ORIGINAL ARTICLE

Clinical outcomes of patients with osteosarcoma experiencing relapse or progression: A single-institute experience

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Abbreviations:

CBDCA, carboplatin; CDDP, cisplatin; CI, confidence interval; CR, complete response; CT, computed tomography; DOC, docetaxel; DXR, doxorubicin; ETP, etoposide; GEM,

gemcitabine; HD-MTX, high-dose methotrexate; IFM, ifosfamide; IRI, irinotecan; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFI, relapse-free interval; R/P, relapse or progression; SD, stable disease; TMZ, temozolomide.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

ABSTRACT

Background:

Patients with osteosarcoma who experience relapse or progression (R/P) have a poor prognosis.

Methods:

Data from 30 patients who experienced R/P among 59 with a diagnosis of high-grade osteosarcoma, who were younger than 40 years old between 2000 and 2019, were retrospectively analyzed to identify prognostic and therapeutic factors influencing their outcomes.

Results:

The 5-year overall survival (OS) rates after the last R/P of patients experiencing first (n = 30), second (n = 14), and third (n = 9) R/P were 50.3%, 51.3%, and 46.7%, respectively. Multivariate analysis did not identify any independent risk factors affecting OS. The 5-year PFS rate of the 30 patients after first R/P was 22.4%, and multivariate analysis identified histological subtype and curative local surgery as independent risk factors influencing PFS. Long (> 6 months) partial response was observed in three patients treated using temozolomide+etoposide, irinotecan+carboplatin, or regorafenib.

Conclusions:

OS rate in the patients with osteosarcoma experiencing R/P included in this study was markedly higher than that reported previously, mainly due to the surgical total removal of tumors, even after subsequent R/P. The recent establishment of salvage chemotherapy or molecular targeted therapy may also increase survival rates in a subgroup of patients.

Key Words: osteosarcoma, relapse, progression, chemotherapy, molecular targeted therapy

INTRODUCTION

Osteosarcoma is the most frequent malignant bone tumor in children, adolescents, and young adults, representing approximately 30% of bone sarcomas. Introduction of first-line multidrug neoadjuvant and adjuvant chemotherapy, including doxorubicin (DXR), cisplatin (CDDP), and high-dose methotrexate (HD-MTX), with or without ifosfamide (IFM), has led to markedly improved patient outcomes; however, 30–40% of those with localized osteosarcoma and up to 70% of those with metastatic osteosarcoma experience relapse or progression (R/P).[1–3] The prognosis of these patients is extremely poor, with a long-term survival rate of less than 20%.[3–6] Time of R/P, number of lesions, and curative local surgery and/or salvage chemotherapy after R/P are strong prognostic factors for survival in patients with recurrent or refractory osteosarcoma.[3]

The effects of salvage chemotherapy regimens, such as IFM+etoposide (ETP) and gemcitabine (GEM)+docetaxel (DOC),[7,8] as well as that of molecular targeted therapies, such as pazopanib and sorafenib, are unsatisfactory for recurrent or refractory osteosarcoma.[9–12] Recent clinical trials have demonstrated the superior anti-tumor activity of the novel multi-kinase inhibitors, regorafenib and apatinib.[13–15] We recently

85 demonstrated the efficacy of temozolomide (TMZ)+ETP for some patients with
86 frequently recurrent osteosarcoma.[16] In the current study, we retrospectively analyzed
87 the clinical outcomes of patients with osteosarcoma who recently experienced R/P and
88 received these novel treatments to evaluate the prognostic and therapeutic factors that
89 influence patient outcomes.
90
91 **MATERIALS AND METHODS**
92 **Study design and data collection**
93 This study was approved by the institutional ethics committee of Kyoto University
94 Hospital. Data from 66 patients with a diagnosis of high-grade osteosarcoma who were
95 younger than 40 years old between 2000 and 2019 and treated at our hospital were
96 extracted. Of these, seven patients were excluded due to a lack of data on survival
97 status. In total, data from 59 patients were analyzed, including one patient with bilateral
98 retinoblastoma who developed osteosarcoma as a secondary malignancy.
99 Chemotherapy response was evaluated by the degree of necrosis following
100 neoadjuvant chemotherapy as follows: grade 1, < 50%; grade 2, ≥ 50% and < 90%;

