	10/2002	DOD
13	M	16	Left tibia	1/2002	4	95%	62		CDF
14	F	16	Right femur	8/2002	4	90%	54		CDF
15	M	18	Right humerus	9/2002	4	30%	29	12/2003	DOD
16	M	47	Right femur	2/2004	5	95%	36		CDF

Abbreviations: IA: intraarterial; FU: follow up duration; CDF: continuously disease free; NED: no evidence of disease; DOD: died of disease; mo: month.

All patients in the study had histological and radiological diagnosis of osteosarcoma without metastasis, adequate liver and renal function, and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Disease assessment at entry included complete medical history, thorough physical examination, and a series of laboratory tests (including a complete blood count with differential and complete assessment of renal and hepatic function). Primary sites were located using plain radiographs and computed tomography (CT), and metastases were located using Technetium 99m diphosphate bone scans and CT scans of the chest.

Response to treatment was assessed in terms of extent of reduction in symptoms (pain, tenderness, local heat and size of tumor) and in tumor neovascularity (size, tumor vessels and diminished tumor stain on serial angiographic study) (Fig. 1). If the decrease of neovascularity toward the end of planned preoperative protocol was questionable, the patient was

given one more cycle of chemotherapy. Once a maximum angiographic response was reached and the hematogram recovered from the preceding cycle of neoadjuvant chemotherapy, limb salvage surgery was performed as soon as possible.

The percentage of tumor necrosis induced by neoadjuvant chemotherapy was confirmed after surgery by a histological examination. Patients with few or no viable tumor cells ($\geq 90\%$ tumor necrosis) were categorized as good responders. All the others were considered poor responders ($< 90\%$ tumor necrosis).^(12,23,24)

Two to five courses of intravenous adjuvant chemotherapy were administered. The regimen for intravenous adjuvant chemotherapy was chosen according to the histological response. During the evaluation for discontinuing chemotherapy, radiographies of the primary disease site and chest were obtained.

Kaplan-Meier methodology was used to esti-

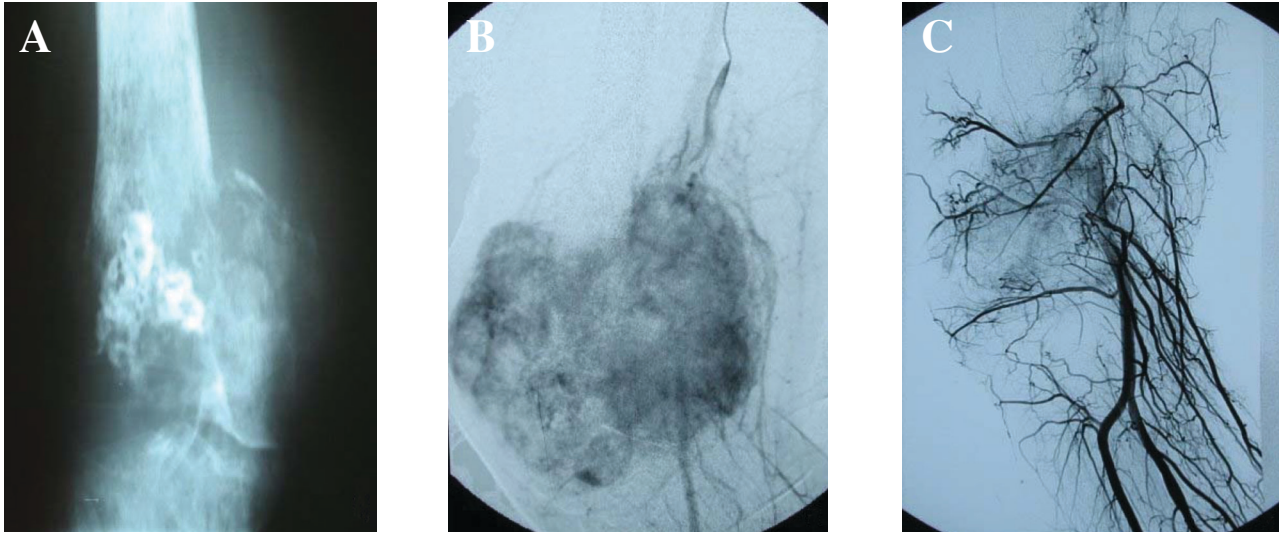


Fig. 1 (A) A radiogram of a man with osteosarcoma of the distal femur. (B) An arteriogram after the first course of chemotherapy shows viable tumor area with tortuous vessels and intense contrast uptake. (C) An arteriogram after the fourth course shows a decrease in contrast uptake with little evidence of residual tumor staining. It was estimated that there was >90% decrease in neovascularity.

mate the probability of survival calculated from the day on which preoperative chemotherapy was initiated to the first adverse event or until the date of the most recent follow-up.

