

Treatments and prognostic factors for bone and soft tissue sarcoma in non-urban areas in Japan.

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Abstract

(Background) Although bone and soft tissue sarcoma is recognized as a rare cancer that originates throughout the body, few comprehensive reports regarding it have been published in Japan.

(Patients and Methods) Bone and soft tissue sarcomas were tabulated from the Cancer Registries at eight university hospitals in the Chugoku-Shikoku region. Prognostic factors in cases were extracted in a single facility and have been analyzed.

(Results) From 2016 to 2019, 3.4 patients with bone and soft tissue sarcomas per a general population of 100,000 were treated at eight university hospitals. The number of patients who underwent multidisciplinary treatment involving collaboration among multiple clinical departments has been increasing recently. In the analysis carried out at a single institute (Ehime University Hospital), a total of 127 patients (male/female: 54/73) with an average age of 67.0 y (median 69.5) were treated for four years, with a 5-year survival rate of 55.0%. In the analysis of prognostic factors by multivariate, disease stage, renal function (creatinine), and a patient's mobility and physical capability were strongly associated with patient prognosis regarding bone and soft tissue sarcomas. Interestingly, age did not affect the patient's prognosis (> 70 vs ≤ 70).

(Conclusion) Physical and social factors may affect the prognosis of patients with bone and soft tissue sarcomas, especially those living in non-urban areas.

Introduction

Bone and soft tissue sarcoma is recognized as a malignant tumor that occurs throughout the body, including in subcutaneous tissue, bone, and muscle, and this disease contains several pathological entries. It is also recognized that this malignancy is one of the rare cancers (fewer than 6 cases per 100,000 population) and the majority of them do not have established standard treatments. Patients with bone and soft tissue sarcoma whose tumors can not be removed with surgical treatment have shown very poor and lethal prognoses. Recently, for rare cancers like bone and soft tissue sarcoma it has been considered better to make integrated therapeutic bases such as treatment centers and to treat patients intensively by specialists in this field. The Chugoku-Shikoku region in Japan has ten university hospitals and two cancer centers, and their institutes provide intensive cancer care for not only general cancer patients but also those with bone and soft tissue sarcoma living in several non-urban areas.

In the current study, we have focused on the treatment outcome of bone and soft tissue sarcoma in the Chugoku-Shikoku region, and discussed the prognostic factors and disease-related problems of patients with this rare cancer living in non-urban areas in Japan.

Materials and Methods

Patient with bone and soft tissue sarcoma and the excluding criteria

To avoid looking at cases during the COVID-19 pandemic from January 2016 to December 2019, cases of newly diagnosed and treated *de novo* bone and soft tissue sarcoma were reviewed based on their electronic medical records from the Cancer Registries at eight university hospitals in the Chugoku-Shikoku region (Ehime, Kagawa, Tokushima, Kochi, Yamaguchi, Hiroshima, Okayama, and Kawasaki university hospitals). The annual frequency of incidence by histopathology was summarized. In the single institute analysis, (Ehime University Hospital), three histological types of patients, such as Ewing sarcoma, rhabdomyosarcoma, and gastrointestinal stromal tumor (GIST), have been excluded as unsuitable cases for the current prognostic analysis, because these three types have a standard and effective treatment and they can be curable.

Analysis of overall survival according to several prognostic factors

Survival time was from the date of enrollment in any treatment to the date of the last follow-up (at the end of 2022) or death. Overall survival (OS) curves were calculated for each prognostic group according to the Kaplan-Meier method and analyzed using the log-rank univariate test. Fisher's exact test and Chi-squared test were performed to detect the statistical differences among the groups. *P* values less than 0.05 were considered significant. Prognostic factors were subjected to univariate and multivariate analyses, using Cox's proportional hazard model, against OS. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics of the study

This study was approved by the Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine (study IRB #2102015), and carried out in accordance with the ethical standards of the 1995 Declaration of Helsinki (as revised in Brazil 2013). Informed consent was by the opt-out principle; we disclosed information about the study on the associated website (https://www.m.ehime-u.ac.jp/school/clinical.oncology/?page_id=25) and provided an opportunity to decline to participate in this study.

