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International Orthopaedics (SICOT) (2013) 37:27–30
DOI 10.1007/s00264-012-1688-1

ORIGINAL PAPER

Cutting and implanting errors in minimally invasive total knee arthroplasty using a navigation system

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Received: 4 October 2012 / Accepted: 12 October 2012 / Published online: 28 October 2012

Abstract
Purpose The purpose of this study was to evaluate the accuracy of bone cutting and implantation in minimally invasive total knee arthroplasty with image-free navigation.
Methods The alignment of the tibial and femoral bone resection was measured in 40 knees during surgery. The alignment measurement was repeated after cementing the tibial and femoral components. We evaluated the cutting error and the implanting error.
Results The mean tibial cutting errors were 0.5 and 0.7° in the frontal and sagittal planes, respectively. The mean femoral cutting errors were 0.5 and 0.9° in the frontal and sagittal planes, respectively. The mean tibial implanting errors were 1.0 and 0.9° in the frontal and sagittal planes, respectively. The mean femoral implanting error was 0.7° in the frontal plane.
Conclusions Computer-assisted navigation was useful in checking the alignment of both bone cut and cementation.

Introduction

Computer-assisted navigation systems were introduced to improve component alignment accuracy in total knee arthroplasty (TKA). Many cohort studies have shown improved prosthetic radiographic alignment associated with the use of computer-assisted navigation when compared to standard instrumentation [1–4]. The use of computer-assisted surgery has also reduced the risk of malalignment associated with minimally invasive surgery (MIS) [5, 6], which has potential issues with component malpositioning arising from the limited surgical view [7]. However, there were still errors in component alignment with computer-navigated TKA associated with the jig cutting setting, bone cutting and component implantation [8–11]. Navigation systems recommend checking for alignment of the bone cutting surface just after cutting the bone. In addition, they recommend checking for the lower limb alignment only after the trial or final components are introduced. The importance of the final positioning of the femoral and tibial components seems to be particularly underestimated [9]. However, we can use the navigation system at the time of the final tibial and femoral component implantation. There is little published information available regarding bone cut accuracy and implant fixation in TKA performed with the combined techniques of computer-assisted navigation and MIS [12].

The purpose of this study was to evaluate the accuracy of bone cutting and implantation in MIS TKA with image-free navigation. Our hypothesis was that navigation could be useful to check the alignment of both bone cut and cementation. In addition, we evaluated postoperative radiographic and intraoperative navigation alignment measurements.

Materials and methods

This prospective study involved 40 consecutive patients who had a primary TKA. MIS was performed in all knees through a mini-midvastus approach without patellar eversion by one experienced surgeon. Posterior stabilised (PS) designs were used for all cases, and all components (Columbus, Aesculap, Tuttlingen, Germany) were fixed with cement. The navigation system used for the measurements was the image-free navigation system (OrthoPilot, Aesculap, Tuttlingen, Germany). There were 12 men and 28 women with a mean age of 74 years (range 58–88 years) and a mean body mass index of 26.6 kg/m^2 (range 19.1–39.8 kg/m^2). The diagnosis for all patients was

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knee osteoarthritis. The mean ± standard deviation (SD) preoperative mechanical axis deviation in degrees of valgus was measured at 11.1±6.5° of varus alignment (range 20° of varus to 6° of valgus). The tibial and femoral cuts were targeted to be perpendicular to the mechanical axis in the coronal and sagittal planes using the tibia first gap technique [13]. The saw blade thickness used was 1.27 mm. The alignment of the tibial bone resection plane in the frontal and sagittal planes was measured with the instrumented probe positioned on the proximal tibial cut and was recorded from the navigation system screen. The alignment of the femoral bone resection plane in the frontal and sagittal planes was measured using the instrumented probe. The orientations of these resection planes were recorded with a resolution of 1°. The tibial component was cemented. The cement mantle was digitally pressurised into the cancellous bone before component insertion. Tibial component alignment was measured by the same instrumented probe after impaction (Fig. 1a). The patellar component was cemented, and then the femoral component was cemented. After impaction, femoral component alignment was also measured with the instrumented probe. The probe was then positioned on the most distal part of the femoral component condyles. (Fig. 1b). Only the alignments in the coronal plane for the femur and the frontal and sagittal planes for the tibia were recorded due to the shape of the components. The mechanical axis measurement was recorded after implanting all components and was measured without applying any axial force.

The cutting error was defined and measured as any deviation between the cutting surface and the planned angle in the frontal and sagittal planes. The deviation between the component alignment and the corresponding cutting surface was calculated and defined as implanting error. Full-length standing anteroposterior and lateral radiographs were completed three weeks after surgery to determine the alignment of the components. We assessed the frontal femoral component angle, the frontal tibial component angle, the sagittal tibial component angle and the tibiofemoral angle, as described previously [6]. The deviations between the radiographic and intraoperative component angles were calculated, and we defined these deviations as the radiographic error. The mean absolute error of the mechanical leg axis was also evaluated.

Statistical analysis

The relationships between alignment parameters were analysed by Spearman's rank correlation, with the level of significance set at 0.05.

Results

The mean absolute tibial cutting error was 0.5±0.6° (0.1±0.8° varus, range 3° varus to 1° valgus) and 0.7±0.7° (0.4±1.0° anterior slope, range 1° posterior slope to 2° anterior slope) in the frontal and sagittal planes, respectively. The mean absolute femoral cutting error was 0.5±0.5° (0.3±0.6° valgus, range 1° varus to 1° valgus) and 0.9±0.7° (0.5±1.1° anterior slope, range 2° posterior slope to 3° anterior slope) in the frontal and sagittal planes, respectively. The mean absolute tibial implanting error was 1.0±0.9° (0.6±1.2° valgus, range 1° varus to 3° valgus) and 0.9±0.9° (0.2±1.3° anterior slope, range 2° posterior slope to 3° anterior slope) in the frontal and sagittal planes, respectively. The mean absolute femoral implanting error was 0.7±0.6° (0.2±0.9° varus, range 2° varus to 2° valgus) in the frontal plane. We found no cutting or implanting error that was greater than 3°. The mean absolute tibial radiographic error was 0.8±1.0° (0.5±1.1° varus, range 3° varus to 2° valgus) and 1.3±1.1° (0.9±1.5° posterior slope, range 4° posterior slope to 3° anterior slope) in the frontal and sagittal planes, respectively. Only one knee showed sagittal tibial plane radiographic error of more than 3°. The mean absolute femoral radiographic error was 1.0±0.9° (range 3° varus to 3°

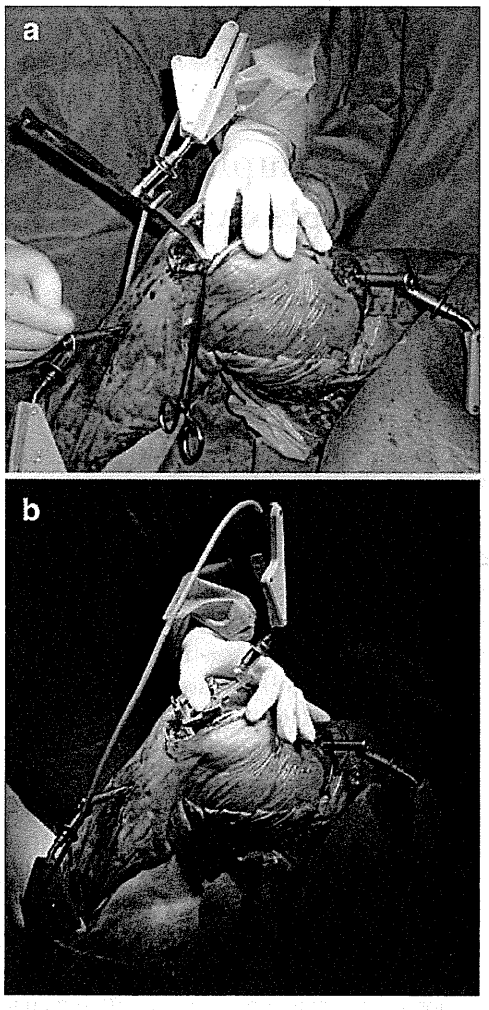

Fig. 1 Intraoperative navigation measurements of the tibia (**a**) and the femur (**b**) after implanting

Table 1 Cutting error

	Bäthis et al. [1]	Yau et al. [14]	Kim et al. [12]	Nakahara et al. [10]	This study
Femur					
Frontal alignment (°)	0.6[a]	0.8[a]	0.1	0.5	0.3 (0.5[a])
Sagittal alignment (°)	1.4[a]	1.6[a]	0.7	1.6	0.5 (0.9[a])
Tibia					
Frontal alignment (°)	0.5[a]	1.3[a]	0.3		0.1 (0.5[a])
Sagittal alignment (°)	1[a]	1.3[a]	0.3		0.3 (0.7[a])

[a]Absolute values are expressed

valgus) in the frontal plane. The mean absolute error of the mechanical leg axis was 1.9±1.2° (range 5° varus to 3° valgus). In four cases (10 %), radiographic errors for the mechanical leg axis were more than 3°.

