Development of Multidisciplinary Approach for Bone and Soft-tissue Sarcomas in Japan

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SUMMARY

Recent development of multidisciplinary approach, comprising wide surgical tumor resection, chemotherapy, and radiotherapy, as well as modern radiographic diagnostic modalities such as CT and MRI to evaluate extent of disease and staging, for the treatment of bone and soft-tissue sarcomas has dramatically improved patients' survival, and limb-salvage surgery for extremity sarcomas is now an established standard procedure. In this review article, we describe the development of multidisciplinary approach for patients with bone and soft-tissue sarcoma mainly progressed in Japan over the last 30 years, and a prospect for the future.

INTRODUCTION

Recent development of multidisciplinary approach, comprising wide tumor resection, chemotherapy, and radiotherapy, as well as modern radiographic diagnostic modalities such as CT and MRI to evaluate extent of disease and staging, for the treatment of bone and soft-tissue sarcomas has dramatically improved patients'

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survival, and limb-salvage surgery for extremity sarcomas is now established as a standard treatment procedure. Especially in extremity osteosarcoma and Ewing's sarcoma, the postoperative survival rates of which had been formerly less than 10-20% after limb-amputation without adjuvant therapy, their survival rates have been markedly improved by "neoadjuvant chemotherapy". The cumulative 5-year overall survival rates in patients with localized extremity osteosarcoma and Ewing's sarcoma have now reached 60-80%[1-3] and 50-70%,[4-6] respectively. A variety of reconstructive techniques following wide tumor resection of affected limbs, such as tumor megaprosthesis, osteoarticular allograft and recycling autobone re-implantation, have also contributed to the improvement of affected limb function. As for pulmonary metastases, aggressive metastasectomy have been applied and improved patients' survival in collaboration with thoracic surgeons.[7-10]

Meanwhile, in soft-tissue sarcomas, their histological heterogeneity and diagnostic difficulty have disrupted to make proper treatment strategies, however, recent advancement in the field of molecular cytogenetics for sarcomas and establishment of appropriate histological grading system in soft-tissue sarcomas have promoted therapeutic strategies according to their malignancy grade and histological type. It is getting obvious that high-grade extremity soft-tissue sarcomas can benefit from adjuvant chemotherapy by a meta-analysis for 14 randomized clinical trials of doxorubicin-based adjuvant chemotherapy for localized resectable soft-tissue sarcomas of adults,[11] and multimodality treatment strategy, combining surgery, radiotherapy, and adjuvant chemotherapy, will be hopefully established in individual histological type of soft-tissue sarcomas.

Furthermore, novel treatment modalities have been expected to improve prognosis of sarcoma patients, such as carbon-ion particle radiotherapy for pelvic and spinal/paraspinal unresectable sarcomas,[12] clinical trials of various molecular-targeting agents and tumor-specific immunotherapy for locally advanced and/or metastatic sarcomas. This article reviews the development of multidisciplinary approach for bone and soft-tissue sarcomas mainly progressed in Japan, and states a prospect for the future.

I. DEVELOPMENT OF ADJUVANT/ NEOADJUVANT CHEMOTHERAPY

1. Neoadjuvant chemotherapy for osteosarcoma

Formerly, the progonosis of osteosarcoma patients was dismal, accounting for their survival rate after surgery, being amputation for extremity cases, was less than 10-20%. In the 1970s, doxorubicin (adriamycin) (DOX/ ADR) and high-dose methotrexate (HD-MTX) with leucovorin rescue (LVR) were introduced to the pre- and post-operative adjuvant treatment for osteosarcoma patients, then the 5-year survival rate improved to approximately 40-50%. Further in the 1980s and 1990s, cisplatin (CDDP) and then, ifosfamide (IFO) were introduced, and the 5-year overall survival rate of localized extremity osteosarcoma patients now reached 60-80%.[1-3] The three chemotherapeutic agents including DOX, HD-MTX, and CDDP with/or without IFO are presently consisting worldwide standard chemotherapy regimens for osteosarcoma. The use of preoperative chemotherapy in patients with osteosarcoma offers the following advantages: 1) early institution of systemic chemotherapy to eradicate micrometastases which could eventually lead to the patients' metastases and death; 2) reduction in bulk and size of primary tumors, frequently making limb-salvage surgery possible and safe; 3) definition of the optimal mode of administration of chemotherapeutic agents by clinically evaluating the response of the primary tumor to chemotherapy in each patient; 4) selection of high-risk patients requiring addition/or change of chemotherapy regimen prior to relapse by estimation the histological response to preoperative chemotherapy (% tumor necrosis).[13] The use of preoperative chemotherapy for osteosarcoma patients has termed "*neoadjuvant chemotherapy*" first, and it is then applied widely to the field of oncology for other solid cancers, such as breast cancer and esophageal cancer.

The Osaka University Orthopaedic Oncology Group has also first introduced systemic neoadjuvant chemotherapy for osteosarcoma patients since 1976, and then we have revised the regimens, named OOS-D at present (Fig. 1). The 5-year cumulative overall and event-free survival rates following start of treatment for OOS-A, -B, -C, and –D regimens are 48.6%, 71.9%, 77.9%, 95.5% in overall, and 40.6%, 67.5%, 72.5%, 78.9% in event-free, respectively, with dramatically improvement compared with their historical control group of 12.5% and 12.0% (Fig. 2).[1, 14] The neoadjuvant chemotherapy is now a standard and essential treatment modality, and plays a central role together with surgical tumor resection in osteosarcoma patients.

The future problems in chemotherapy for osteosarcoma are: 1) to reduce long-term complications following chemotherapy such as infertility and second malignancy risk; 2) development of new chemotherapeutic regimen for high-risk group such as patients with pelvic primary