Results

Diagnosis and qualified doctors for bone and soft tissue sarcomas in Chugoku-Shikoku region

Pathological variation of patients with bone and soft tissue sarcoma treated in the Chugoku-Shikoku region in the current study period is indicated in Fig. 1. GIST and liposarcoma are the most common sarcomas, and angiosarcoma, fibrosarcoma, and leiomyosarcoma are the secondary common sarcomas.

The annual incidence of bone and soft sarcoma in this area is 3.4 patients per a general population of 100,000 in the current study area. Next, we examined what kinds of qualified doctors engaged with the patients with bone and soft tissue sarcoma in this area. The majority were orthopedic surgeons with oncological qualifications. However, multidisciplinary treatment had been increasing, and it was supported that medical oncologists might be involved in those treatments (Fig. 2).

Patient characteristics and the survival with bone and soft tissue sarcoma in Ehime prefecture.

In the next study, we analyzed the prognosis of patients with bone and soft tissue sarcoma in the Chugoku-Shikoku region. This area covers a 50,725.53 km² surface area, and has an 11,375 x 10³ population. We have focused on a single prefecture, Ehime, and examined it in detail. Ehime University Hospital is located in the middle of Ehime Prefecture, which has a very long coastline dotted with about 270 islands and has many mountainous areas. This topography suggests that Ehime prefecture constitutes a typical non-urban medical environment in this country. In this analysis of Ehime prefecture, we encountered one hundred twenty-seven patients with bone and soft tissue sarcoma from 2016 to 2019 in Ehime prefecture, and the patient characteristics including their organ functions at the time of diagnosis, their treatments, and their social backgrounds are shown in Tables 1 and 2. The overall survival (OS) of a total of 127 patients is shown in Fig. 3, and the 5-year survival rate is 55.0% (Fig. 3).

Table 1
Patient characteristics in Ehime prefecture

		n (%) (n = 127)
<i>age</i>	> 70	67(53)
	≤ 70	60 (47)
<i>sex</i>	female	73 (57)
	male	54 (43)
<i>stage</i>	I	55 (43)
	II	15 (12)
	III	20 (16)
	IV	37 (29)
<i>disease site(s) of the organ</i>	head and neck	4 (3)
	chest	13 (10)
	abdomen	69 (54)
	limb	34 (27)
	others	7 (6)
<i>mobility and ability</i>	normal	79 (62)
	disturbed	48 (38)
<i>ability of self-judgment (mental illness)</i>	normal	107 (84)
	disturbed	20 (16)

Table 2
 Patient characteristics according to organ functions, treatments, and social backgrounds (Ehime prefecture)

		n (%) (n=127)
Laboratory data		
<i>BNP/LVEF</i>	normal	41 (32)
	abnormal	28 (22)
	unknown	58 (46)
<i>SpO2</i>	> 96%	86 (68)
	≤ 96%	34 (27)
	unknown	7 (5)
<i>HbA1c</i>	< 6.2%	67 (53)
	≥ 6.2%	21 (16)
	unknown	39 (31)
<i>ALT/AST</i>	normal	122 (96)
	abnormal	5 (4)
<i>creatinine</i>	normal	120 (94)
	abnormal	7 (6)
<i>LDH</i>	normal	97 (76)
	abnormal	30 (24)
Treatments		
<i>local therapy</i> (operation and/or radiotherapy)		81 (64)
<i>chemotherapy</i>		36 (28)
<i>best supportive care</i>		10 (8)
Social backgrounds		
<i>numbers of family supporters</i>	0 or 1	56 (44)
	≥ 2	71 (56)

		n (%) (n = 127)
<i>distance to the treatment hospital</i>	areas around the hospital [Matsuyama, Toon, and Imabari cities]	78 (61)
	others	49 (39)

Patient prognosis according to several patient factors such as baseline patient characteristics, organ function, treatments, and patient social background in Ehime prefecture.