Positive correlations were found between the femoral cutting surfaces and the angle planned in the frontal and sagittal planes (R^2=0.358, p<0.001; and R^2=0.194, p=0.006, respectively). The tibial cutting surface showed a significant positive correlation with the angle planned in the sagittal plane (R^2=0.215, p=0.004); however, there was no correlation between the tibial cutting surface and the angle planned in the frontal plane (R^2=0.006, p=0.612). There was a positive correlation between the frontal alignment of the femoral component and the corresponding cutting surface (R^2=0.408, p<0.001). A positive correlation was found between the sagittal alignment of the tibial component and the corresponding cutting surface (R^2=0.144, p=0.018). There was no correlation between the frontal alignment of the tibial component and the corresponding cutting surface (R^2=0.007, p=0.604). There was also no correlation between the navigation and radiographic measurements in terms of the postoperative mechanical axis, frontal femoral frontal alignment, or tibial frontal and sagittal alignments (R^2=0.004, p=0.689; R^2=0.003, p=0.744; R^2=0.111, p=0.564; and R^2=0.069, p=0.100, respectively).

Discussion

This study showed no cutting or implanting errors of more than 3°, but 10 % of the cases showed radiographic errors of more than 3°. Our results were comparable to previous studies when evaluating cutting error [1, 10, 12, 14] (Table 1), implanting error [9] (Table 2) and radiographic error [15, 16] (Table 3). Our study is the first to evaluate all types of errors (cutting, implanting and radiographic error). Choi et al. [16] reported the correlation between postoperative navigation and radiographic alignment. However, the frontal femoral and tibial alignments were measured by the instrumented probe of the navigation system positioned onto the relevant bone cuts after a final cut of the femur or tibia without implanting the components in this study. Our study and the study by Catani et al. [9] checked the component alignment after component implantation. Previous studies evaluated the standard TKA except the study by Kim et al. [12] who used the MIS technique. We used the surgical instruments specifically designed for MIS; however, Kim et al. [12] used the standard surgical instruments because MIS instruments were not available at their institute. Our study together with that of Kim et al. [12] showed that accuracy could be achieved with MIS TKA using computer-assisted navigation. Our study demonstrates that the surgical instruments designed for MIS provided accuracy which was similar to that achieved with the standard instruments.

The bone cut measurements in our study showed significant correlation between the targeted and the actual alignments in the frontal and sagittal planes for the femur and in the sagittal plane for the tibia. However, a more accurate procedure is required in the tibial frontal plane. Techniques which included avoiding the movement of cutting blocks and the deflection of the saw blade at the time of bone cut produced greater accuracy. Several previous studies reported that a considerable amount of error could occur in the process of bone cutting with the oscillating saw systems [1, 8, 10, 12, 14]. A cadaver study

Table 2 Implanting error

	Catani et al. [9]	This study
Femur		
Frontal alignment (°)	0.2	0.2 (0.7[a])
Tibia		
Frontal alignment (°)	0	0.6 (0.9[a])
Sagittal alignment (°)	0.2	0.1 (0.9[a])

[a] Absolute values are expressed

Table 3 Radiographic error

	Yaffe et al. [15]	Choi et al. [16]	This study
Mechanical leg axis (°)	2.7	2.3	1.1 (1.9[a])
Femur			
Frontal alignment (°)			0.1 (1.0[a])
Tibia			
Frontal alignment (°)			0.5 (0.8[a])
Sagittal alignment (°)			0.8 (1.3[a])

[a] Absolute values are expressed

showed that the maximum cutting error relative to the cutting guide was in the range of 1.5–2° for varus/valgus and in the range from 3 to 4° for flexion/extension [17]. Although we can recut the bone to achieve the planned alignment after checking cut surface alignment with the navigation system, we had no need for this correction in this series. Component implantation was achieved accurately in the frontal plane for the femur and sagittal plane for the tibia. However, a more accurate procedure is required for the tibial component in the frontal plane, during bone cutting. A final alignment check should be made after component implantation and before the cement hardens. Component alignment could then be corrected after the probe check.

Most studies reported more accurate alignment with fewer outliers using navigation [1, 2]. However, Bauwens et al. [18] reported that the alignment of the mechanical axes was similar in the navigation and conventional surgery groups in a meta-analysis of 33 studies. The reason for the contradictory results might rest in the implanting and/or radiographic error, which Bauwens et al. [18] did not assess. Ninety-eight per cent of patients had a frontal tibiofemoral angle that was within 3° of the ideal with radiographic measurement in our study. However, we confirmed that all cases showed angles that were within 3° on the intraoperative navigation screen. This may have occurred because the joint was unloaded intraoperatively and was weight-bearing postoperatively when the radiographs were taken. This difference in loading conditions would influence the lower limb alignment measurement in the radiographs. Another possible explanation for radiographic error is that postoperative knee flexion contracture may have been present at the time of radiographic evaluation, but would not have been present intraoperatively.

Limitations of this study include a small sample size and the different loading conditions between intraoperative navigation and postoperative radiography. Additional studies comparing the navigation or radiographic measurements to measurements using a three-dimensional imaging procedure will be needed [16].

In conclusion, our hypothesis was supported. It would be useful to check the alignment of both the bone cut and cementation using navigation.

Conflict of interest The authors declare that they have no conflict of interest.

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European Journal of Cancer (2013) 49, 377–385

Available at www.sciencedirect.com

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The value of C-reactive protein and comorbidity in predicting survival of patients with high grade soft tissue sarcoma

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Available online 8 October 2012

KEYWORDS
C-reactive protein
Soft tissue sarcoma
High grade tumour
Comorbidity
Charlson index score

Abstract ***Background:*** The aim of this study was to determine whether C-reactive protein (CRP) levels or patient's comorbidity before treatment predicted the overall disease-specific survival and local tumour control in high grade soft tissue sarcoma patients.
Methods: A total of 332 primary adult soft tissue sarcoma patients were retrospectively reviewed. CRP levels were obtained prior to treatment for all patients. The Charlson comorbidity index (CCI) was used for evaluation as a measure of comorbidity. Patients that presented with metastases at diagnosis were excluded from this study.
Results: Elevated CRP levels were seen in 152 patients. CCI score varied from 0 to 4. Two-hundred and sixty-five patients had a score of 0 (no identified comorbidity), and 67 patients had a score of 1 or more. Patients with elevated CRP levels prior to initial treatment had a poorer disease-specific survival (42% at 5 years) than patients with normal CRP levels (82% at 5 years) ($p < 0.0001$). Patients with elevated CRP levels had a poorer local recurrence-free rate after initial treatment (75% at 5 years) than patients with normal CRP levels (89% at 5 years) ($p = 0.0004$). Multivariate analysis also showed the preoperative CRP level to be an independent predictor of survival and local control. Although age in patients with identified comorbidity was significantly higher than those in patients with no-identified comorbidity, CCI was not a predictive factor for either survival or local control.
Conclusion: Pretreatment elevated CRP levels were found to be a poor prognostic factor for disease-specific survival and local control for soft tissue sarcoma patients.

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0959-8049/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejca.2012.09.004

1. Introduction

Several relevant prognostic factors have been defined for soft tissue sarcomas. Tumour size, depth, histological tumour grade and age are predictive factors of survival.[1–3] Especially, patients with high grade tumours are at significant risk for relapse, and as many as 50% of these patients die of their disease.[3] Elevated preoperative serum C-reactive protein (CRP) levels are found in a variety of cancers and an elevated serum CRP level is an indicator of a poorer prognosis in many cancers, such as renal cell carcinoma,[4] gastric cancer,[5] breast cancer,[6] colorectal cancer,[7] non-small cell lung cancer,[8,9] prostate cancer,[10] gastrointestinal cancer,[11] pancreatic cancer[12] and oesophageal cancer.[13] On the other hand, the amount of comorbidity a patient has at the time of diagnosis can also significantly impact on survival for some cancer patients. Correlations between the severity of comorbid conditions and diverse outcomes have been observed in patients with colorectal,[14] head and neck,[15] lung,[16] bladder,[17] renal cell[18] and ovarian cancer.[19]

Elevated CRP levels have been shown to be a poor prognostic factor in patients with soft tissue sarcoma in two previous small studies.[20,21] The author, however, raised the possibility that the patient's medical condition may have caused its raised CRP levels and therefore has affected survival.