Chemotherapy-related follow-up laboratory tests included complete blood count, serum creatinine, electrolytes, alkaline phosphatase, and lactate dehydrogenase. Echocardiography to determine the left ventricular ejection fraction was also done if the patient had symptoms/signs of heart failure. All toxicities were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 2.

RESULTS

Sixteen patients (7 male and 9 female; age 13-49 years; mean age: 24.6 years) were treated with the regimen and evaluated. The Table summarizes patient characteristics and distribution of primary sites. There was no sexual preponderance. The primary sites were the distal femur (12 patients), proximal tibia (2 patients), and proximal humerus (2 patients). All patients had clinical and angiographic evidence of response from neoadjuvant chemotherapy. However, 1 patient (No. 15) suffered from an incidental traumatic fracture of his affected humerus

during neoadjuvant chemotherapy and died of lung metastasis.

All patients with angiographic evidence of response from administration of neoadjuvant chemotherapy had improvement in pain and decreased local heat at the primary site. They also underwent limb-preservation surgery with wide local resection and endoprosthetic replacement. Twelve patients (75%) had $\geq 90\%$ tumor necrosis on histological evaluation.

During the follow-up period (29-198 months; mean, 93 months), 8 patients remained continuously free of disease and 8 patients relapsed. Six of the 8 patients who relapsed had metastases and 2 had local recurrences. The metastases were mainly localized in the lung (6 patients), including 1 patient (No. 12) who refused adjuvant chemotherapy. Two patients survived nearly 10 years after palliative chemotherapy for their metastatic disease. The average time to relapse was 18.6 months (range: 5-72 months) and the lung was the first site of metastasis in all 6 patients, 5 of whom died of their tumor 29-64 months (mean = 41.8 months) after diagnosis. Metastatic disease was treated with repeated metastasectomy and chemotherapy. The primary tumors of the two patients who developed local recurrence were in the femur and tibia. The histological

response was good in one and poor in the other. The patient who had a good histological response survived 8 years after amputation and chemotherapy.

At 5 years, the Kaplan-Meier estimate of overall survival was 61%. For good responders, the 5-year overall survival was 60%, compared with 25% for poor responders. The result was statistically significant for survival ($p = 0.015$) (Fig. 2). Survival data are listed in the Table.

Patients received an average of four neoadjuvant courses (range from two to five). Myelosuppression was common and cumulative. After granulocyte-colony stimulating factor (G-CSF) became available in 1991, it was prescribed for neutropenia. Febrile neutropenia occurred infrequently and was manageable. Of the total 61 courses of neoadjuvant chemotherapy, hematologic toxicities (> CTCAE grade 2) included 9 episodes of leucopenia (15%), 3 episodes of anemia (5%), and 5 episodes of thrombocytopenia (8%). Only two patients needed hospitalization due to febrile neutropenia or bacteremia and there were no toxic deaths.

No patient developed clinically detectable car-

diac toxicity after receiving adriamycin. Ototoxicity was also mild. There were two episodes of grade 3 mucositis (3%) and one patient had neurotoxicity. Nausea and vomiting were the most common non-hematologic side effects (10%).

DISCUSSION

The introduction of neoadjuvant chemotherapy into the multi-modality of treatment of osteosarcoma is the most important advancement in treatment of the disease. However, for the last 10 years, there has been less significant improvement in survival with the use of multiagent neoadjuvant chemotherapy. In these patients, the extent of chemotherapy-induced tumor necrosis is strictly correlated with prognosis.⁽¹⁴⁻¹⁸⁾ To increase the rate of chemotherapy-induced tumor necrosis, delivery of larger doses of drugs to the primary tumor has been attempted using intraarterial chemotherapy. Of the drugs which are effective in osteosarcoma, cisplatin is considered the most suitable for intraarterial infusion because intraarterial cisplatin is not associated with a significant local