Next, we performed Kaplan-Meier survival analysis to estimate the OS of the patients based on several patient factors in Ehime prefecture. Figures 4 and 5 indicate Kaplan-Meier OS curves of the currently analyzed patients (n = 127) with bone and soft tissue sarcoma according to several patient characteristics, and Tables 3 and 4 show univariate and multivariate analyses of patient-related factors. The strongest prognostic factor of then patients with bone and soft tissue sarcoma living in Ehime prefecture was the disease stage, indicating that patients with bone and soft tissue sarcoma still had not received any effective and curative chemotherapeutic agents and their disease prognosis was poor without complete resection with an operative therapy. A patient's mobility and physical capability was also one of prognostic factors, suggesting that it might be associated with easy access to the treatment hospital for the patients, especially for those living in non-urban areas. Because patients farther from the treatment hospital and with few family supporters tended to have their worse prognosis (Fig. 5). Renal function may be involved as one prognostic factor in the implementation and continuation of treatment. In addition, LDH as a tumor-related factor and a patient's ability and self-judgment might be associated with patient prognosis (Table 3). However, these factors were not statistically significant in the multivariate analysis (Table 4) because of the number of patients in the current study.

Table 3
Univariate analysis (*p*-value) according to prognostic factors (Ehime prefecture)

prognostic factors	HR (95% CI)	<i>P</i> value
age (> 70 vs ≤ 70)	1.34 (0.78–2.27)	0.29
sex (male vs female)	1.35 (0.78–2.35)	0.28
stage (IV vs I, II, III)	5.80 (3.36–10.0)	< 0.001
disease site(s) (others vs limb)	2.59 (1.22–5.48)	0.013
mobility and physical capability (abnormal vs normal)	4.68 (2.68–8.19)	< 0.001
ability of self-judgement (abnormal vs normal)	2.16 (1.31–3.54)	0.0024
BNP/LVEF (abnormal vs normal)	1.61 (0.81–3.19)	0.17
SpO2 (abnormal vs normal)	0.96 (0.52–1.77)	0.88
HbA1c (abnormal vs normal)	0.99 (0.47–2.10)	0.98
ALT/AST (abnormal vs normal)	1.64 (0.51–5.26)	0.41
creatinine (abnormal vs normal)	5.46 (2.44–12.2)	< 0.001
LDH (abnormal vs normal)	2.23 (1.28–3.19)	0.0048
treatment (others vs operation /operation + radiotherapy)	3.30 (1.92–5.67)	< 0.001
number of family supporters (0, 1 vs ≥ 2)	1.44 (0.85–2.44)	0.18
distance to the hospital (areas around the hospital [Matsuyama, Toon, and Imabari cities] vs others)	1.11 (0.65–1.91)	0.70

Table 4
Multivariate analysis (*p* - value) according to prognostic factors (Ehime prefecture)

prognostic factors		HR (95% CI)	<i>P</i> value
stage	I , II	1.00	
	IV	3.59 (1.91–6.74)	< 0.001
mobility and physical capability	normal	1.00	
	disturbed	2.33 (1.24–4.37)	0.0083
ability of self-judgement	normal	1.00	
	disturbed	1.62 (0.85–3.09)	0.14
creatinine	w.n.l	1.00	
	> normal	3.17 (1.26–7.96)	0.014
LDH	w.n.l	1.00	
	> normal	1.58 (0.85–2.95)	0.15
treatment	operation/ operation + chemotherapy	1.00	
	others	1.37 (0.73–2.58)	< 0.32
w.n.l : within normal limits			

Interestingly, our examination did not show any statistical differences between patients with bone and soft tissue sarcoma aged 70 years or more and those younger than 70 years of age. This result might indicate that proper treatment such as operative resection for bone and soft tissue sarcoma was leading to improvement in patient prognosis even if the patients were elderly.

Discussion

We reached two major conclusions in the current retrospective study of patients with bone and soft tissue sarcoma.

As a first conclusion, patients with bone and soft tissue sarcoma were diagnosed with a frequency of 3.4 per 100,000 population. The ratios for this rare cancer have no regional differences among urban and non-urban regions in Japan (1) (2) (3). In addition, the majority of the patients had received their

treatments at university hospitals and cancer centers located in their prefectures. Bone and soft tissue sarcomas had been fundamentally addressed by orthopedic oncologists. However, patients had already undergone regional consolidation and received multidisciplinary team care by specialists in major general hospitals. Increased frequency of regional consolidation seems to be an effective strategy by concentrating limited medical resources for treatment of this rare cancer (4) (5) (6).