The aim of this study was to determine whether the serum CRP levels or the extent of comorbidity before treatment could predict the disease-specific survival and local tumour control in adult patients with high grade soft tissue sarcoma and also if there was any link between increased CRP levels and comorbidity.

2. Patients and methods

2.1. Patients

A total of 543 adult patients with primary histological high grade soft tissue sarcoma were treated with surgical resection of their primary tumour between January 2003 and August 2010. Patients that presented with recurrent disease, distant metastasis at diagnosis or who were referred for additional resection after a previous inadvertent excision were excluded from this study. Of 543 patients treated with surgical resection, 211 patients had incomplete clinical history or laboratory data. The remaining 332 patients were retrospectively analysed. Among the 332 patients in the cohort, the average follow-up was 28.4 months (range, 1–101). All patients had pretreatment staging with a lung CT scan to rule out the presence of metastases. The histopathological diagnosis and tumour grade was determined using the French Federation of Cancer Centers Sarcoma Group (FNCLCC) grading system for all patients by experienced musculoskeletal pathologists. Treatment decisions were made by a multi-disciplinary team according to UK Guidelines.[22] In general most patients had surgical resection aiming to achieve clear margins followed by radiotherapy for large or deep tumours. CRP levels were obtained prior to treatment for all patients and were measured using an auto analyser as part of a routine biochemical examination. The normal serum CRP level is $\leqslant$10 mg/L at our institution.

Table 1
Charlson comorbidity index score.[22]

Score	Condition
1	Myocardial infarction, cerebrovascular disease Congestive heart failure, dementia, chronic pulmonary disease, peripheral vascular disease, peptic ulcer disease Mild liver disease, diabetes without end-organ damage Connective tissue disease
2	Hemiplegia, tumour without metastases Moderate or severe renal disease, leukaemia Diabetes with end-organ damage, lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour, AIDS

Abbreviations: AIDS, acquired immune deficiency syndrome.

Co-morbidity was evaluated using the Charlson comorbidity index (CCI).[23] CCI consists of a list of 19 comorbid conditions and is weighted according to the degree to which they predict mortality among an inpatient cohort (Table 1).[23] The CCI was calculated by the West Midlands cancer Intelligence Unit for all patients using data obtained from the Hospital Episodes and Statistics database (HES). Hospital admissions or comorbidity identified in the preceeding nine months or the one month following the date of definitive surgical excision was used to calculate the CCI score. A clinicopathological analysis was performed comparing the CRP level and CCI to the various factors including age, gender, tumour size, tumour depth, the American Joint Committee on Cancer (AJCC) classification[24] and tumour histological grade.

The primary purpose of this study was to examine the prognostic factors including CRP level and CCI associated with the patient's survival using univariate and multivariate analyses. The following factors were studied: patient's age (>60 versus $\leqslant$60), gender, tumour depth (superficial versus deep), tumour size (>10 cm versus $\leqslant$10 cm), AJCC classification,[24] surgical margin (negative versus positive), adjuvant chemotherapy, tumour histological grade (grade 2 versus grade 3), CCI (no identified versus identified comorbidity) and CRP level (>10 mg/L versus $\leqslant$10 mg/L). The further aims were to examine the prognostic factors associated with the patient's local tumour control and also to investigate if CRP levels link CCI.

2.2. Statistical analysis

The statistical association of the clinicopathological factors was evaluated using the Mann–Whitney U test

for quantitative data, and the χ^2 test for qualitative data. Disease-specific survival time was taken from the date of initial treatment of the primary tumour to the date when the patient was documented to be alive or the date when the patient passed away from sarcoma. Survival curves were constructed using the Kaplan–Meier method. The log-rank test was used to compare the survival of the patients with high and normal CRP levels. CRP was also investigated as continuous variable with univariate Cox regression analysis. A multivariate analysis was performed using a Cox proportional hazard model. The variables included in the multivariate analysis were the significant factors identified in the univariate analysis. A value of $p < 0.05$ was considered to be significant in all statistical analyses. Receiver operative characteristic (ROC) analysis was done to determine threshold of CRP at risk of further disease or death at 2 years. Statistical software packages Stata, version 11, and Stat View version 5.0 were employed for analysis.

3. Results

3.1. Patient, tumour and treatment characteristics

A total of 322 patients were studied including 194 males and 138 females and their details are shown in Table 2. The tumours were histologically classified as follows: 119 malignant fibrous histiocytomas (MFH), 67 liposarcomas, 43 myxofibrosarcomas, 33 leiomyosarcomas, 23 synovial sarcomas, 11 fibrosarcomas, 10 malignant peripheral nerve sheath tumours (MPNST) and 26 other tumours. The primary tumour sites were the thigh ($n = 165$), leg ($n = 31$), forearm ($n = 20$), upper arm ($n = 19$), buttock ($n = 15$), knee ($n = 14$), chest wall ($n = 11$), back ($n = 10$) and other sites ($n = 47$).

Table 2
Patients characteristics.

Patient demographic		
Age (years)	Average	61 (20–92)
	Median	63
Gender	Male	194 (58%)
	Female	138 (42%)
Tumour depth	Superficial	82 (25%)
	Deep	250 (75%)
Tumour size (cm)	Average	10.6 (1–30)
AJCC stage	2A	42 (13%)
	2B	69 (21%)
	3	221 (66%)
Tumour grade	2	80 (24%)
	3	252 (76%)
Surgical margin	Positive	58 (17%)
	Negative	274 (83%)
Adjuvant radiation	Preoperative	9 (3%)
	Postoperative	265 (80%)
	No	58 (17%)
Adjuvant chemotherapy	Preoperative	4 (1%)
	Postoperative	10 (3%)
	No	318 (96%)

Abbreviations: AJCC, American Joint Committee on Cancer.

CRP levels were measured before preoperative radiotherapy and chemotherapy in these patients.

3.2. The relationship between Charlson comorbidity index and clinical characteristics

CCI score varied from 0 to 4. Two-hundred and sixty-five patients had a score of 0 (no identified comorbidity), and 67 patients had a score of 1 or more

Table 3
The relationship between Charlson comorbidity index and clinical characteristics.

variables		*n*	CCI score 0	CCI score 1–4	*p* Value
Age	>60	181	128	53	<0.0001
	⩽60	151	137	14	
	Average		59	69	<0.0001*
Gender	Male	194	159	35	0.25
	Female	138	106	32	
Tumour size	>10 cm	145	115	30	0.84
	⩽10 cm	187	150	37	
	Average		10.6	10.9	0.69*
AJCC	2A	42	31	11	0.53
	2B	69	57	12	
	3	221	177	44	
Tumour grade	2	80	66	14	0.49
	3	252	199	53	
CRP	>10 mg/L	152	118	34	0.36
	⩽10 mg/dl	180	147	33	

Abbreviations: CRP, C-reactive protein; CCI, Charson co-morbidity index; AJCC, American Joint Committee on Cancer.
* Mann–Whitney U test. Others: Chi-square test.

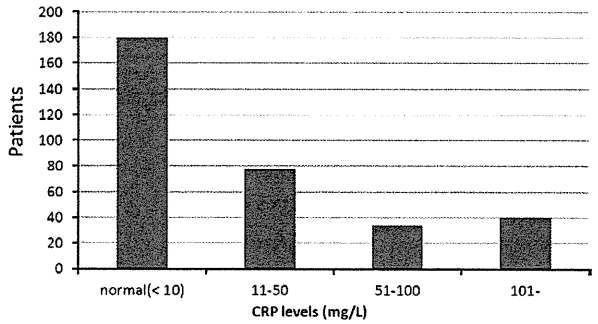

Fig. 1. The figure shows the distribution of patients concerning C-reactive protein (CRP) levels.

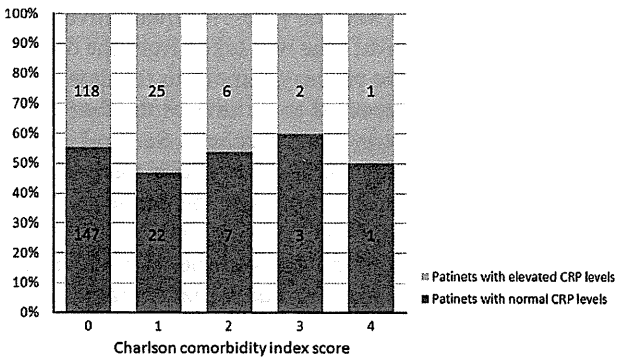

Fig. 2. The figure shows the relationship between C-reactive protein (CRP) and Charlson comorbidity index score.