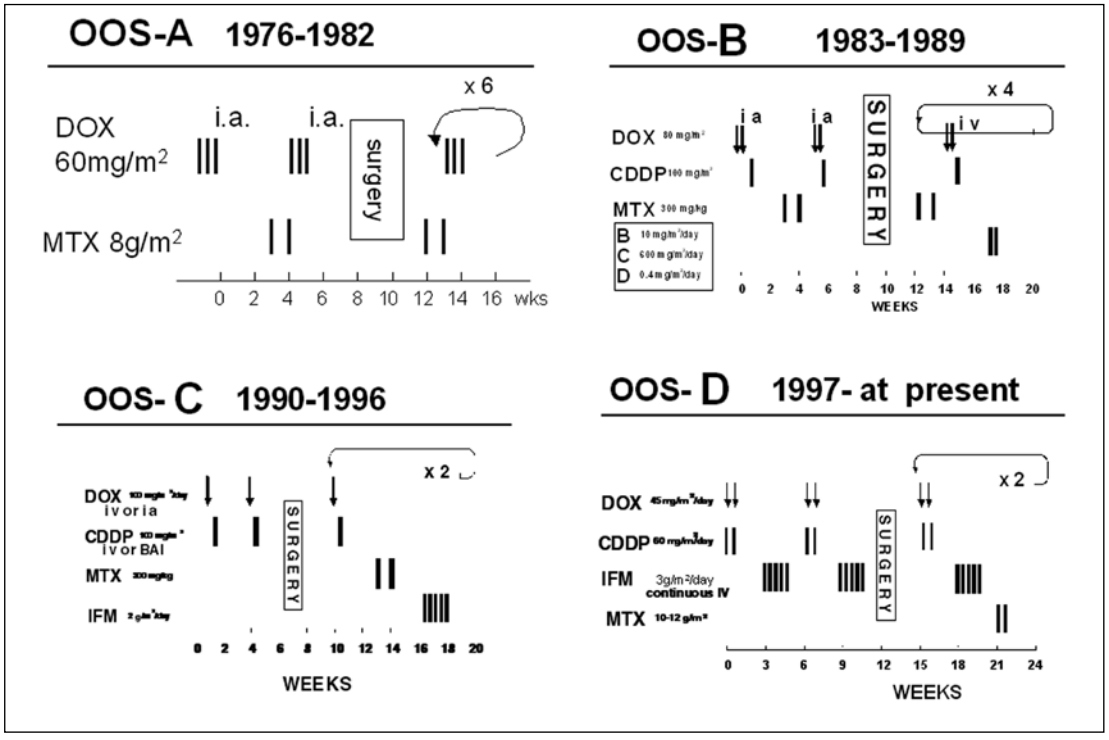

Fig.1 Updated chemotherapeutic regimens for osteosarcoma in Osaka University Orthopaedic Oncology Group.[1, 14]

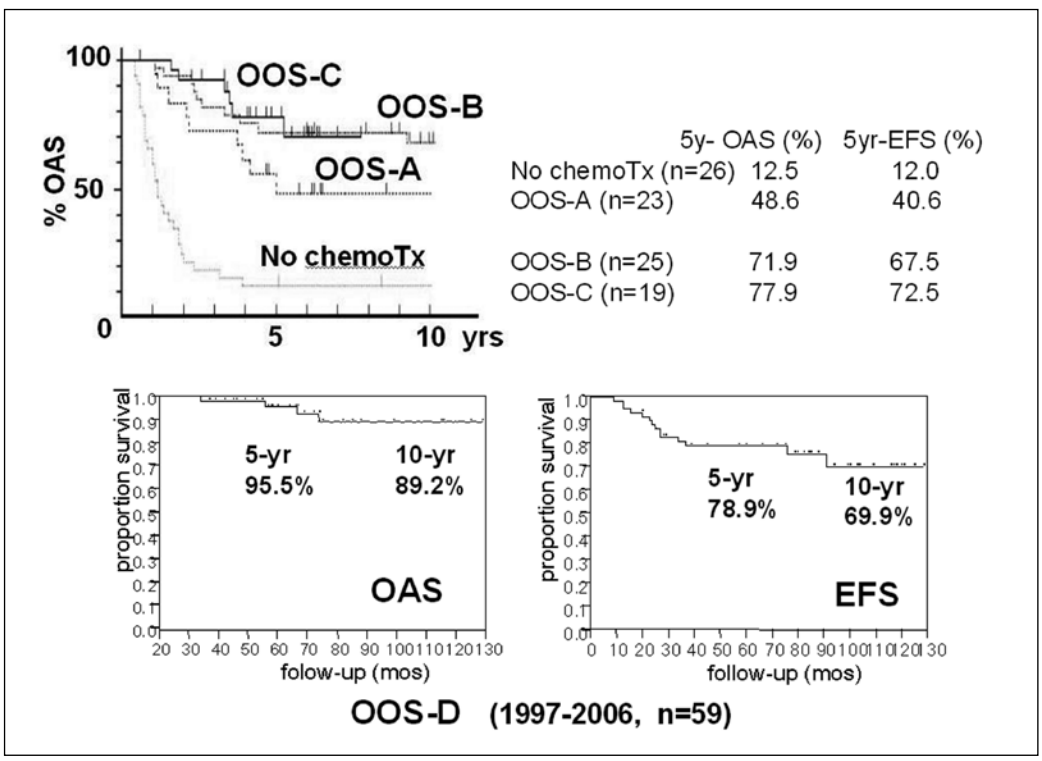

Fig. 2 Kaplan-Meier's cumulative overall and event-free survival curves according to chemotherapeutic regimens OOS-A, -B, -C, and -D in localized (M0) extremity conventional osteosarcoma patients. OAS: overall survival, EFS: event-free survival.

lesion, metastasis at presentation, poor responder for preoperative chemotherapy; 3) development of a safe and effective chemotherapeutic regimen for elderly patients with osteosarcoma more than 40 years, because the incidence of which will increase according to the drastic aging of our society in Japan.

2. Chemotherapy for Ewing's sarcoma

According to the finding that Ewing's sarcoma of bone shares a common fusion gene, namely *EWS-FLI1/ERG*, with extraskeletal Ewing's sarcoma, primitive neuroectodermal tumor (PNET), peripheral neuroepithelioma, and Askin's tumor, they are interpreted to have the same, probably neuroectodermal origin, and are commonly treated as Ewing's sarcoma family of tumors (ESFT). ESFT has been an extremely poor prognostic disease historically treated only by surgical resection with 5-year overall survival of less than 10%. In the 1970s, however, Western pediatric oncology groups, such as Cooperative Ewing's Sarcoma Studies (CESS), Intergroup Ewing's Sarcoma Study (IESS), Pediatric Oncology Group (POG), and Childres's Cancer Group (CCG), started multicenter clinical trials for ESFT using multidrug chemotherapy including vincristine (VCR), actinomycin-D (ACT-D), cyclophosphamide (CPA), DOX, and they further added two drugs of IFO and etoposide (ETP/VP-16), then the prognosis of patients with ESFT has dramatically improved. The 5-year overall survival rate of localized extremity ESFT has presently reached 50-70%. [4-6]

We have also started multimodality treatment consisting of systemic chemotherapy, wide tumor resection, and radiotherapy for patients with Ewing's sarcoma of bone since 1976.[15] We adopted a chemotherapeutic regimen based on Rosen's T-11 protocol in 1982, and have changed a regimen consisting of VCR+DOX+CPA (VDC) added by IFO+ETP (VDC+IE) since 1997. The 5-year cumulative overall survival rate of patients with Ewing's sarcoma of bone was 40.0% for all patients, and 44.3% for those with localized disease at presentation. The VDC+IE regimen group showed better 5-year overall survival rate of 66.7% than the former T-11-based regimen group (47.7%), but we could not show a statistically significant superiority of VDC-IE regimen to T-11 protocol because of the small number of patients. Clinical outcomes of Western group studies for localized ESFT compared with our results are shown in Table 1.

The rarer incidence of ESFT in Oriental countries including Japan and lack of multicenter group study have disturbed establishment of a standard treatment strategy for ESFT patients in Japan. Thus, we have conducted a multi-institutional retrospective study in Japanese Musculoskeletal Oncology Group (JMOG) to investigate clinical outcome of patients with ESFT of bone in Japan [6]. The study included 243 patients with ESFT of bone

Table 1. Cumulative survival rates of patients with localized (M0) ESFT according to multidrug chemotherapy regimens.