Patients with rare cancers such as bone and soft tissue sarcoma are currently treated by specialists in this field by establishing treatment bases. In our study in Ehime Prefecture, factors affecting the patient's prognosis were the disease stage, the type of treatment, and renal function as reported before (7) (8) (9) (10). Recently two cytotoxic agents (eribulin and trabectedin) (11) (12) (13) and one small molecular compound (pazopanib) (14) have been introduced for the treatment of bone and soft tissue sarcomas. In addition, some new therapeutic agents (15) (16) are about to be introduced clinically. However, even with the introduction of new agents, our results still show no effective treatment other than surgery especially for advanced stage patients. Furthermore, analyses of other prognostic factors here suggested that the mobility and overall physical capability of the patients, number of family supporters, and the distance to the treatment hospitals had a certain impact on patient prognoses. Whether patients can easily go to the hospital depends on transportation facilities and social care systems for patients. Automobiles are one of the dominant means of transportation in non-urban areas with little public transportation available (17). Patients living in non-urban areas need to be mobile and have some support from family members or have other social resources in order to continue receiving treatments. Therefore, our prognostic analyses suggest that the concentration of treatment bases in urban areas may be somewhat disadvantageous for patients with rare cancer living in non-urban areas as a result they may give up and discontinue their treatment.

As a second conclusion, another consideration came up in our current study. Looking at 'real world' data analyses for rare cancer treatment, we believe that social background is an important factor that affects treatment continuation and disease prognosis (18) (19) (20). The centralization of rare cancer treatment bases in urban areas may have achieved certain positive results. However, equality in medical care is also necessary as well as centralization. From these observations, it is seen that some systems or specialists to manage rare cancers are needed even in local hospitals for patients living in non-urban areas.

One other conclusion pointed out in our study is that there is no major significance regarding a cut-off age of seventy years in relation to the prognosis of patients with bone and soft tissue sarcoma. There are several explanations for this result. First, the existence of no effective treatment for advance-staged patients other than surgery may have a strong impact on patient prognosis, more than the factor of age. Second, even if the patients were elderly, adequate multidisciplinary management and treatment might improve the prognosis of patients with bone and soft tissue sarcoma. The latter interpretation may suggest that the need for equality in medical care is as important as centralization.

Our current analysis is an observational study of a relatively moderate number of patients in a limited geographic area. We need to study more patients in the future to prove our hypothesis.

Declarations

Authors' contribution

NN and YY carried out the design of the study, collected the clinical data, and drafted the manuscript. TF, TF, TK, KT, YS, YS, TO, TN, and MT participated in the design of the study and oversaw the clinical data. SH and SY carried out the statistical analysis of the study. YY conceived of the study, participated in its design and coordination and helped to draft the manuscript. All authors read the draft, revised it critically, and approved the final manuscript.

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Conflict of interest

The authors have no conflict of interest.