(identified comorbidity). Forty-seven patients had a score of 1, 13 had 2, 5 had 3 and 2 had 4. The relationship between the clinicopathological features and CCI is shown in Table 3. Age of patients with identified comorbidity was significantly higher than those in patients with no-identified comorbidity ($p < 0.0001$).

3.3. The relationship between CRP and clinical characteristics

Elevated CRP levels (>10 mg/L) were seen in 152 patients (range; 11–342, average; 75) (Fig. 1). These included 73 with MFHs, 27 with liposarcomas, 18 with myxofibrosarcomas, 11 with leiomyosarcomas, 6 with MPNSTs, 6 with fibrosarcomas, 2 with synovial sarcomas and 11 with other tumours. The relationship between the clinical characteristics and preoperative serum CRP level is shown in Table 4. The tumour histological grade and age and tumour size in the patients with elevated CRP levels were significantly higher than in patients with normal CRP levels. There was no relationship between CRP and CCI score (Fig. 2).

3.4. Overall disease-specific survival and predictors of mortality

Two-hundred thirty-seven of the 332 patients (71.4%) were alive as of August 2011, but 75 had died of disease and 20 had died of other causes. Seventy-three patients died of distant metastasis and the remaining 2 patients died of local tumour invasion. The disease-specific survival was 63.9% at 5 years.

Patients with elevated CRP levels prior to initial treatment had a poorer disease-specific survival than patients with normal CRP levels ($p < 0.0001$). The disease-specific survival estimates at 3 and 5 years were 49.5% and 42.2%, for those with an elevated CRP, versus 88.8% and 81.8%, for those with a normal CRP (Fig. 3). Univariate analysis of all possible prognostic factors confirmed the poor predictive values for larger

Table 4
The relationship between CRP levels and clinical characteristics.

variables		*n*	CRP > 10 mg/L	CRP ⩽ 10 mg/L	*p* Value
Age	>60	181	95	86	0.01
	⩽60	151	57	94	
	Average		64.8	58.1	0.001*
Gender	Male	194	87	107	0.68
	Female	138	65	73	
Tumour size	>10 cm	145	92	53	<0.0001
	⩽10 cm	187	60	127	
	Average		12.6	9	<0.001*
AJCC	2A	42	6	36	<0.0001
	2B	69	15	54	
	3	221	131	90	
Tumour grade	2	80	16	64	<0.0001
	3	252	136	116	
CCI	Score 0	265	118	147	0.36
	Score 1–4	67	34	33	

* Mann–Whitney U test. Others: Chi-square test.

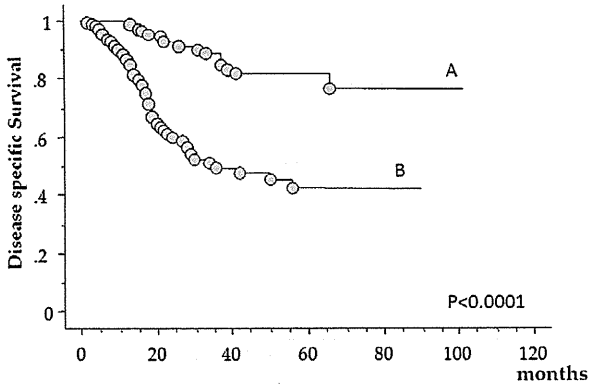

Fig. 3. The Kaplan–Meier curve shows the overall disease-specific survival of the 332 soft tissue sarcoma patients (A – Patients with normal C-reactive protein (CRP) levels. B – Patients with elevated CRP levels).

(>10 cm) tumour size ($p = 0.0006$), higher AJCC stage ($p = 0.0006$) and histological grade 3 tumour ($p = 0.004$) (Tables 5a and 5b). CCI was not a predictive factor ($p = 0.58$). Only elevated CRP levels remained their prognostic significance in the multivariate analysis (Table 6).

When patients were divided into 3 groups according to CRP levels, the patients with higher CRP levels had a poorer disease-specific survival than patients with lower CRP levels. The survival rate at 5 years was 33.5% for those with >50 mg/L CRP levels, 49.2% for those with 10-50 mg/L and 83.3% for those with normal CRP levels ($p < 0.0001$) (Fig. 4).

Table 5b
Univariate Cox regression analyses of factors as continuous variables.

Variables	HR	95% CI	*p* Value
Age	1.008	0.995–1.022	0.25
Tumour size	1.085	1.044–1.128	<0.0001
Charlson comorbidity index	1.306	0.932–1.831	0.12
CRP	1.008	1.005–1.011	<0.0001

Abbreviations: HR, hazard risk; CRP, C-reactive protein; 95% CI, 95% confidential interval.

3.5. Local recurrence-free rate and predictors of events

Thirty-eight of the 332 patients (11%) developed local tumour recurrence. The 5-year local recurrence-free rate was 83.0%.

Patients with elevated CRP levels prior to initial treatment had a poorer local recurrence-free rate after initial treatment than patients with normal CRP levels ($p = 0.0004$). The local recurrence-free rate estimates at 3 and 5 years were 74.5% and 74.5% versus 91.9% and 89.0% (Fig. 5). Univariate analysis also revealed significantly poorer outcomes for patients with positive surgical margin ($p = 0.0002$), no adjuvant radiation therapy ($p < 0.0001$), histological grade 3 tumour ($p = 0.002$), higher AJCC stage ($p = 0.047$) and older age

Table 5a
Univariate disease-specific survival analysis in 332 patients with soft tissue sarcoma.

Variables		*n*	3-Y survival	5-Y survival	Log-rank *p* Value
Age	>60	181	74	67	0.16
	⩽60	151	69.1	61.4	
Gender	Male	194	74.1	66.9	0.8
	Female	138	68.8	61.2	
Tumour depth	Superficial	82	70.4	61.4	0.45
	Deep	250	74	70.8	
Tumour size	>10 cm	145	58.1	49.7	0.0006
	⩽10 cm	187	80.6	73.6	
Surgical margin	Positive	58	65.5	62.4	0.18
	Negative	274	72.4	63.3	
Chemotherapy	Yes	14	71.4	65.1	0.69
	No	332	70.7	50.5	
CCI	Score 0	265	71	65	0.58
	Score 1–4	67	73.6	58.9	
AJCC stage	2A + 2B	111	88.9	77.4	0.0006
	3	221	62.1	57.2	
Tumour grade	2	80	89.8	77.4	0.004
	3	252	65.1	59.6	
CRP levels	>10 mg/L	152	49.4	42.2	<0.0001
	⩽10 mg/dl	180	88.8	81.8	

Abbreviations: CRP, C-reactive protein; CCI, Charson co-morbidity index; AJCC, American Joint Committee on Cancer; 3-Y, 3-years; 5-Y, 5-years.

Table 6
Multivariate analysis for predictable factors of disease-specific survival.

Variables		HR	95% CI	p Value
Tumour size	>10 cm	1	0.426–1.138	0.15
	⩽10 cm	0.696		
AJCC stage	3	1	0.334–1.956	0.98
	2	0.984		
Tumour grade	3	1	0.183–1.956	0.4
	2	0.599		
CRP	>10 mg/L	1	0.144–0.449	<0.0001
	⩽10 mg/L	0.254		

Abbreviations: CRP, C-reactive protein; AJCC, American Joint Committee on Cancer; HR, hazard risk; CI, confidence interval.

($p = 0.001$) (Table 7). A multivariate analysis showed that the pretreatment CRP levels, tumour grade, surgical margin, adjuvant radiation therapy and age were independent predictors of local recurrence (Table 8).

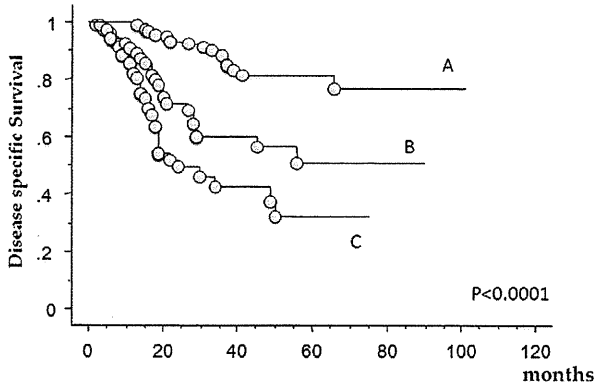

Fig. 4. The Kaplan–Meier curve shows the overall disease-specific survival of the 332 soft tissue sarcoma patients, who were divided into 3 groups (A – Patients with normal C-reactive protein (CRP) levels. B – Patients with 10–50 mg/L CRP levels C; Patients with >50 mg/L CRP levels).