Study Group	Patient No.	Survival Rate
IESS-II nonpelvic	214 (1978-1982)	5-year OAS 77% (trt 1) 63% (trt 2)
IESS-II pelvic	59 (1978-1982)	5-year OAS 63%
CESS 86[4]	301 (1986-1991)	10-year OAS 57%
EICESS 92	637 (1992-1999)	3-year EFS 66%
SE 91-CNR (Italy)	160 (1991-1997)	3-year OAS 83.6%
UKCCSG-ET2 (UK)	191 (1987-1993)	10-year OAS 69%
EW88 (France, Belgium)	141 (1988-1991)	5-year OAS 66%
POG-CCG (USA) VACD	200 (1988-1993)	5-year OAS 61%, EFS 54%
VACD+IE	198 (1988-1993)	5-year OAS 72%, EFS 69%
Osaka Univ. T-11 based	18 (1982-)	5-year OAS 47.7%
VDC+IE	10 (1997-)	5-year OAS 66.7%

OAS: overall survival, EFS: event-free survival

treated in 29 tertiary referral institutes between 1980 and 2003. They originated from extremies in 115 cases (47.3%) and from trunks in 128 cases (52.7%) including 62 cases of pelvic origin. The 5-year cumulative overall and event-free survival rates in all patients were 48.7% and 40.4%, respectively. As for patients with localized disease at presentation (M0), they were 54.9% and 46.6%, respectively. Distant metastases at presentation (M1), primary trunk location, age over 16 years, maximal tumor size more than 10cm, and poor radiographic and/or histological response to preoperative chemotherapy, proved to be independent unfavorable prognostic factors, and an important role of surgical treatment compared to radiotherapy alone as local treatment was also suggested in this study. Furthermore, patients treated with chemotherapy regimens adding IFO+ETP (IE) significantly showed better prognosis than those without IE (5-year event-free survival rates; IE(+) group 67.6% vs IE(-) group 41.2%, log-rank test, p=0.0054) (Fig. 3), confirming the results in Western group studies [5] and the data in the small number of patients treated in our Osaka University Orthopaedic Oncology Group. Addition of IFO and ETP to standard chemotherapy (VDC+IE, EVAIA, VACD+IE, etc) is getting now a golden standard chemotherapy regimen for ESFT in the world. The Japan Ewing Sarcoma Study Group (JESS) has been conducting a multicenter prospective phase II clinical trial (JESS041) for patients with ESFT of bone using VDC+IE regimen since December 2004, and the results are expected to be coming out soon.

However, prognosis of high-risk patients with ESFT such as primary pelvic location, metastases at presentation (M1) is still poor, and high-dose intensive chemotherapy supported by peripheral blood stem cell transplantation (PBSCT) has been tried for those patients, but its usefulness is not yet established.[16]

3. Chemotherapy for adult-type soft-tissue sarcomas

Various regimens of DOX-based, and recently adding IFO, chemotherapy has been applied to patients with soft-tissue sarcoma, however, the response rate was at most 20-40% and efficacy of chemotherapy for adult-type soft-tissue sarcomas has been still controversial in contrast to pediatric small-round cell sarcomas such as rhabdomyosarcoma and extraskeletal ESFT in which systemic chemotherapy is an essential modality of treatment. Difficulty to define efficacy of chemotherapy for adult-type soft-tissue sarcomas is mainly caused by their histological heterogeneity with a wide variety of malignancy grade. Thus, it is important to investigate prognostic factors for soft-tissue sarcomas and to select high-risk patients that should be indicated to receive chemotherapy. Histological grade, as well as tumor size,

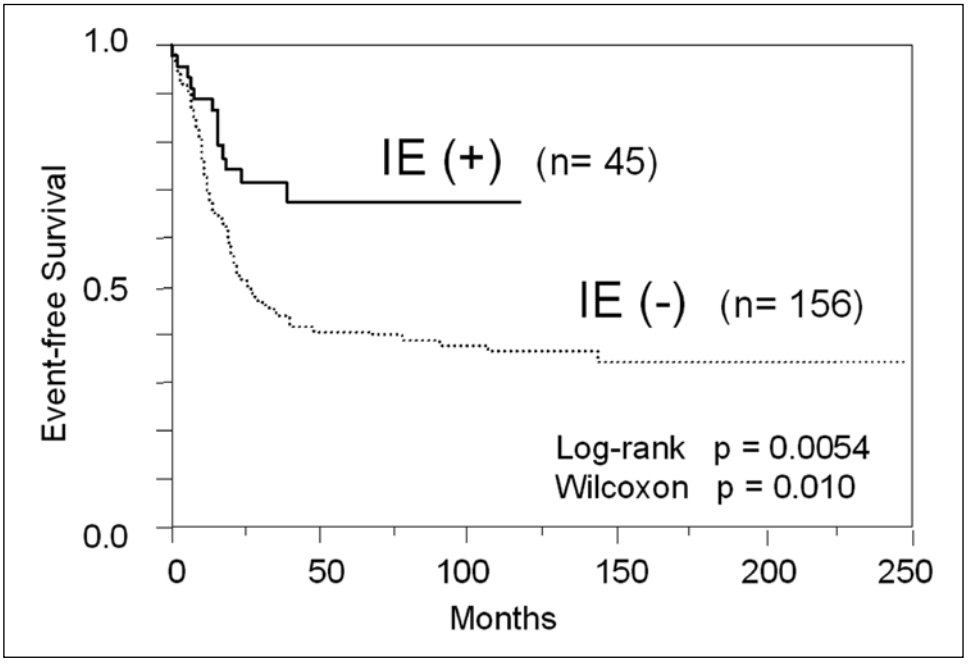

Fig. 3 Kaplan-Meier's event-free survival curves according to chemotherapy regimens including IFO+ETP (IE)(+) vs. IE(-) in patients with localized (M0) ESFT.[6]

Table 2. Histological grading systems for soft-tissue sarcoma

	cellularity	differentiation	pleomorphism	mitotic count	tumor necrosis
Markhede (1982)	+	–	+	+	–
Myhre-Jensen (1983)	+	–	+	+	–
Costa (NCI* system) (1984)	+	–	+	+	+
Trojani (FNCLCC** system) (1984)	–	+	–	+	+
Osaka Univ. (1993)[21, 22]	+	–	–	+	+

* NCI: National Cancer Institute
** FNCLCC: Fédération Nationale des Centres de Lutte Contre le Cancer

tumor depth, and lymph node/distant metastasis, are the major prognostic factors, which are used for clinical staging in soft-tissue sarcomas,[17, 18] and a number of histological grading systems have been published and used internationally (Table 2).[17] We have also advocated a grading system for soft-tissue sarcoma comprising three histological parameters, *i.e.*, 1) cellularity, 2) mitotic count or instead a more objective cell proliferative parameter, Ki-67 (MIB-1) labeling index or AgNOR (argyrophilic nucleolar organizer regions) count, and 3) tumor necrosis (Fig. 4), and validated our grading system.[19-22] Cumulative overall survival curves of patients with soft-tissue sarcoma treated according to our grading system are chronologically shown in Fig. 5. There seems to be a trend that AJCC (American Joint Committee on Cancer) stage III patients (with histological grade 2 or 3, maximal tumor size larger than 5 cm, deep-seated tumor, and without distant/or regional lymph