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Figures

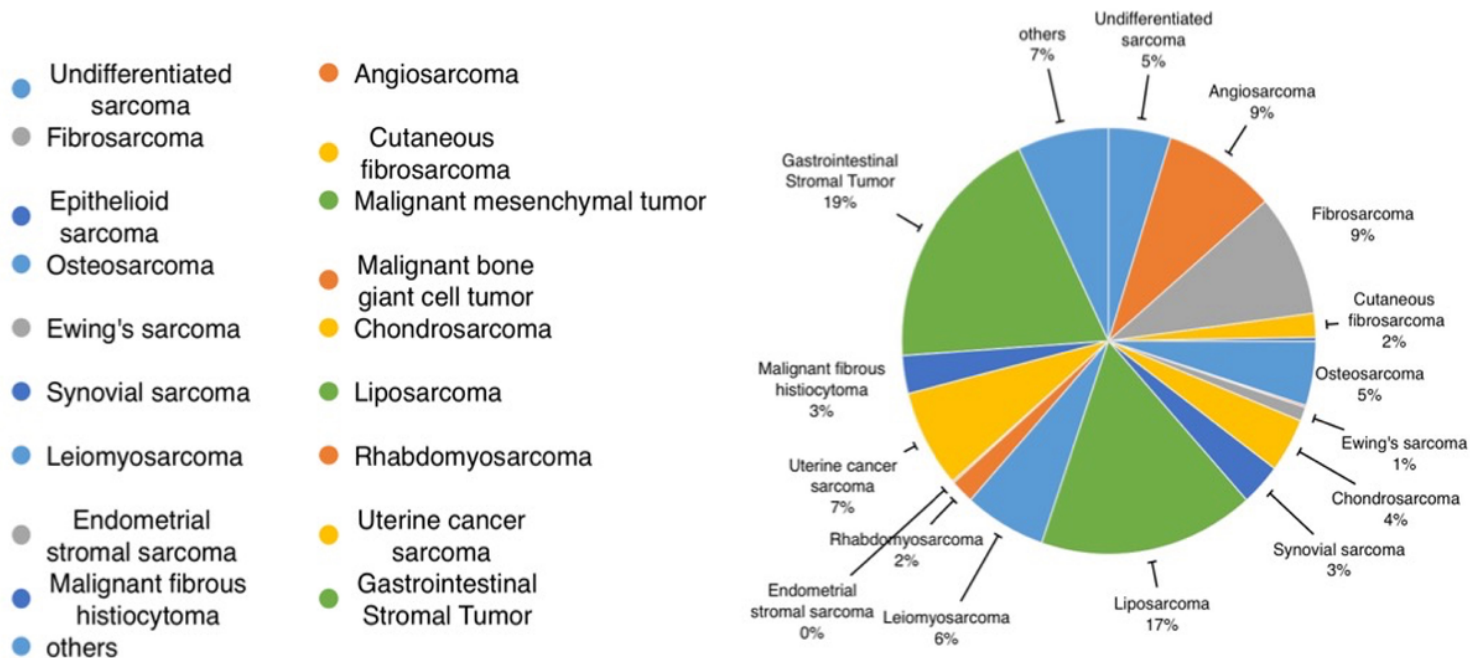


Figure 1

Pathological incidents of bone and soft tissue sarcoma in the Chugoku-Shikoku region (659 cases / year).