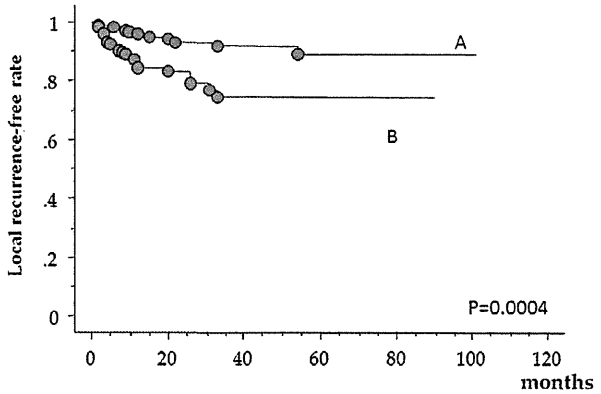

Fig. 5. The Kaplan–Meier curve shows the local recurrence-free survival of 332 soft tissue sarcoma patients (A – Patients with normal C-reactive protein (CRP) levels. B – Patients with elevated CRP levels).

On ROC analysis, a value of 12 mg/L is an appropriate threshold to identify if patients are at risk from further disease or death at 2 years (Fig. 6).

4. Discussion

Elevated preoperative serum CRP levels are found in a variety of cancers, and considered to be strongly associated with risk of cancer death.[4–13] The current univariate and multivariate analyses showed that elevated pretreatment CRP levels were associated with decreased disease-specific survival and local recurrence-free rate in 332 adult patients with high grade soft tissue sarcoma. No studies have so far shown the relationship between CRP and survival and local control in soft tissue

Table 7
Univariate analysis for predictable factor of local control in 332 patients with soft tissue sarcoma.

Variables		n	3-Y LR	5-Y LR	p Value
Age	>60	181	77.5	77.5	0.001
	⩽60	151	92.7	89.5	
Gender	Male	194	88.3	88.3	0.09
	Female	138	80.3	76.1	
Tumour depth	Superficial	82	80.1	80.1	0.07
	Deep	250	86.6	83.9	
Tumour size	>10 cm	145	84	84	0.65
	⩽10 cm	187	85.5	82.8	
Surgical margin	Positive	58	68	68	0.0002
	Negative	274	88.6	86	
Radiation	Yes	274	88.1	88.1	<0.0001
	No	58	66.2	52.9	
AJCC stage	2A + 2B	111	88.9	77.4	0.0006
	3	221	62.1	57.2	
Tumour grade	2	80	91.6	87.5	0.047
	3	252	81.1	81.1	
CRP levels	>10 mg/L	152	74.5	74.5	0.0004
	⩽10 mg/L	180	91.9	89	

Abbreviations: CRP, C-reactive protein; AJCC, American Joint Committee on Cancer; 3-Y LR, 3-years local recurrence-free rate; 5-Y LR, 5-years local recurrence-free rate.

Table 8
Multivariate analysis predictable factor of local control in 332 patients with soft tissue sarcoma.

Variables		HR	95% CI	*p* Value
Age	>60	1	0.179–0.819	0.01
	⩽60	0.383		
Surgical margin	Positive	1	0.142–0.562	0.003
	Negative	0.282		
Radiation	Yes	1	2.246–9.335	<0.0001
	No	4.579		
AJCC stage	3	1	0.701–4.734	0.22
	2	1.822		
Tumour grade	3	1	0.03–0.762	
	2	0.15		0.02
CRP	>10 mg/L	1	0.206–0.976	0.04
	⩽10 mg/L	0.448		

Abbreviations: CRP, C-reactive protein; AJCC, American Joint Committee on Cancer; HR, hazard risk; CI, confidence interval.

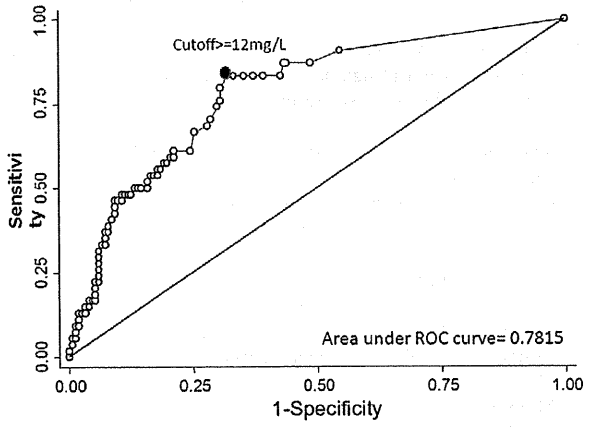

Fig. 6. ROC curve shows appropriate threshold of C-reactive protein (CRP) to identify if patients are at risk from further disease or death at 2 years.

sarcoma patients on multivariate analysis although previous work has shown it's effect on event-free survival.[21]

There are several possible mechanisms for the production of CRP in patients with malignant tumours. First, tumour growth can cause tissue inflammation, and hence elevate the CRP level.[25] Second, tumour-associated mononuclear cells are able to produce high amounts of IL-6 as the immune cytokine response to tumour growth.[26,27] The production of CRP in hepatocytes appears to be principally induced at the transcriptional level following the elevation of circulating IL-6.[28] Finally, there is evidence that cancer cells can increase the production of inflammatory proteins, which could explain the high CRP levels in patients with malignancies.[29–31] Concerning soft tissue sarcoma, Tabibzadeh[32] showed strong-to-moderate IL-6 immunoreactivity was observed in leiomyosarcoma. Furthermore, Rutkowski[30] showed that increased serum levels of IL-6 were found in 61% of soft tissue sarcoma patients, and that its levels were correlated with tumour size and grade.

Nakanishi[20] found elevated pretreatment serum CRP levels in 65% of their 46 MFH patients. Nakamura[21] found elevated pretreatment serum CRP levels in 18% of their 102 patients with histological grade 1–3 soft tissue sarcoma using the FNCLCC. The current study showed elevated pretreatment serum CRP levels in 46% of the 322 patients with high grade sarcomas. Furthermore, the tumour histological grade and tumour size in the patients with elevated CRP levels were significantly higher than those in patients with normal CRP levels. Elevated CRP levels are reported in patients with many diseases, including the cardiovascular disease,[33,34] type 2 diabetes.[35] Although we did not investigate other possible causes for an elevated CRP, we showed that there was no correlation of CRP level with comorbidity assessed using the Charlson index. The elevated CRP levels are therefore possibly implicated as aggressive characteristics in these soft tissue sarcoma patients. Patients with elevated CRP levels seem to be at particular risk for local recurrence and/or metastasis. Although local condition could be controlled by surgical treatment and adjuvant radiotherapy in patients with elevated CRP levels, these treatments did not contribute to improving disease-specific survival in our cases. The cohort with elevated CRP may be suitable for future trials of intensive therapy (e.g. chemotherapy).

The amount of comorbidity significantly impacts on survivals in various cancer patients.[14–19] Comorbidity may influence clinical decision-making concerning treatment, so that comorbidity affects cancer survival by limiting treatment choices. Correlations between the severity of comorbid conditions, assessed by means of the Charlson comorbidity index, and diverse outcomes have been observed in patients with a variety of cancers.[14–19] However, this study showed no relationship between comorbidity and survival, although age in patients with identified comorbidity was significantly higher than those in patients with no-identified comorbidity. It may affect the present analysis that the age at diagnosis in patients with soft tissue sarcoma is relatively younger than other types of cancers. Yancik showed that of 12 common cancers evaluated, the average proportion of persons with cancers who are aged 65 or older was 59.7%.[36] In this study, the proportion of patients aged 65 years or older was 48%.

There are a few limitations to the present study. First, the presence of systemic diseases may be associated with possible higher levels of markers of inflammation. Although there was no correlation between CCI score and elevated CRP level on the statistical analysis, other chronic inflammatory conditions were not taken into consideration in calculating CCI due to lack of informa-

tion. The limited follow up in some patients will also somewhat affect the results although the statistical methods used have largely taken this into account. The retrospective nature of the study is another limitation. Further studies may be required to confirm these results and a validation will be performed on a large-scale independent database prospectively.

5. Conclusions

Elevated CRP levels prior to initial treatment were found to be a poor prognostic factor for disease-specific survival and local recurrence-free rate in both uninvariate and multivariate analyses for adult high grade soft tissue sarcoma. We recommend routine measurement of the CRP level as this test is familiar to most physicians and is readily accessible.

Conflict of interest statement

None declared.