grade 3, ≥ 90%; and grade 4, no viable tumor cells, according to a previous report.[17] Patients were defined as good responders if their chemotherapy response was grade 3 or 4, or poor responders if it was grade 0–2. During 2000 and 2009, ETP was preferably added to the conventional MAP (CDDP, DXR, and HD-MTX)[18] or CDDP+pitarubicin+HD-MTX regimen for good responders (type A regimen). Since 2010, the MAP regimen has been preferably used as neoadjuvant and adjuvant chemotherapy (type B regimen). For both regimens, IFM was added to adjuvant chemotherapy for poor responders. GEM, DOC, irinotecan (IRI), TMZ, pazopanib, and regorafenib were used after receiving approval for the use of unapproved drugs from the Patient Safety Unit of Kyoto University Hospital,

Radiological response to chemotherapy was evaluated according to the RECIST guidelines (version 1.1).[19] R/P was generally confirmed in all patients by imaging, including computed tomography (CT), magnetic resonance imaging, or positron emission tomography-CT. Relapse-free interval (RFI) was defined as the time from initial diagnosis or R/P to subsequent R/P, and a cut-off value of 18 months for first RFI (between initial diagnosis and the first R/P) was set, as previously reported.[3,5]

117

118 **Statistical analysis**

119 The probabilities of overall survival (OS), defined as the duration of survival between
120 the first R/P and either death or the last follow-up, and that of progression-free survival
121 (PFS), defined as the duration of survival between the diagnosis and either disease
122 progression, death, or the last follow-up, but not the development of secondary
123 malignancy, were estimated using the Kaplan-Meier method. The log-rank test and the
124 Cox proportional hazard model were used for univariate and multivariate analyses,
125 respectively. Factors included in the analyses were sex, patient age group, primary
126 tumor site, site of metastasis, number of lesions, histological subtype, type of first-line
127 chemotherapy, year of first R/P, time to R/P, degree of necrosis, year of first R/P, time
128 of R/P, R/P site, salvage chemotherapy after first R/P, and curative local surgery after
129 first R/P. Year of diagnosis was not included in this analysis, since type A and type B
130 regimens were preferably used between 2000 and 2009 and since 2010, respectively.
131 Factors with $P < 0.1$ in univariate analysis were included in the multivariate analysis.
132 All statistical analyses were performed using EZR (version 1.32, Saitama Medical

Center, Jichi Medical University), which is a graphical user interface for R (the R Foundation for Statistical Computing).[20]

RESULTS

Patient characteristics and clinical outcomes after initial diagnosis

The characteristics at initial diagnosis and the treatments of the 59 patients included in the study are presented in Table 1. Median age at initial diagnosis was 14 years (range, 5–39 years). Type A and B regimens were administered to 32 and 26 patients, respectively.

The 5-year OS and PFS rates of the entire cohort were 82.2% [95% confidence interval (CI), 69.3–90.0%] and 51.9% (95% CI, 38.4–63.8%), respectively. Treatment-related death was observed in one patient with refractory disease who died due to systemic fungal infection after autologous stem cell transplantation. Another patient, who received type A regimen treatment and developed acute myeloid leukemia 9 months after initial treatment for osteosarcoma, survived and was free from disease after bone marrow transplantation.

149

150 **Characteristics of patients experiencing first R/P**

151 The characteristics of the 30 patients experiencing first R/P are shown in Table 2.

152 Median first RFI was 22.8 months (range, 1.4–85.3 months). Of the 30 patients, eleven

153 experienced first R/P within < 18 months. Twenty-seven patients (90.0%) received

154 various first-line salvage regimens. Twenty-two patients (73.3%) underwent curative

155 local surgery for primary lesion and metastases, one of whom also received local

156 radiotherapy, after first R/P.

157

158 **Clinical outcomes of patients after first R/P**

159 Among the 59 patients, six experienced first progression on therapy, whereas

160 24 experienced first relapse. The clinical outcomes of the 30 patients experiencing first

161 R/P are presented schematically in Figure 1. Of the 6 patients experiencing first

162 progression, one survived and five died. Of the 24 patients experiencing first relapse,

163 one died during treatment and nine survived and were in second remission. The

164 remaining 14 patients experienced a second R/P after second remission. All remissions

were obtained by surgical total removal of tumors, except for one, who obtained a fifth remission during IRI+carboplatin (CBDCA) treatment. Two patients underwent curative surgery after obtaining partial response (PR) to salvage chemotherapy (Fig. S1). Median (range) RFI between the first and second R/P, second and third R/P, and third and fourth R/P were 1.06 (0.57–2.20), 1.14 (0.22–3.16), and 0.44 (0.19–1.05) years, respectively (Fig. 1). One patient survived without disease for > 6 months after second R/P. At the time of writing, 13 patients were alive and free from disease, and four were alive with disease.