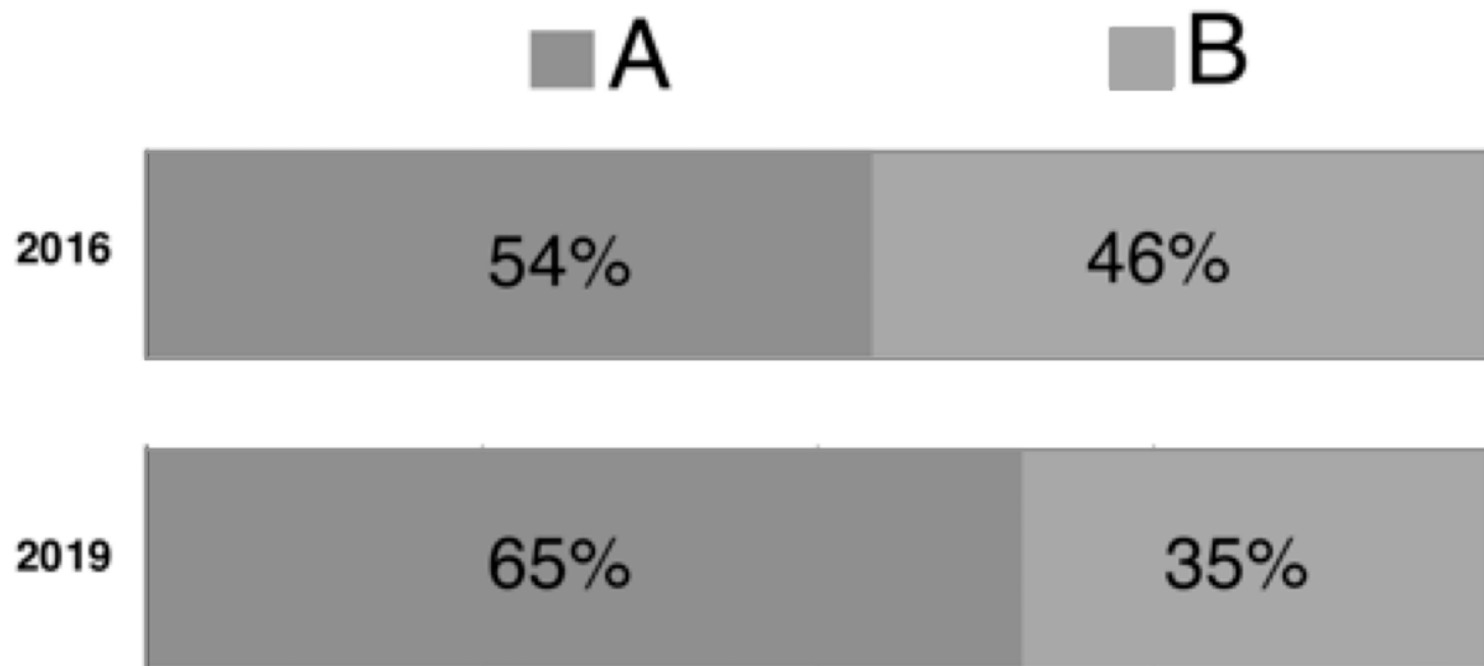


Figure 2

With (A) or without (B) multidisciplinary treatment of patients with bone and soft tissue sarcoma in the Chugoku-Shikoku region according to treatment periods.