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Clin Orthop Relat Res (2013) 471:792–802
DOI 10.1007/s11999-012-2616-9

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SYMPOSIUM: PAPERS PRESENTED AT THE 2011 ISOLS MEETING IN BEIJING, CHINA

Can a Less Radical Surgery Using Photodynamic Therapy With Acridine Orange Be Equal to a Wide-margin Resection?

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Published online: 25 September 2012

Abstract

Background Wide-margin resections are an accepted method for treating soft tissue sarcoma. However, a wide-margin resection sometimes impairs function because of the lack of normal tissue. To preserve the normal tissue surrounding a tumor, we developed a less radical (ie, without a wide margin) surgical procedure using adjunctive photodynamic therapy and acridine orange for treating soft tissue sarcoma. However, whether this less radical surgical approach increases or decreases survival or whether it increases the risk of local recurrence remains uncertain.

Questions/purposes We determined the survival, local recurrence, and limb function outcomes in patients treated with a less radical approach and adjunctive acridine orange therapy compared with those who underwent a conventional wide-margin resection.

Methods We treated 170 patients with high-grade soft tissue sarcoma between 1999 and 2009. Fifty-one of these patients underwent acridine orange therapy. The remaining 119 patients underwent a conventional wide-margin resection for limb salvage surgery. We recorded the survival, local recurrence, and functional score (International Society of Limb Salvage [ISOLS]) score) for all the patients.

Results The 10-year overall survival rates in the acridine orange therapy group and the conventional surgery group were 68% and 63%, respectively. The 10-year local recurrence rate was 29% for each group. The 5-year local recurrence rates for Stages II, III, and IV were 8%, 36%, and 40%, respectively, for the acridine orange group and 13%, 27%, and 33%, respectively, for the conventional surgery group. The average ISOLS score was 93% for the acridine orange group and 83% for the conventional therapy group.

Conclusion Acridine orange therapy has the potential to preserve limb function without increasing the rate of local recurrence. This therapy may be useful for eliminating tumor cells with minimal damage to the normal tissue in patients with soft tissue sarcoma.

Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of the levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.
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Introduction

High-grade soft tissue sarcoma resection with an adequate wide margin reportedly inhibits local tumor recurrence and

improves patient prognosis compared with a marginal or intralesional margin [8, 11, 13, 14, 41, 44]. However, if the tumors are located near major nerves, vessels, bones, or joints (ie, the knee, hip, shoulder, or elbow), these structures might need to be sacrificed during a wide-margin resection, resulting in various degrees of impaired limb function. Furthermore, the resection of tumors with a wide resection margin is sometimes difficult, and postoperative radiation therapy or brachytherapy might be required because of a positive margin status. The long-term effects of radiation therapy can include fibrosis, edema, fractures, and contractures, all of which can substantially impair limb function. Thus, patients frequently experience serious limb dysfunction after surgery [6, 7, 31, 42, 45]. Adjuvant therapies that could reduce the need for a wide surgical margin without increasing the incidence of local recurrence could enable better limb function after the resection of high-grade soft tissue sarcomas.

We have focused on adjuvant photodynamic therapy with photosensitizers as a neoadjuvant therapy to kill tumor cells and thereby reduce the surgical margin. Several photosensitizers are used for cancer treatment. Intravenously administered hematoporphyrin was the first photodynamic therapy agent approved for clinical use in 1993 for treating bladder cancer during endoscopic surgery [38]. The use of hematoporphyrin, marketed under the trade name Photofrin (QLT Inc, Vancouver, Canada), was extended to include the treatment of cancers of the skin [43], lung [24], esophagus [12], stomach [12], and uterus [30]. 5-Aminolevulinic acid has also been used for the treatment of skin cancer [2]. However, 1 or 2 days is required for these two photosensitizers to be delivered to the cancer cells after intravenous injection.

In 1990, we began testing a promising new photosensitizer, acridine orange [10, 16, 17, 21–23], for its usefulness in treating musculoskeletal sarcoma. Acridine orange specifically binds to malignant tumors and immediately accumulates in tumor cells [16, 21–23, 29]. It can be delivered to tumor cells quickly through local administration. Acridine orange binds densely to lysosomes and acidic vesicles, which are rich in tumor cells [29], and is therefore useful for visualizing tumor cells during surgery under a fluorescence microscope. Furthermore, it has a strong cytocidal effect on tumor cells after a single session of blue light excitation or low-dose radiation, allowing residual tumor cells located deep inside the body to be killed [10].

Based on the results of basic studies, in July 1999 we began to develop a therapeutic approach that combined a less radical approach without the intent to achieve a wide margin but supplemented with adjunctive acridine orange photodynamic surgery, photodynamic therapy, and radiodynamic therapy [18–20, 26–28, 32, 47]. Acridine orange therapy can potentially reduce the surgical margin by visualizing tumor cells, thereby enabling the normal surrounding tissue to be preserved. However, given the fact that this approach used a less radical surgical technique, rather than a wide-margin resection, it was unclear whether the overall survival would be higher with this approach and whether the rate of local recurrence would be increased.

We therefore examined the survival, local recurrence, and limb function outcomes in patients who were treated with a less radical approach and adjunctive acridine orange therapy compared with those who underwent a conventional wide-margin resection.

Patients and Methods

From 1999 to 2009, we treated 236 patients with primary soft tissue sarcomas of the limbs, girdle, or trunk. We excluded eight patients with retroperitoneal sarcoma, five with soft tissue sarcoma that could not be resected without amputation, and 53 patients with small superficial tumors or low-grade sarcomas. These exclusions left 170 patients; acridine orange therapy was performed in 51 of these patients, and the remaining 119 patients underwent a conventional wide-margin resection for limb salvage surgery (Table 1). This clinical trial for acridine orange therapy was not designed as a randomized study. Rather, after a full explanation of the acridine orange therapy, a conventional wide-margin resection, and the purpose of the study, each patient and a family member could select the treatment they preferred, and each provided written informed consent before study participation. Briefly acridine orange therapy was described as a procedure in which the surgical margin would be located close to the tumor, and the acridine orange therapy would be used to kill the tumor cells near the margin. We further explained that this therapy was being studied as a clinical trial, and the patients were able to choose to undergo a conventional wide marginal resection with the reconstruction of artificial vessels, a prosthesis, or radiation therapy.

Before surgery, we selected candidates for acridine orange therapy based on the following indications: (1) the tumor was in contact with major nerves or vessels; (2) the tumor was in contact with bone but did not show signs of massive invasion; (3) the MRI results showed a low degree of invasiveness (the tumor margin could be identified on the MRI images) to the normal surrounding tissues; (4) the tumor was in contact with a major organ (ie, knee, hip, shoulder, elbow, inguinal tracts, bone, or tendons); and (5) the tumor biopsy sample showed sensitivity to acridine orange. Tumor samples that were resected during an open biopsy were stained with acridine orange, and the sensitivity to acridine orange was assessed using analytical

Table 1. Patient distributions, histological diagnosis, location, and AJCC staging

	Acridine orange therapy group (n = 51)		Wide-margin resection group (n = 119)		Total (n = 170)
Sex					
Men	28		66		94
Women	23		53		76
Age (years)					
Range	0–87		0–85		*p = 0.2
Mean	44		54		
Histological diagnosis	Synovial sarcoma	9	MFH	29	
	MFH	8	Liposarcoma	26	
	Rhabdomyosarcoma	7	Synovial sarcoma	13	
	Leiomyosarcoma	6	Fibrosarcoma	12	
	Fibrosarcoma	4	Leiomyosarcoma	10	
	Liposarcoma	4	Extraskeletal myxoid		
	Extraskeletal myxoid		Chondrosarcoma	6	
	Chondrosarcoma	4	Undifferentiated sarcoma	6	
	Ewing/PNET	4	Malignant granular cell tumor	4	
	Other	5	Other	13	
Location (%)					
Upper limb	11 (22%)		19 (16%)		30
Lower limb	28 (55%)		60 (50%)		88
Trunk	12 (23%)		40 (34%)		52
AJCC stage (%)					
II	13 (25%)		43 (36%)		56
III	25 (50%)		62 (52%)		87
IV	13 (25%)		14 (12%)		27
Followup (months)					
Range	3–131		3–121		†p = 0.65
Mean	48		46		

* p value of Student's t-test analysis; †p value of Welch t-test analysis; AJCC = American Joint Committee on Cancer; MFH = malignant fibrous histiocytoma; PNET = primitive neuroectodermal tumor.

software [29]. All five criteria had to be satisfied for the patient to be a candidate for acridine orange therapy.