The 5-year OS rates after last R/P of patients experiencing first (n = 30), second (n = 14), and third (n = 8) R/P were 50.3% (95% CI, 28.1–68.9%; Fig. 2A), 51.3% (95% CI, 21.4–74.9%), and 46.7% (95% CI, 7.1–80.3%), respectively. In univariate analysis, time of R/P, R/P site, histological subtype, and curative local surgery after first R/P were identified as risk factors affecting OS; however, multivariate analysis did not identify any independent risk factors for OS after first R/P (Table 3).

The 5-year PFS rate of the 30 patients after first R/P was 23.2% (95% CI, 9.3–40.8%; Fig. 2B). In univariate analysis, time of R/P, R/P site, histological subtype,

and curative local surgery were identified as risk factors for OS. Multivariate analysis identified histological subtype and curative local surgery after first R/P as independent risk factors (Table 3).

Radiological response to first-line or subsequent salvage chemotherapy

IFM- or GEM-based regimens were mostly administered for first R/P, whereas TMZ- or IRI-based regimens, or pazopanib, were used for a considerable proportion of patients experiencing subsequent R/P (Table S1). Of the 11 patients evaluable for radiological response to first-line neoadjuvant chemotherapy, six had stable disease (SD) and five had progressive disease (PD), with an objective response rate [complete response (CR)+PR] of 0% (Fig. 3A). Of the 14 patients receiving adjuvant therapy, six were in continuous remission, whereas eight patients experienced a second R/P (Fig. 3B). Fifty-two courses of salvage chemotherapies, consisting of 31 neoadjuvant and 21 adjuvant chemotherapies, were administered to 19 patients for subsequent R/P. Among 29 courses of neoadjuvant chemotherapies evaluable for radiological response, there were one CR, three PR, three SD, and 22 PD, with an objective response rate of 13.8% (Fig.

3C). Long (> 6 months) PR was obtained in three patients treated with TMZ+ETP, IRI+CBDCA, or regorafenib. Among 15 courses of neoadjuvant chemotherapies, two were in continuous remission, whereas 13 experienced subsequent R/P (Fig. 3D). There was no significant difference in response according to the type of chemotherapy.

DISCUSSION

The OS rate in patients with osteosarcoma experiencing R/P in the current study was markedly higher than that reported previously (< 20%), particularly in those experiencing subsequent R/P.[4–6] Multivariate analysis identified curative local surgery as an independent risk factor affecting PFS after first R/P; however, these data should be interpreted with caution since an expected poor prognosis tended to be a contraindication for curative local surgery. Nonetheless, aggressive local surgery even after subsequent R/P, achieved by cross-department collaboration, is a major factor contributing to the relatively superior survival.

Compared with previous reports, in the current study, median RFI between the first and second R/P (1.06 years *vs*. 0.8 years) and the second and third R/P (1.14 years

213 *vs*. 0.54 years) were relatively long. These observations suggest that recently established
214 chemotherapy or molecular targeted therapy result in longer OS, despite low objective
215 response rates. Furthermore, these salvage treatments contribute to long-term
216 stabilization of disease or bridge to surgical remission in some patients. Osteosarcoma
217 is characterized by widespread and recurrent somatic copy number alterations and
218 structural rearrangements, with few recurrent point mutations, suggesting the
219 heterogeneity of targetable driver pathways.[21,22] Hence, multi-gene panel testing is
220 required to tailor personalized molecular targeted therapy against recurrent or refractory
221 osteosarcoma.

222 Multivariate analysis also demonstrated that fibroblastic subtype was an
223 independent prognostic factor for PFS, as reported previously.[23] By contrast, time of
224 R/P, number of lesions, and salvage chemotherapy after first R/P did not retain
225 significance for survival, partly because of the paucity of available data.

226 The present study had several limitations. First, it was a retrospective study
227 with a relatively small population of patients experiencing R/P. Second, ascertainment
228 bias (i.e., adult patients tended to opt for shorter-term, less extensive treatment, due to

the higher cost of medical care) may have influenced clinical outcomes. Finally, the follow-up period was too short for evaluation of final clinical outcomes. Nonetheless, our data demonstrate that the survival rate of osteosarcoma patients experiencing R/P has been increasing recently due to aggressive local surgery and, to a lesser extent, introduction of novel treatments. Further prospective studies are required to establish personalized targeted therapies, based on comprehensive molecular profiling.