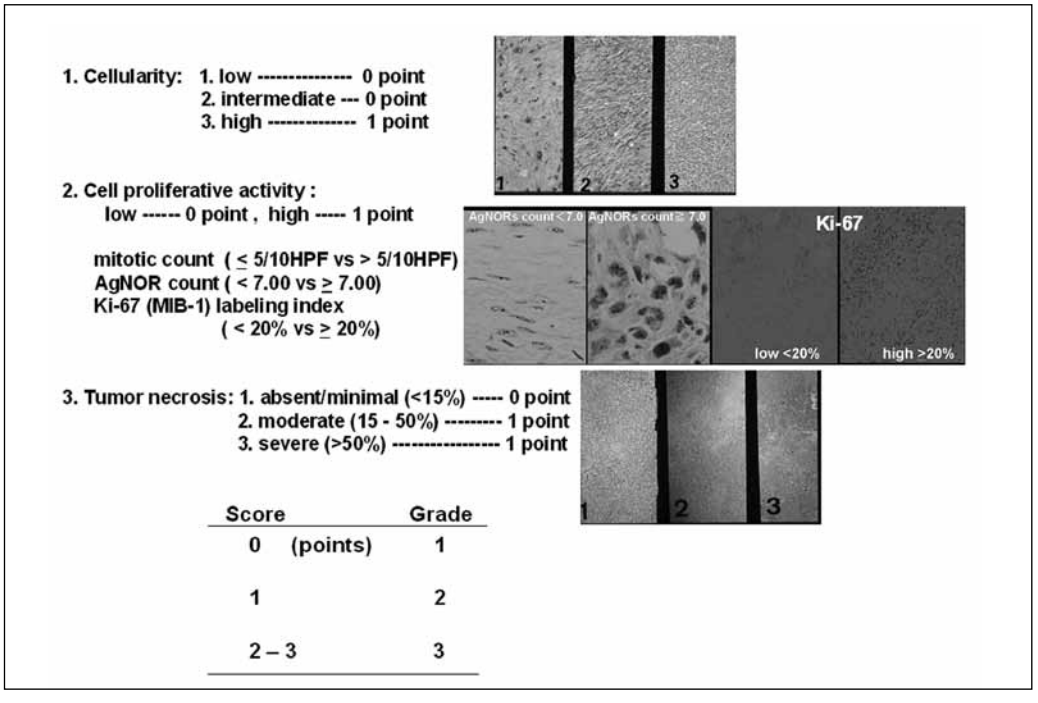

Fig. 4 Osaka University histological grading system for soft-tissue sarcoma[18-21]

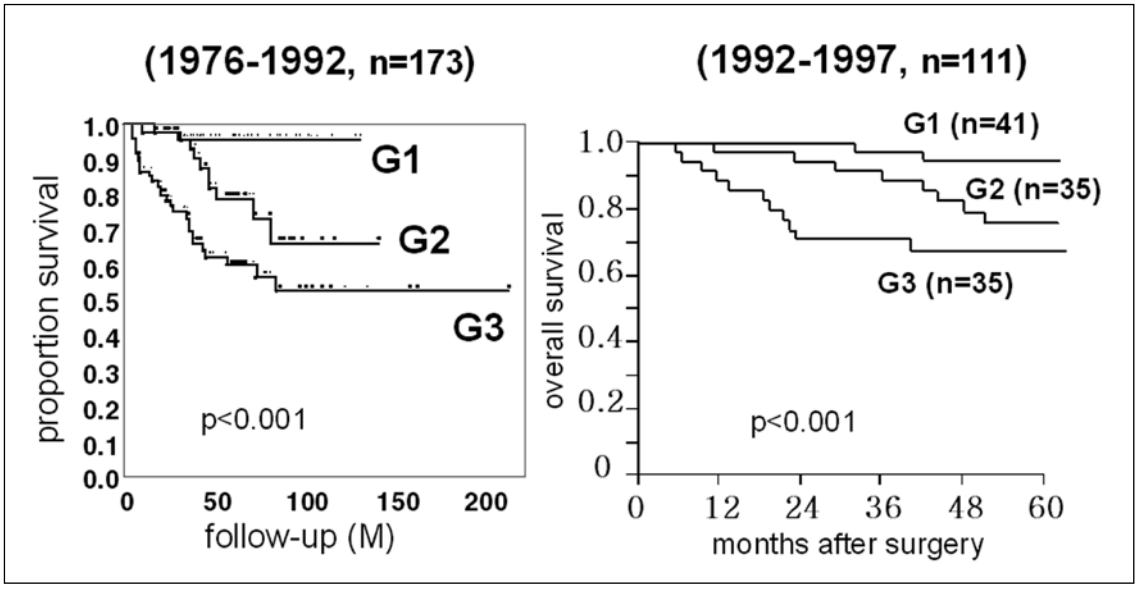

Fig. 5 Kaplan-Meier's overall survival curves of patients with localized (M0) extremity and trunk soft-tissue sarcoma according to Osaka University histological grading system. (A) 1976-1992, (B) 1992-1997. [22]

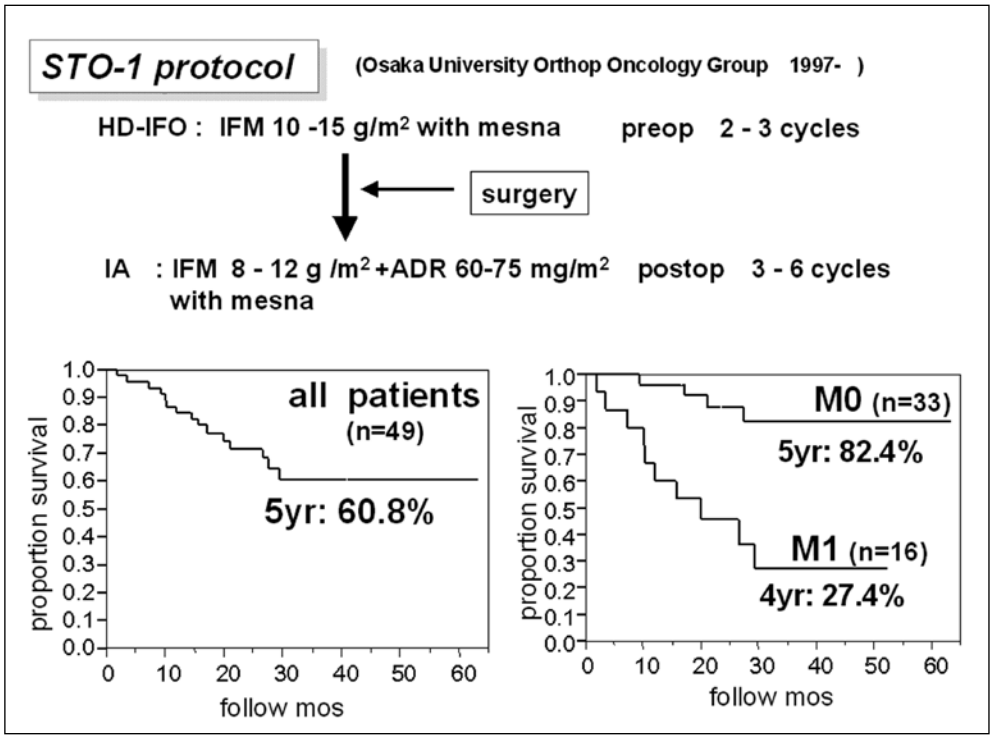

Fig.6 STO-1 protocol for patients with high-grade soft-tissue sarcoma and Kaplan-Meier's overall survival curves treated with STO-1.