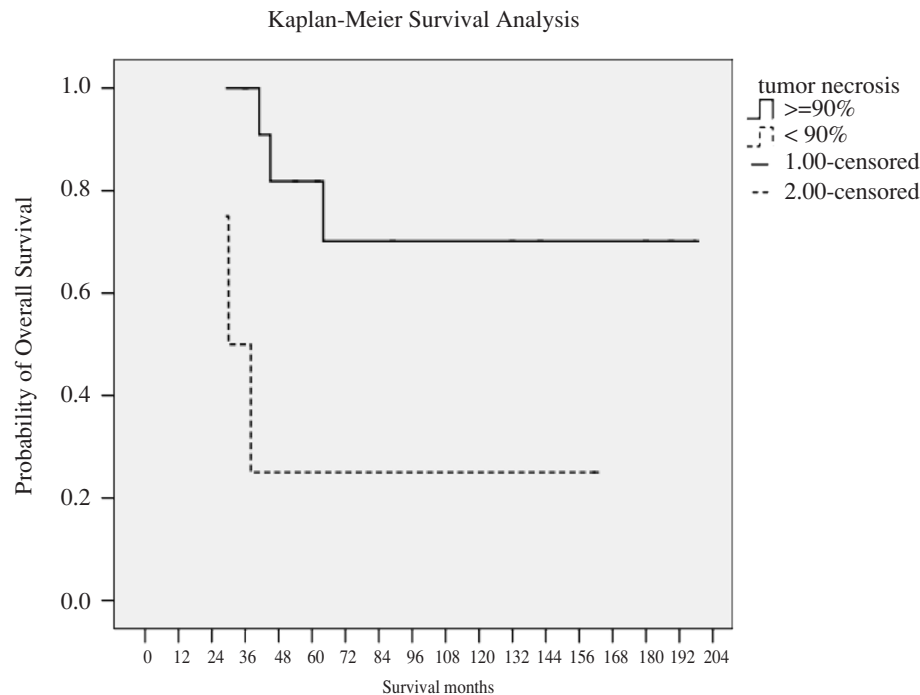


Fig. 2 Kaplan-Meier survival curve of these 16 patients with nonmetastatic osteosarcoma of an extremity after intraarterial neoadjuvant chemotherapy, limb-preservation surgery and adjuvant chemotherapy.

reaction and systemic drug levels are not compromised by intraarterial infusion.^(22,25)

The COSS-86 study was the only prospective controlled study designed to verify whether intraarterial infusion of cisplatin was more effective than intravenous infusion in a multiagent pre-operative chemotherapy setting. In this study, intraarterial or intravenous cisplatin were given with HD-MTX, adriamycin and ifosfamide and the response rate and 10-year event free survival were also identical. The authors themselves suggested that a selection bias may have influenced outcome. In addition, the different times of infusion in intraarterial and intravenous cisplatin could have influenced the results. Benjamin et al. reported that incrementation of the intraarterial time from 2 to 24 hours increases the local response rate.⁽²⁶⁾ In Bacci et al's study, the doses and the time infusion of cisplatin were the same for patients treated intraarterially and intravenously. When used within a three-drug regimen (HD-MTX, cisplatin, adriamycin), intraarterial cisplatin was significantly more effective on the primary tumor than the intravenous infusion. When cisplatin was delivered within a four-drug regimen (HD-MTX, cisplatin, adriamycin and ifosfamide), which significantly increased the good responses, the advantage of intraarterial cisplatin disappeared.⁽²⁷⁾ Therefore, it seems that the addition of another active drug to cisplatin and adriamycin concealed the difference.

In patients with nonmetastatic disease, the most important prognostic factor is the percentage of tumor necrosis after neoadjuvant chemotherapy. Thus the most important issue is how to achieve a good initial tumor response. In our study, we used only intravenous adriamycin over 48 hours followed by intraarterial cisplatin over 3 hours. The drugs were given every 4 weeks in a neoadjuvant setting. The number of cycles given before surgery was individualized on the basis of tumor responses, and evaluated by a decrease in tumor neovascularity on an arteriogram. This method led to a good response rate over 75%. One patient developed a traumatic fracture of his affected limb. Scully et al reported that patients with osteosarcoma who present with pathologic fracture during neoadjuvant chemotherapy have an increased risk of local recurrence and a decreased rate of survival.