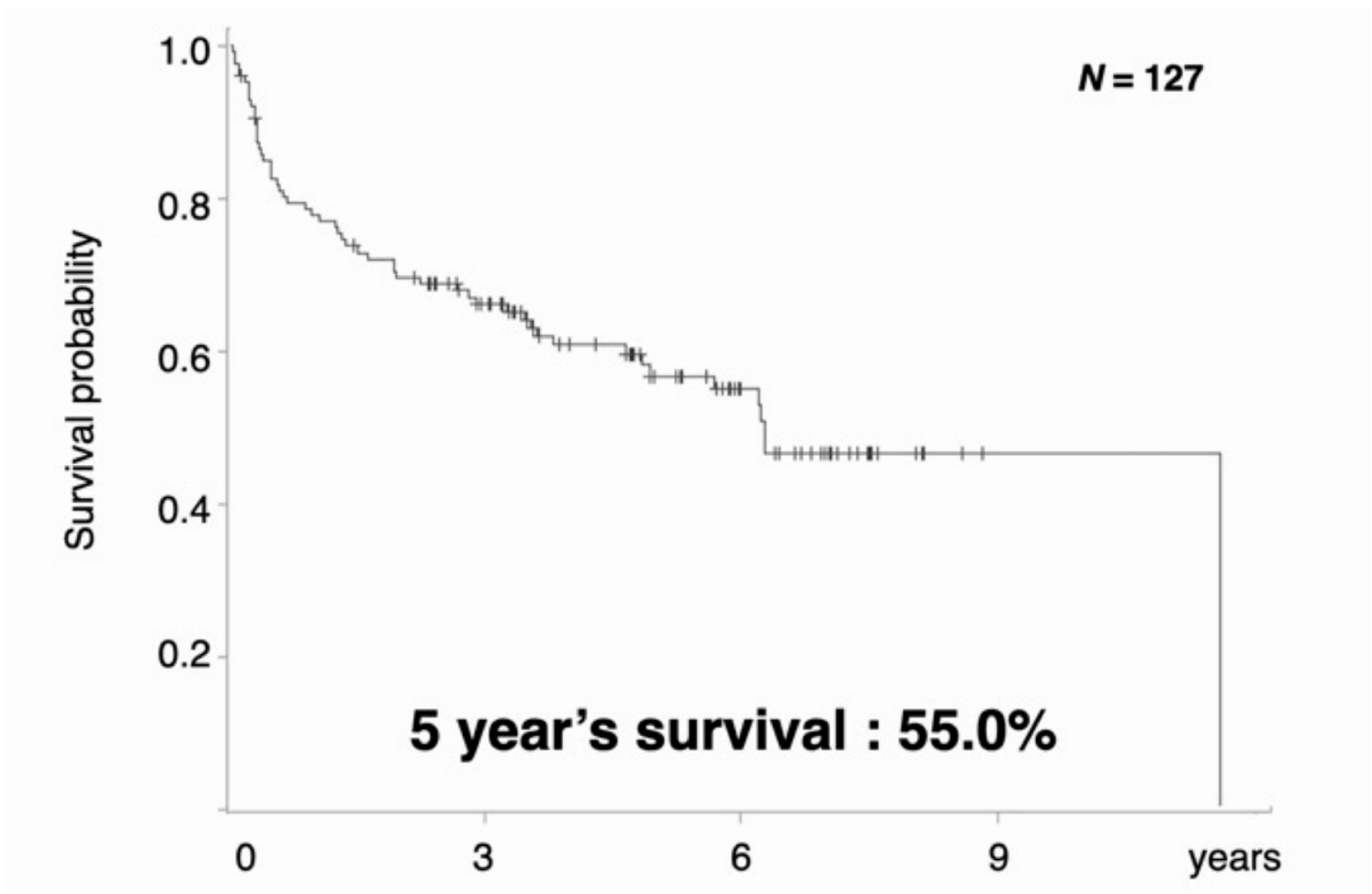


Figure 3

Overall survival of patients with bone and soft tissue sarcoma in Ehime Prefecture from 2016 to 2019 (n=127).

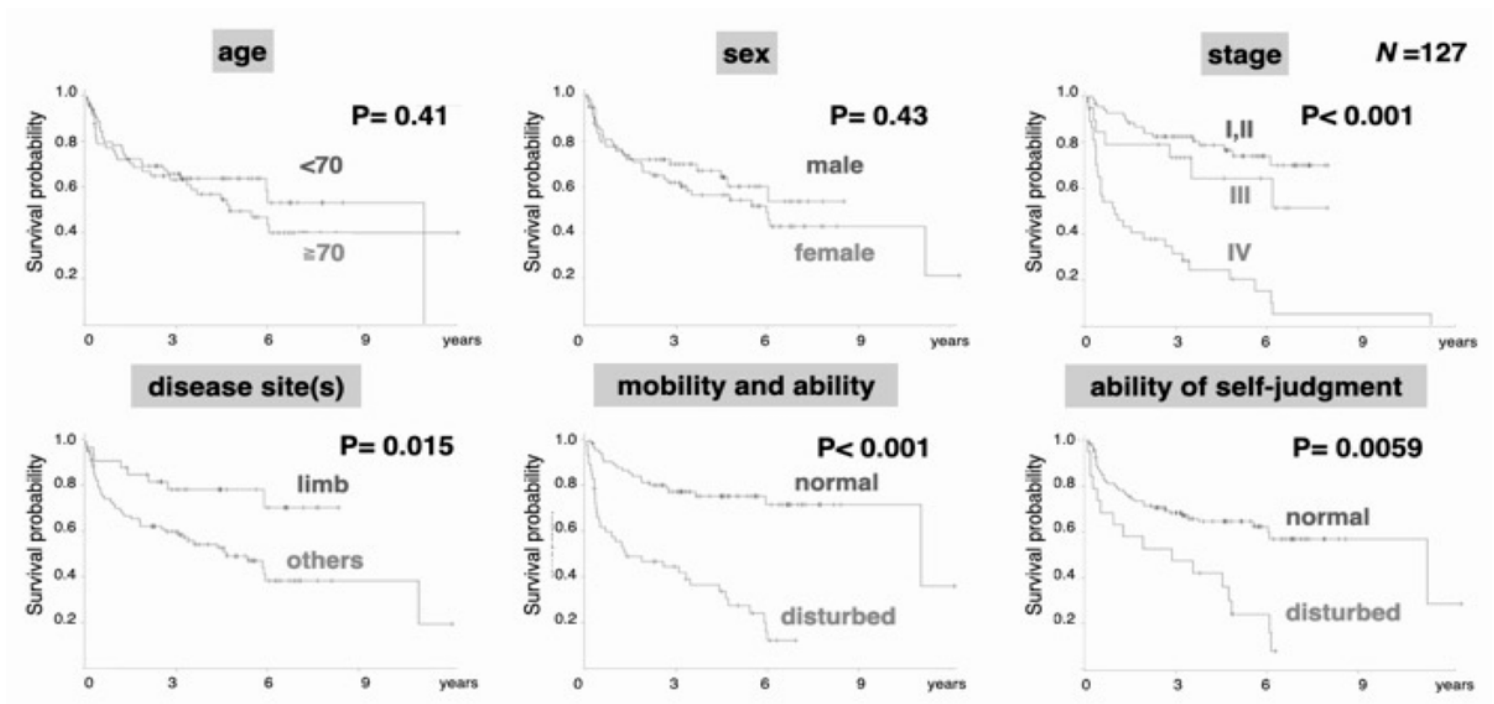


Figure 4

Overall survival of patients with bone and soft tissue sarcoma in Ehime Prefecture according to patient characteristics from 2016 to 2019 (n=127).