node metastasis) treated with DOX and IFO- based adjuvant chemotherapy between 1992-1997 showed more favorable prognosis than those treated without systemic chemotherapy between 1976-1992. Furthermore, we have newly introduced a neoadjuvant chemotherapy regimen, named STO-1 protocol, consisting of preoperative high-dose IFO and postoperative DOX+IFO with mesna for patients with high-grade (grade 2 or 3) extremity/

or trunk soft-tissue sarcoma since 1997, and achieved overall survival rates of 60.8% for all patients and 82.4% for localized (M0) patients at presentation (Fig. 6). In order to estimate an efficacy of adjuvant chemotherapy for adult-type soft-tissue sarcomas, a multicenter phase II clinical trial conducted by the Japan Clinical Oncology Group (JCOG) is ongoing using pre- and post-operative IFO+DOX adjuvant chemotherapy for patients with localized high-grade non-small round cell soft-tissue sarcoma (JCOG0304).

II. DEVELOPMENT OF SURGICAL TREATMENT

1. Concept of surgical margin and expansion of limb-salvage indication

Limb-salvage surgery for extremity bone and soft-tissue sarcomas are basically consisted of tumor wide resection and a variety of reconstructive procedures. Formerly, surgical excision of bone and soft-tissue tumors including sarcomas was vaguely termed curettage (debulking excision, piecemeal removal), simple excision (extirpation), en bloc resection, wide resection, and amputation/disarticulation, etc, and there was no consensus of surgical margin among surgeons. In the 1980s, Enneking et al, members of Musculoskeletal Tumor Society (MSTS) in the United States, proposed the term " surgical margin" based on the concept of normal-tissue barriers against tumor and anatomical compartment, and termed radical, wide, marginal, and intralesional surgical margins.[23] Kawaguchi et al at the Cancer Institute Hospital, Japan, also postulated an original concept of "surgical margin" for bone & soft-tissue sarcomas more elaborately.[24] These consecutive works have established an objective and reproducible concept of surgical margin in the field of musculoskeletal oncology, and safely support limb-salvage surgery for extremity sarcomas.

There has been a limit to perform limb-salvage surgery for cases such as those with invasion to major neurovascular bundles, intraarticular invasion, extensive soft-tissue defect after wide tumor resection, younger children less than 10-12 years, etc, however, development of a variety of surgical techniques including arterial bypass using artificial vascular graft or saphenous vein autograft, extraarticular wide resection, local-pedicled/or free-vascularized musculocutaneous flaps and free skin graft, extendable tumor endoprosthesis, and bone-transport limb-lengthening have enabled limb-salvage for such patients. Thus, limb-salvage surgery can be presently applied to almost all patients with extremity sarcoma except for those with huge primary or repeatedly recurrent tumors, or peripherally located tumors.

2. Reconstructive techniques of limb-salvage surgery

After wide tumor resection, there are several reconstructive procedures to supplement massive osteoarticular/or intercalary defect: 1) tumor endoprosthesis ("megaprosthesis"); 2) massive bone allograft; 3) recycling autobone graft, 4) vascularized fibular autograft, etc, and we mainly use 1) and 3) (especially extracorporeal radiated autobone graft) in our group.

1) Tumor endoprosthesis ("megaprosthesis")

We launched for the first time a limb-salvage surgery to 13-year-old girl with proximal tibial osteosarcoma after preoperative chemotherapy using ceramic spacer and two-staged custom-made tumor endoprosthesis replacement fixated with bone cement at Osaka University Hospital in 1981. Thereafter, a number of modular-type tumor endoprostheses have been developed, among which HMRS (Howmedica Modular Resection System) developed by Kotz et al. is the most popular and worldwide tumor endoprosthetic system clinically used more conveniently than custom-made megaprostheses. We also developed KLS (Kyocera Limb Salvage) modular-type tumor endoprosthetic system in JMOG cooperated with Japan Medical Materials (JMM) Inc. in order to provide smaller size fitting for Oriental patients (Fig. 7). Moreover, the KLS system is available combined with a constrained acetabular cup system for total hip joint replacement, which we have developed for the purpose of preventing postoperative dislocation in patients with periacetabular malignant tumors (Fig. 8).[25, 26]

For younger children less than 10-12 years, extendable tumor endoprostheses, such as "Growing Kotz custom-made reconstruction system", can be presently available, or phased surgery are applied combined with temporary spacer reconstruction followed by permanent endoprosthetic revison, and bone transport/distraction osteogenesis technique to correct future limb-length discrepancy. In younger children, however, they are generally active and tend to experience frequent postoperative complications such as fracture, endoprosthetic breakage and loosening, thus meticulous long-term follow-up is necessary collaborated with their parents.