The Instituto Ortopedico Rizzoli (IOR-OS) 2 and 3 studies demonstrated that the rate of histologi-

cal response was significantly higher in the intraarterial cisplatin regimen than the IV regimen.⁽²⁸⁾ In our study, there were four poor responders. Two developed metastatic disease and one had local recurrence. All three died due to severe distal metastasis.

While highly effective, the COSS-86 regimen was rather toxic and the ifosfamide/cisplatin combination had significant myelotoxicity.⁽²⁹⁾ The incidence of treatment-related death had been reported at 1.6%⁽³⁰⁾ to 4.1%⁽³¹⁾ and leucopenia and thrombocytopenia were frequent (45% and 18%, respectively)⁽²⁹⁾ when giving high dose ifosfamide, high dose MTX, adriamycin and cisplatin. Severe ototoxicity developed (16.9%) and some patients required a hearing aid, especially those who received cisplatin at 150 mg/m² over one hour.⁽³¹⁾ In contrast, in our study, there was no treatment-related mortality, and myelotoxicity was mild. The incidences of leucopenia and thrombocytopenia (more than CTCAE grade 2) were only 15% and 8%, respectively. In addition, no patient had significant hearing impairment, or needed a hearing aid. The ability to perform limb-salvage procedures was not adversely affected by intraarterial cisplatin. Arteriograms were well tolerated, and no unexpected complications were seen.

Our study found that combined intraarterial cisplatin and intravenous adriamycin infusion in neoadjuvant chemotherapy for primary nonmetastatic osteosarcoma of the extremities was as effective as the COSS-86 regimen. The intraarterial route was associated with minimal morbidity and few complications, and may be associated with lower costs in Taiwan because it reduces the need for hospitalization. However, the number of patients with these rare tumors was limited to a single hospital and our study obviously recruited too few patients for its results to be considered significant. Future endeavors should involve a multi-institutional randomized study comparing this approach with another multiagent intravenous neoadjuvant protocol.

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以經動脈注射給予順鉑及靜脈注射速溶艾黴素方式來治療 非轉移性之四肢惡性骨肉瘤：台灣單一醫學中心之經驗

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背景：對於原發於四肢非轉移性惡性骨肉瘤的治療，目前以合併使用多種化學治療藥物在肢體保留手術前後 (neoadjuvant and adjuvant chemotherapy, limb-sparing surgical procedures) 的治療方式為主。而在手術前化學治療所造成腫瘤壞死的程度則是一個預後重要的指標。因此，可以在手術前化學治療給予動脈順鉑及靜脈給予速溶艾黴素兩種藥物造成腫瘤壞死甚至痊癒來達成。

方法：自 1989 年 1 月到 2004 年 7 月，共有 16 位原發於四肢非轉移性惡性骨肉瘤的病人，接受了 2-5 次不等的手術前動脈給予順鉑及靜脈給予速溶艾黴素的治療，並且以血管攝影的方式來評估在數次化學治療後，是否腫瘤的新生血管已有明顯減少。一旦有臨床症狀改善及血管攝影顯示腫瘤新生血管減少已達最大反應，就會進行肢體保留手術。在手術後，如果手術前化學治療所造成腫瘤壞死的程度大於 90%，就靜脈給予每三週 1 次順鉑及速溶艾黴素直到共 6 次化學治療完成。而腫瘤壞死的程度小於 90% 則給予其它化學治療處方。

結果：病患接受了平均 4 次的手術前化學治療，在 16 位接受肢體保留手術中，有 12 位病患達到 90% 以上的惡性骨肉瘤細胞壞死。在平均 93.5 個月的追蹤，有 8 位病患未再復發，6 位病患因病死亡，而 2 位在復發治療後至今不再復發。5 年存活率為 61%。這和其它多種化學治療藥物合併治療的結果相近。且心毒性，耳毒性及白血球低下所造成發燒等副作用較不常見。

結論：這研究可顯示，使用手術前動脈給予順鉑及靜脈給予速溶艾黴素來治療原發於四肢非轉移性的惡性骨肉瘤，就可以達到和合併四種化學治療藥物時相當的效果。但由於病人數尚不多，仍需進一步收集更多病人研究。
(長庚醫誌 2009;32:72-80)

關鍵詞：惡性骨肉瘤，非轉移性，化學治療，腫瘤細胞壞死

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