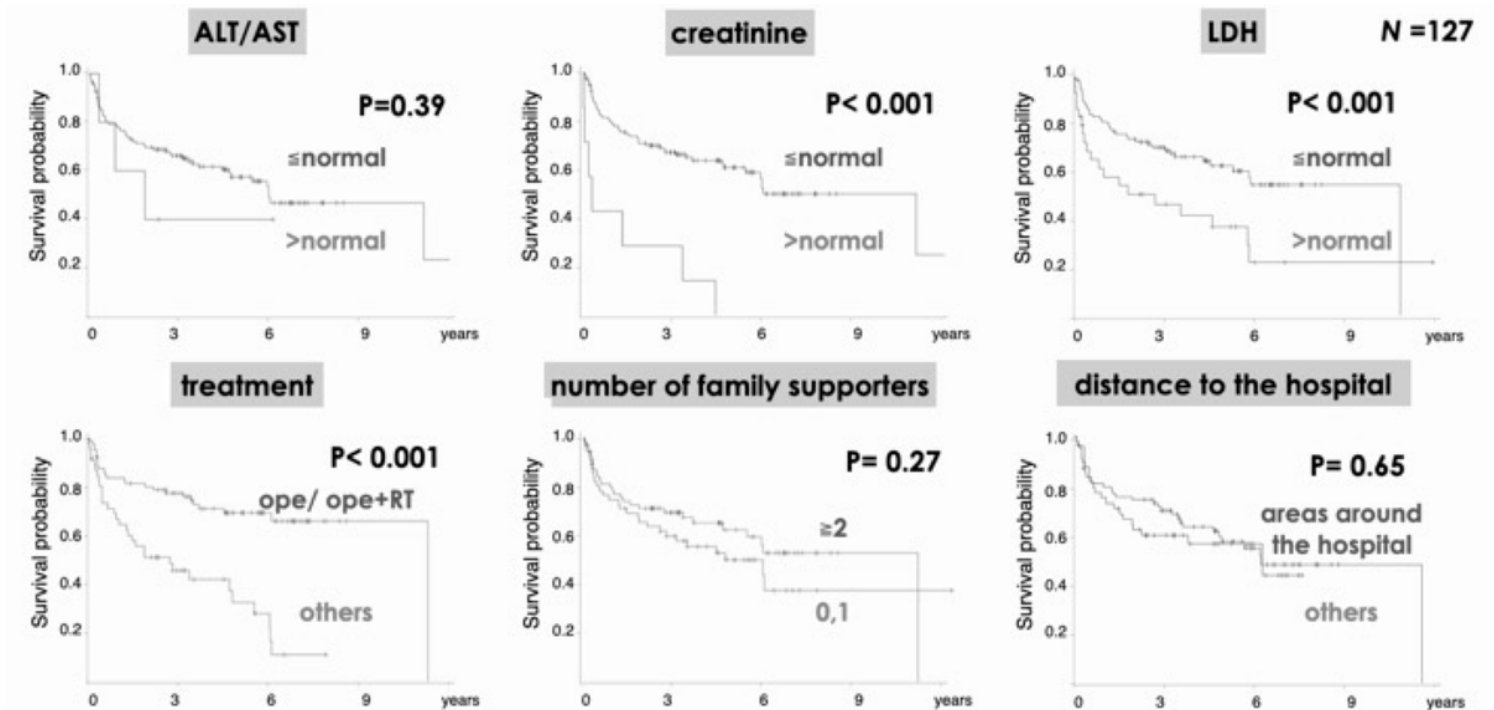


Figure 5

Overall survival of patients with bone and soft tissue sarcoma in Ehime Prefecture according to patient organ functions, treatments, and social backgrounds from 2016 to 2019 (n=127).