2) Massive bone allograft reconstruction

Massive bone allograft is relatively used as a

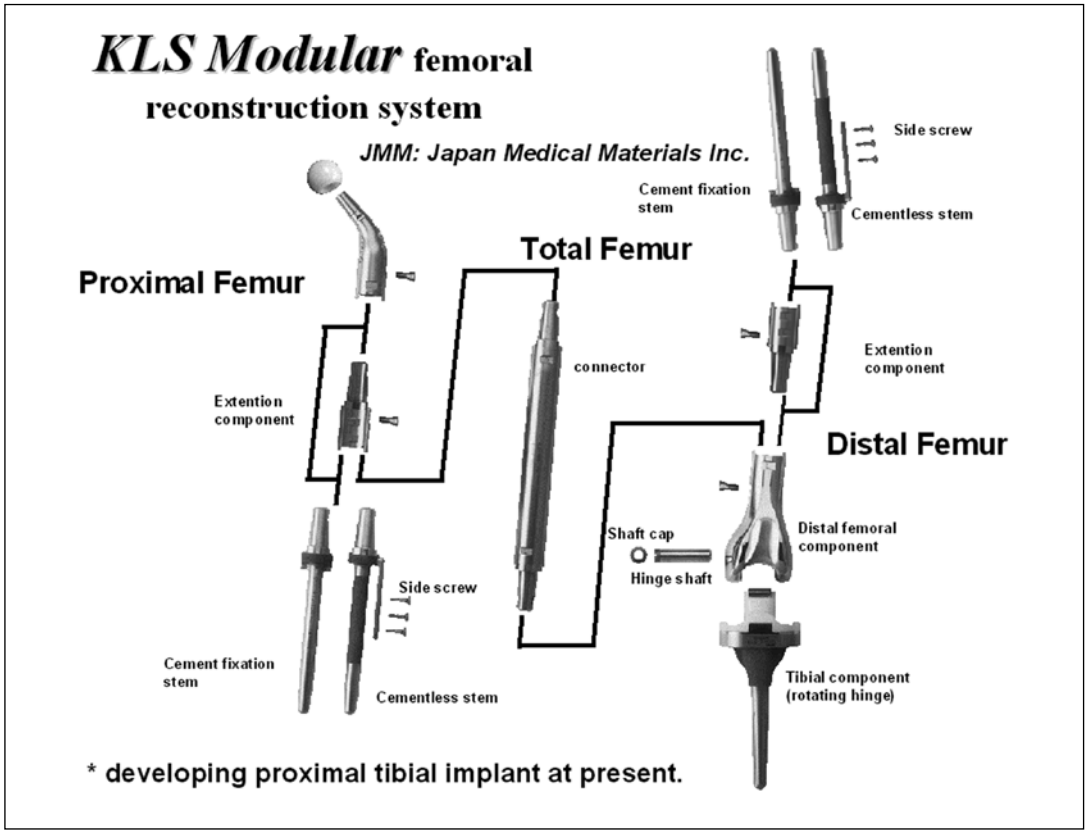

Fig. 7 KLS (Kyocera Limb Salvage) modular-type tumor endoprosthetic system developed in Japan.

Fig. 8 Constrained acetabular cup reconstruction system for total hip joint replacement, which is developed for the purpose of preventing postoperative dislocation after wide resection of periacetabular malignant tumors.

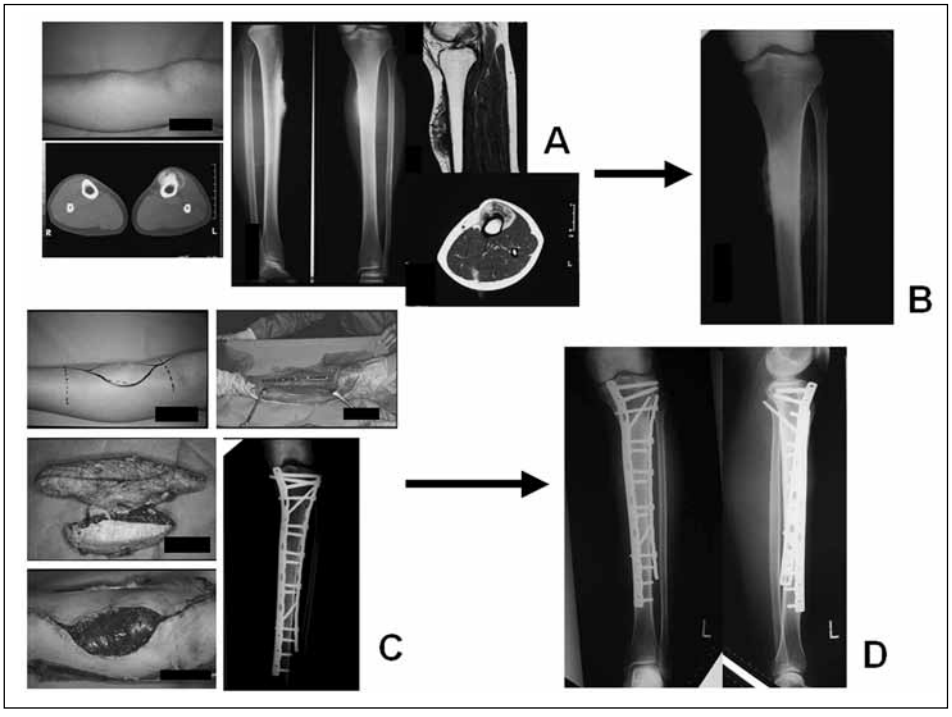

Fig.9 16-year-old girl with left-proximal tibial shaft periosteal osteosarcoma locally recurrent after resection elsewhere. A) preoperative macroscopic, plain X-ray, CT, and MRI findings, B) plain X-ray after preoperative chemotherapy, showing sclerotic change of extraosseous lesion, C) intercalary IORBG with dual-plate fixation + gastrocnemius muscle flap reconstrucition, D) plain X-ray 12 years postoperatively shows complete bony union at both IORBG-host bone junctions.

reconstruction method for a large bony defect after wide resection of sarcoma in Western countries,[27] however, it is a limited procedure for lack of its source of supply in Asia, especially in Japan by our religious and cultural reasons. Thus, we usually substitute recycling autobone graft for massive bone allograft as described in the next paragraph.

3) Recycling autobone graft reconstruction

As an alternative reconstructive technique for massive bony defect after wide resection of bone and soft-tissue sarcomas, there is a "recycling autobone graft", or otherwise named "biological reconstruction", which has been widely spread in Asian countries including Japan. This is a way that is treated by extracorporeal irradiation,[28, 29] Pasteur's hyperthermia,[30] or liquid nitrogen freezing and thawing[31] intraoperatively as a tumoricidal procedure after tumor wide resection, and then re-implanted into an original place for reconstruction. Boiling, alcohol-, phenol-, and autoclave treatment were also used formerly, but they are now abandoned because of their insufficient tumoricidal activity and deterioration of quality after treatment. Among these procedures, intraoperative extracorporeal radiated bone graft (IORBG) method was originally reported (300Gy x1 irradiation) by Uyttendaele from Belgium in 1988,[28] and we have also applied this method (50Gy x1 by Liniac, or 80Gy x1 for radioresistant chondrosarcoma) since 1989.[29] Although there are somewhat differences depending on tumoricidal procedeures, the advantages of these "recycling autobone re-implantation" are as follows: 1) lower cost compared with tumor endoprosthesis or massive bone allograft to reconstruct following tumor wide resection; 2) superior conformity in size and shape; 3) neither risk of viral disease transmission nor host-versus-graft rejection; 4) easy soft-tissue (tendoligamentous) reattachment on re-implantation; 5) superior bony union at osteotomized junction compared with allograft because of preservation of bone matrix proteins such as osteopontin and bone morphogenetic protein (BMP). Moreover, there is also a possibility of tumor immunogenic activity by tumoricided affected bone re-implantation. On the other hand, relatively high incidence of postoperative infection, non-union of osteotomized junction, and osteoarticular deformity after grafted bone fracture and subchondral collapse, are the considerable disavantages of recycling autobone graft. The points of this method are: 1) to select a certain tumoricidal procedure; 2) to firmly fixate a recycling autobone graft using such as dual-plates, or Hackstep intramedullary nail with screws; 3) to reinforce