Of the 170 patients, five patients were eligible for acridine orange therapy but chose to undergo a conventional wide-margin resection with 40 to 60 Gy of radiation therapy after surgery. Thirty-four patients who agreed to undergo acridine orange radiodynamic therapy received low-dose (5 Gy) radiotherapy after the closure of the surgical wound without washing out the acridine orange solution (Table 2). Thirty-two patients in the wide-margin resection group received radiation therapy or brachytherapy after surgery. These 32 patients included five patients who refused acridine orange therapy and 27 patients whose surgical margins were assessed as being less than 5 mm according to macroscopic findings or pathological findings. Of the 170 patients, 51 patients received acridine orange therapy and 119 patients received a wide-margin resection. We compared the clinical results for survival, local recurrence, and limb function between the two groups. The mean ages of the patients in the acridine orange therapy group and the wide-margin resection group were 44 and 54 years, respectively, and the minimum followup was 3 months (mean, 48 months; range, 3–131 months) and 3 months (mean, 46 months; range, 3–121 months), respectively. None of the patients were lost to followup. None of the patients were recalled specifically for the purposes of this study; all the data were obtained from the patients' medical records. The ethics committee of our university hospital approved this study.

No difference in age or the followup period was observed between the two groups when examined using a Student's or Welch t-test (Table 1). Both groups included

Table 2. Procedures and adjuvant therapies

	Acridine orange therapy group (n = 51)		Wide-margin resection group (n = 119)		Total (n = 170)
Procedures	PDS + PDT	17	Wide-resection	114	
	PDS + PDT + RDT	34	Wide-resection + prosthesis	4	
			Wide-resection + RBG	1	
Adjuvant therapy	Chemotherapy	26	Chemotherapy	28	
			Radiation therapy	15	
			Brachytherapy	17	
Tumor size (mean)	9.4 cm		8.0 cm		p = 0.06

PDS = photodynamic surgery; PDT = photodynamic therapy; RDT = radiodynamic therapy; RBG = intraoperative irradiated auto bone graft; Chemotherapy = mainly performed with Adriamycin and ifosfamide. For rhabdomyosarcoma cases, chemotherapy with vincristine, actinomycin-D, and cyclophosphamide was performed following the regimen of Japanese rhabdomyosarcoma study.

American Joint Committee on Cancer (AJCC) Stage IV patients. Thirty-four patients who agreed to undergo acridine orange radiodynamic therapy received 5 Gy of radiation immediately after surgery (Table 2). We determined the tumor size according to the Response Evaluation Criteria in Solid Tumors, Version 1.1 [4]. The average tumor sizes in the acridine orange therapy group and wide-margin resection group were 9.4 cm and 8.0 cm, respectively. The average tumor size tended to be larger in the acridine orange therapy group than in the wide-margin resection group (95% CI, 8.3–10.7 versus 7.1–8.9). Thirteen patients in the acridine orange therapy group and nine patients in the wide-margin resection group were recurrent cases at the time of the definitive operation. The acridine orange therapy group included 13 patients with AJCC Stage IV disease (25%), whereas the wide-margin resection group included 14 patients with Stage IV disease (12%) at the time of referral.

All the patients with soft tissue sarcomas who underwent acridine orange therapy received intentional marginal or intralesional tumor excisions around the major nerves, vessels, or organs. These procedures were used to minimize damage to the intact muscles and bones as well as the major nerves and vessels that were in close contact with the tumor and were important for the maintenance of limb function. Next, we performed microscopic curettage using an ultrasonic surgical scalpel (Olympus, Tokyo, Japan). We sprayed a 1-μg/mL solution of acridine orange (Sigma Aldrich Co, St Louis, MO, USA) over the resected surfaces using a syringe; excess solution was removed with saline. We then observed the fluorescence using a surgical microscope (Carl Zeiss, Oberkochen, Germany) equipped with an interference filter (450–490 nm) to select the blue light emitted by a xenon lamp and an absorption filter (>520 nm) to allow for the observation of the green acridine orange fluorescence under fluorescence surgical microscopy. Microscopic curettage was then repeated until the green fluorescence had disappeared completely from the remnant tumor mass. Acridine orange photodynamic therapy was subsequently applied to the area of tumor curettage by illuminating the area with > 100,000 lx of unfiltered light from a xenon lamp for 10 minutes followed once again by fluorescence surgical microscopy.

A wide-margin resection was performed with a 2- to 5-cm surgical margin [13, 14], which is regarded as a safe surgical margin. When the surgical margins of the patients in the wide-margin group were assessed as being less than 5 mm on macroscopic findings or pathological findings, including those patients with positive margins, 40 to 60 Gy of radiation therapy or brachytherapy was performed after the surgery. Between 1999 and 2001, we performed brachytherapy for patients in the wide-margin resection group who had a surgical margin of less than 5 mm macroscopically at the closest point [35, 46]. In the wide-margin resection group, four patients required two total femur prostheses, one required a proximal femur prosthesis, one required a proximal tibia prosthesis, and one required an intercalary radiated bone autograft because of severe bone defects.

We typically evaluated the patients according to the following schedule: 2 weeks postoperatively, followed by 6 weeks, 3 months, and then every 3 months for 2 years and every 6 months thereafter. Functional evaluations were obtained for all 51 patients who underwent acridine orange therapy and 119 patients who underwent a conventional wide-margin resection using the revised 30-point functional classification system established by the International Society of Limb Salvage (ISOLS) [40] and the Musculoskeletal Tumor Society [5]. For lower limbs, the functional score measures pain, function, emotional acceptance, use of walking support, walking ability, and gait. For upper limbs, the functional score measures pain, function, emotional acceptance, hand positioning, dexterity, and lifting ability. Each of these six parameters is given a value ranging from 0 to 5 according to specific criteria. The individual scores are added to obtain an overall functional score with a maximum of 30 points. The overall functional

score was then expressed as a percentage of normal. To compare the acridine orange therapy group with the wide-margin resection group, we collected the following data: age, sex, tumor size, type of definitive surgery (intralesional or marginal resection with or without acridine orange radiodynamic therapy), status as primary or recurrent disease at the time of definitive surgery, and AJCC stage (II, III, or IV) [34]. Complications were recorded and classified according to the Dindo classification [3]. Minor complications were managed clinically and major complications required surgical intervention.

We defined local recurrence-free survival as the time from study entry until the local recurrence of disease or until the last contact. Survival was defined as the time from study entry until death or the last contact. We calculated the local recurrence-free survival and the 5- and 10-year survival rates using Kaplan-Meier analysis. The survival rates and local recurrence rates in both groups were assessed using Kaplan-Meier estimates and differences in the rates were determined using log-rank test and StatView, Version 5.0 (SAS Institute, Inc, Cary, NC, USA). A multivariate analysis was performed to determine potential prognostic factors with respect to the two study end points: time until death and time until local recurrence. In the multivariate analysis, local control and survival were examined using the Cox proportional hazards model based on the age at the time of diagnosis, sex, tumor size, type of definitive surgery (surgical margin or photodynamic surgery), status as primary or recurrent disease at the time of definitive surgery, and AJCC stage (II and III versus IV).

Results

The 10-year overall survival rates in the acridine orange therapy group and the wide-margin resection group were similar ($p = 0.75$), 68% and 63% (95% CI, 54%–81% versus 51%–76%, respectively). The 10-year local recurrence rate was also similar ($p = 0.36$; 95% CI, 15%–42% versus 17%–39%), 29% for each group (Fig. 1). We observed no differences in the overall survival rates between the acridine orange therapy and the wide-margin resection groups for each AJCC stage: the 5-year survival rates for patients with AJCC Stage II, III, and IV was 100%, 87%, and 0%, respectively, in the acridine orange therapy group and 95% ($p = 0.41$), 76% ($p = 0.35$), and 0% ($p = 0.78$), respectively, in the wide-margin resection group (Fig. 2A–B). The 5-year local recurrence-free rates for patients with Stage II, III, and IV disease were 92%, 64%, and 60%, respectively, in the acridine orange therapy group and 87%, 73%, and 67%, respectively, in the wide-margin resection group (Fig. 2C–D). Acridine orange therapy was not inferior to wide-margin resection in terms of survival and local recurrence control in each AJCC group.

Regarding the complications after acridine orange therapy, no complications requiring surgical intervention were observed according to the Dindo classification [3].

The average ISOLS limb function score was higher ($p = 0.02$) in the acridine orange therapy group compared with that in the wide-margin resection group (93% versus 83%).