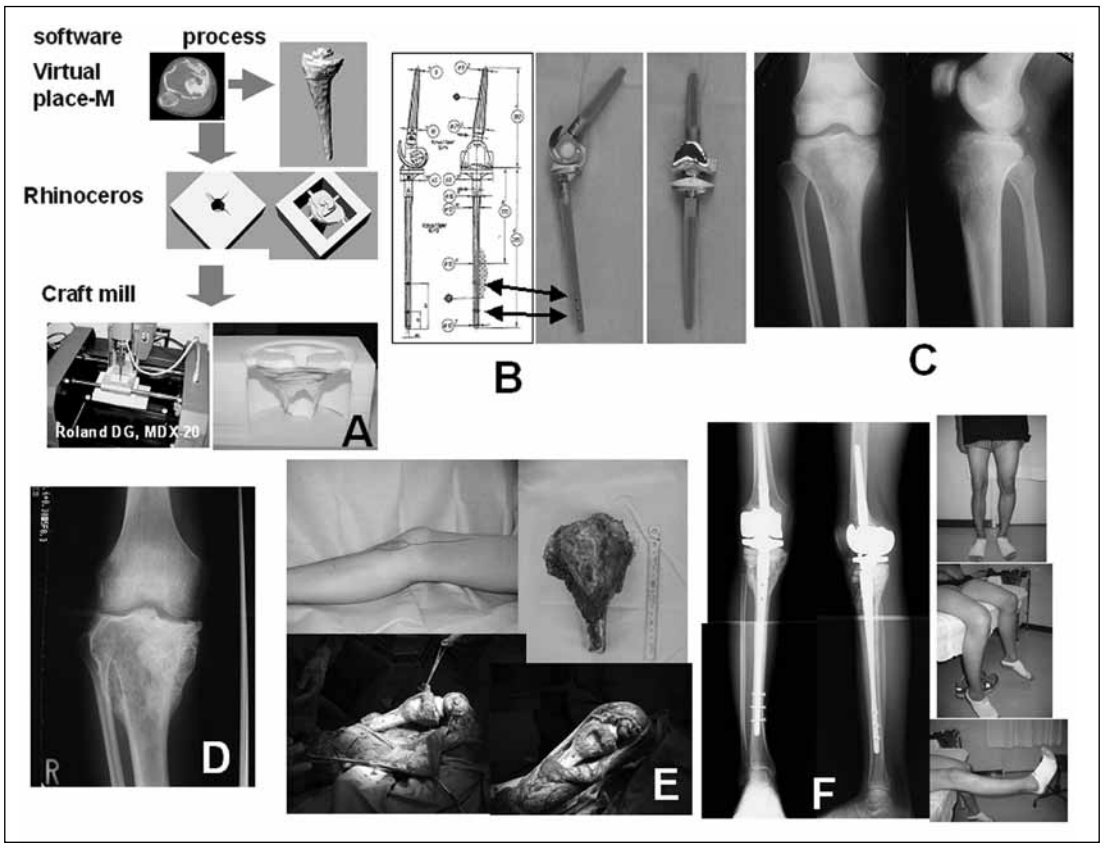

Fig. 10 A new trial of limb-salvage surgery using composite IORBG and custom-made long-stem TKR for proximal tibial osteosarcoma patients. A) preoperative manufacturing of artificial bone spacer (NEOBONE ™) for bony defect using computer-assisted 3-D modeling, B) preparation of Link ENDO-MODEL ROTATIONAL KNEE SYSTEM ™ custom-made long-stem TKR, C) plain X-ray of 16-year-old boy with right-proximal tibial osteosarcoma, D) plain X-ray after 4 cycles of preoperative OOS-D chemotherapy, showing sclerotic change of the tumor, E) composite IORBG + Link custom-made long-stem TKR augmented with premanufactured NEOBONE spacer reconstruction after wide tumor resection, F) plain X-ray 48 months postoperatively, the patient could walk without aids and MSTS functional score was 100%.

bony structural defect of recycling autobone with bone cement augmentation similarly in case of massive bone allograft.

Our present indications for using IORBG are: 1) intercalary IORBG reconstruction after diaphyseal bone resection (Fig. 9): 2) osteoarticular IORBG reconstruction for non-weight bearing site such as humeral and forearm sarcomas; 3) as a temporary spacer for younger childhood patients; 4) for reconstruction of massive bony defect after resection of pelvic, especially periacetabular bone tumors; and 5) as a composite IORBG and custom-made long-stem total knee endoprosthesis, a new trial which can easily reconstruct knee extension mechanism (patellar tendon reattachment), for proximal tibial osteosarcomas[32] (Fig. 10).

4) Other techniques

We also use other reconstructive techniques for limb-salvage after wide resection of bone and soft-tissue sarcomas, such as vascularizd fibular autobone graft (occasionally combined with recycling autobone graft) and vascularized clavicle transfer after wide resection of proximal humeral bone tumor named "claviculo pro humero" procedure.

Development of multidisciplinary approach consisting of orthopaedic oncology, radiation oncology, plastic surgery, and vascular surgery has enabled to perform limb-salvage surgery for almost all cases of extremity sarcomas, however, there is still some limit of limb-salvage for such as huge pelvic tumors considering frequent postoperative infection and postoperative limb function, thus for such