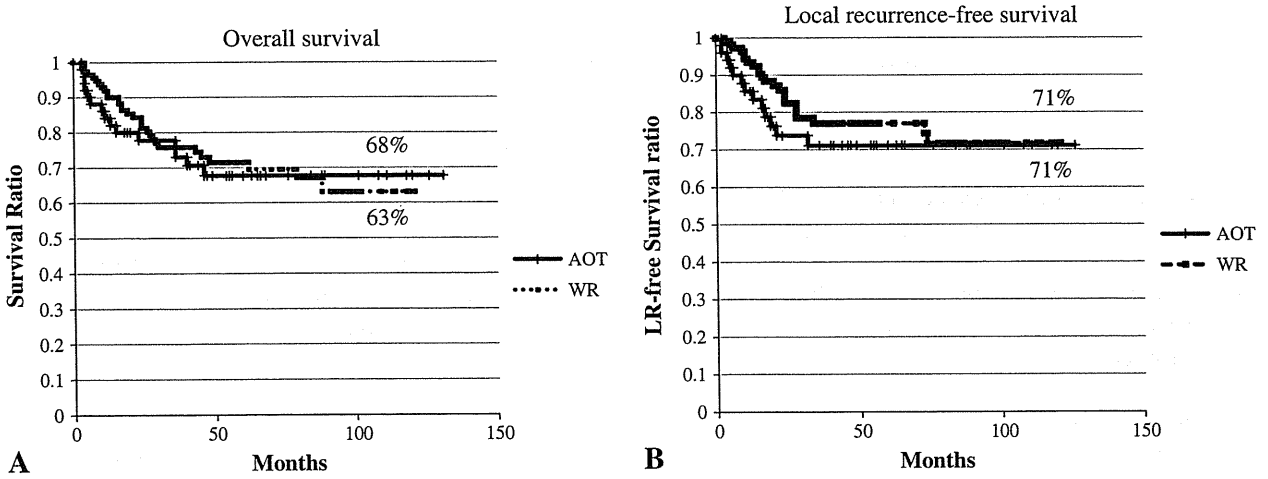

Fig. 1A–B Kaplan-Meier analyses of overall survival (**A**) and local recurrence-free survival (**B**) are shown. The last followup examination was 131 months in the acridine orange therapy (AOT) group and 121 months in the wide-margin resection (WR) group. As of the last followup examination, 95% confidence intervals (95% CIs) for overall survival in the acridine orange therapy group and the wide-margin resection group were 54%–81% versus 51%–76%, respectively. The 95% CI for local recurrence was 15%–42% versus 17%–39%, respectively. Both overall survival and local recurrence-free survival were not significantly different between the acridine orange therapy group and the conventional wide-margin resection group.

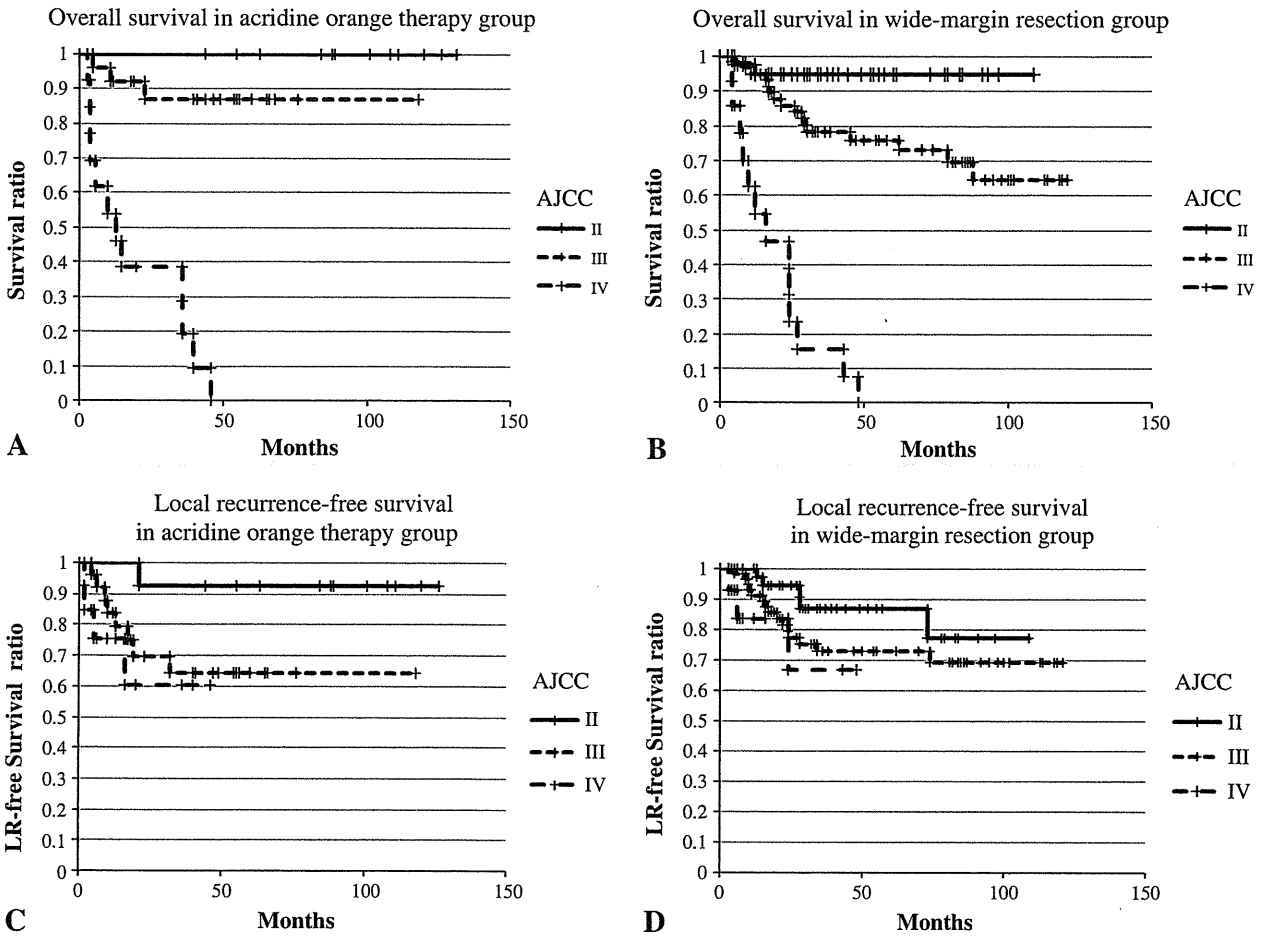

Fig. 2A–D Effect of AJCC stage on overall survival in the acridine orange therapy (AOT) group (**A**) and the wide-margin resection (WR) group (**B**) and on local recurrence-free survival in the AOT group (**C**) and the WR group (**D**). The 95% CIs according to the disease stage were as follows: (**A**) AJCC Stage II, 100%–100%; Stage III, 73%–100%; Stage IV, 0%–0%; (**B**) Stage II, 88%–100%; Stage III, 48%–80%; Stage IV, 0%–0%; (**C**) Stage II, 78%–100%; Stage III, 44%–85%; Stage IV, 27%–93%; and (**D**) Stage II, 56%–98%; Stage III, 56%–83%; Stage IV, 33%–100%. No differences in the overall survival of the patients in the AOT group and the patients in the WR group were seen for the same AJCC stage. AJCC Stage II patients had better survival and local recurrence-free survival rates than the Stage III or IV patients in the same group. LR = local recurrence.

A larger tumor size predicted a poor overall survival and a higher risk of local recurrence, and AJCC Stage IV predicted a poor overall survival in the acridine orange therapy and the wide-margin resection groups (Table 3). Recurrence status was also a risk factor for subsequent local recurrence in the wide-margin resection group but not in the acridine orange therapy group. Furthermore, intralesional resection did not predict local recurrence or poor survival in the acridine orange therapy group. In the acridine orange therapy group, although the numbers of cases belonging to each histological subtype were relatively small, nine cases of synovial sarcoma had no local recurrence (0%), and only one local recurrence (14%) occurred in seven cases of rhabdomyosarcoma (Table 4).

Discussion

Limb salvage in patients with soft tissue tumors occurring in the extremities has now been established as a reasonable option without compromising long-term survival [6, 37, 44]. Adjuvant chemotherapy and radiation therapy also assist in providing a better prognosis [35, 46]. However, en bloc resection or wide tumor resection for high-grade soft tissue sarcomas that are in contact with critical muscles, vessels, nerves, bones, or joints can cause serious deficits in limb function [1, 39]. Some adjuvant therapies such as radiation therapy or brachytherapy can reduce the risk of local recurrence after tumor resections, but the effects of these adjuvant therapies are not superior to those of wide-margin resection