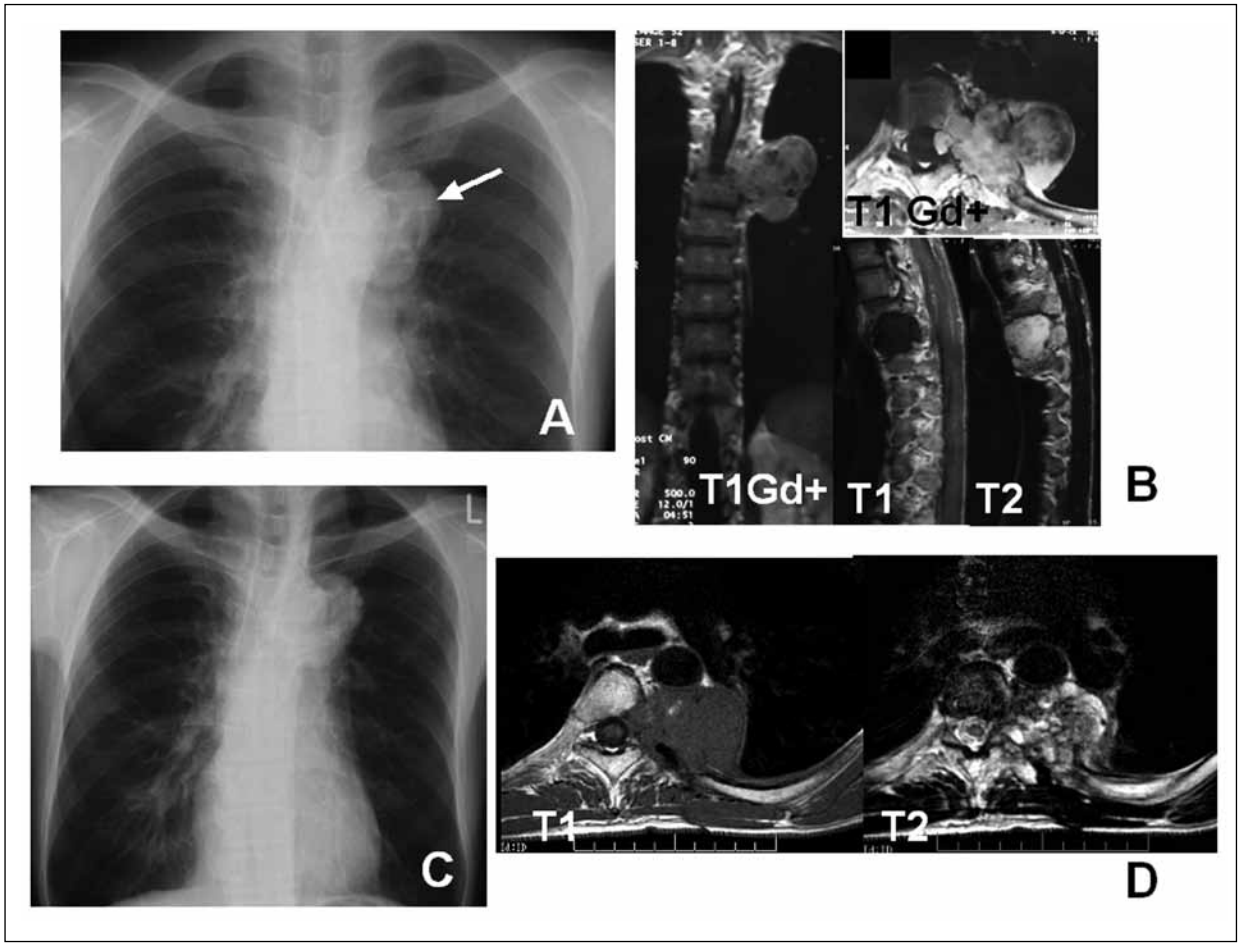

Fig. 11 42-year-old male with grade 2 chondrosarcoma of left-6th rib. The tumor was close to thoracic spine (A) plain X-ray (arrow: tumor), and B) MRI at presentation), then he selected carbon-ion radiotherapy instead of surgical resection. He is alive and well with a slight shrinkage of the tumor 44 months after irradiation (C) plain X-ray, D) MRI).

cases should be indicated ablative hemipelvectomy by generally estimating the patient's age, primary tumor site and local extent, and complication like diabetes.[33)]

Recently, we can clinically use carbon-ion heavy particle radiotherapy as an innovative treatment modality for pelvic (especially sacrum) and spinal/perispinal tumors which are anatomically difficult of surgical wide resection, and the short term result is excellent in local tumor control and physical function,[12] expecting its long term outcome (Fig. 11).

III. DEVELOPMENT OF NEW DRUGS FOR SARCOMAS

In the field of cancer treatment, a variety of chemotherapeutic drugs and more specific molecular-targeting agents have been recently developed, and these new agents are expected to clinically apply to sarcomas depending on each histological type, for example, gemcitabine and docetaxel to leiomyosarcoma, paclitaxel to angiosarcoma, trabectedin (ecteinascidin 743; ET-743) to some types of soft-tissue sarcomas, and imatinib mesilate (Gleevec) to dermatofibrosarcoma protuberans and chordoma. Tumor immunotherapy targeting cancer-specific antigens recognized by cytotoxic T-lymphocytes is also under developed, and clinical trials of WT-1 peptide vaccine immunotherapy for bone and soft-tissue sarcomas and SYT-SSX immunotherapy for synovial sarcoma are now proceeding in Japan.[34, 35]

IV. FUTURE DIRECTION AND ASSIGNMENT

This article has reviewed the development of multidisciplinary approach for bone and soft-tissue

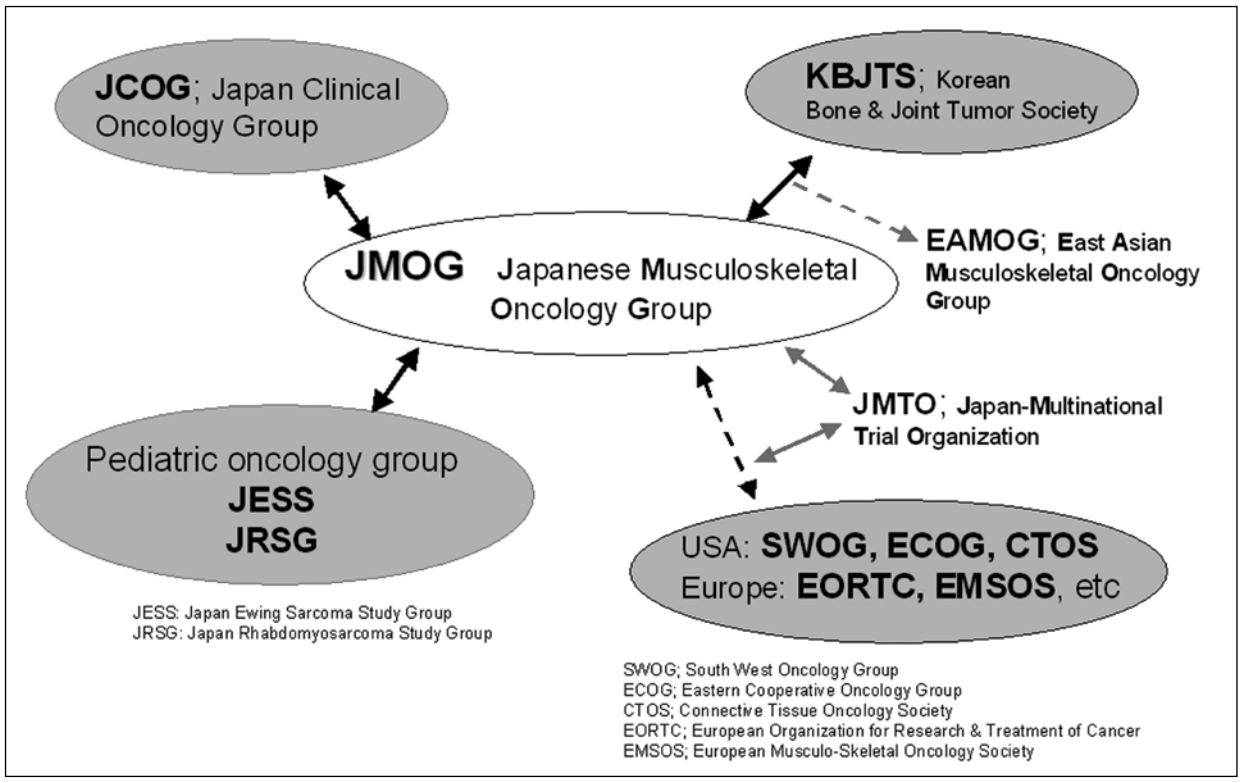

Fig. 12 International network of multi-institutional sarcoma study groups for various clinical trials and translational research in bone and soft-tissue sarcomas as a "rare cancer".

sarcomas mainly progressed in Japan over the last 30 years. To further improve clinical outcomes of patients with sarcoma as a "rare cancer", we would like to provide three important assignments directed in the future: 1) to build up a nationwide network of sarcoma centers to collect more sarcoma patients and to organize more expertise in multidisciplinary approach for sarcoma treatment, 2) to establish a multi-institutional sarcoma study group for various clinical trials and also to collaborate internationally with other clinical oncology groups (Fig. 12), and 3) to simultaneously enrich basic and translational research for sarcomas to develop novel therapeutic drugs and to innovate limb-salvage reconstructive techniques.

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