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FIGURE LEGENDS

FIGURE 1 Outcomes of 30 patients with osteosarcoma experiencing first R/P. REM, remission; MFU, median follow-up; yr, years; R, relapse; P, progression; R/P, relapse or progression; RFI, relapse-free interval.

FIGURE 2 (A, B) OS (A) and PFS rates (B) of 30 patients with osteosarcoma who experienced first relapse or progression (R/P).

FIGURE 3 (A–D) Radiological response to salvage chemotherapy for the first (A, B) and subsequent (C, D) R/P, as adjuvant (A, C) and neoadjuvant (B, D) chemotherapy, grouped by type of chemotherapy. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; R/P, relapse or progression; REM, remission; IFM, ifosfamide; GEM, gemcitabine; TMZ, temozolomide; CDDP, cisplatin; DXR, doxorubicin; IRI, irinotecan.

FIGURE S1 Timing curative local surgery for each R/P.

Table 1. Patient characteristics and treatments after initial diagnosis

Characteristics	All patients (n = 59)	
	No.	%
Gender		
Male	36	61.0
Female	23	39.0
Age at diagnosis, years		
Median (range)	14 (5–39)	
< 19 yr	44	74.6
≥ 20 yr	15	25.4
Year of diagnosis		
2000–2009	32	54.2
2010–2019	27	45.8
Primary tumor site		
Extremity	53	89.8
Axial	6	10.2
Sites of metastasis		
No	48	81.4
Lung alone	9	15.3
Bone and lung	2	3.4
Histological subtype		
Osteoblastic	31	52.5
Fibroblastic	12	20.3
Chondroblastic	10	16.9
Telangiectatic	3	5.1
NA	3	5.1
Type of first-line chemotherapy		
Type A	32	54.2
Type B	26	44.1
Other	1	1.7
Local treatment for primary site		

Surgery	51	86.4
Radiotherapy	2	3.4
Surgery and radiotherapy	3	5.1
No	3	5.1
Local treatment for metastasis		
Surgery	4	6.8
No	55	93.2
Degree of necrosis		
Grade 1	10	16.9
Grade 2	20	33.9
Grade 3	19	32.3
NA	10	16.9
Follow-up, days		
Median (range)	2,779 (203–7,343)	

NA, not available

Table 2. Patient characteristics of 30 patients experiencing first R/P

Characteristics	All patients (n = 30)	
	No.	%
Gender		
Male	19	63.3
Female	11	36.7
Age at diagnosis		
< 19 yr	19	63.3
≥ 20 yr	11	36.7
Year of first R/P		
2000–2009	10	33.3
2010–2019	20	66.7
First RFI, months		
Median (range)	22.8 (1.4–85.3)	
< 18	11	36.7
≥ 18	19	63.3
R/P site		
Local	3	10.0
Lung alone	21	70.0
Bone and lung	5	16.7
Extra	1	3.3
Number of lesions		
One	13	43.3
Two or more	17	56.7
Histological subtype		
Osteoblastic	16	53.3
Fibroblastic	6	16.7
Chondroblastic	7	23.3
Telangiectatic	1	3.3

Type of first-line chemotherapy		
Type A	13	43.3
Type B	17	56.7
Salvage chemotherapy after first R/P		
Yes	27	90.0
No	3	10.0
Curative local surgery after first R/P		
Yes	22	73.3
No	8	26.7

R/P, relapse or progression; RFI, relapse-free interval

Table 3. Univariate and multivariate analyses of factors affecting overall survival after first R/P

Variables	Factors (n)	5yr OS, % (95% CI)	Univariate analysis	Multivariate analysis		5yr PFS, % (95% CI)	Univariate analysis	Multivariate analysis	
			P-value	HR (95% CI)	*P*-value		*P*-value	HR (95% CI)	*P*-value
Age group	0–19 (19)	44.6 (19.8–66.9)	0.156	N.E.	N.E.	15.3 (3.0–36.6)	0.156	N.E.	N.E.
	≥ 20 (11)	62.3 (21.0–86.7)				35.8 (8.8–64.8)			
Gender	Male (19)	49.4 (21.0–72.7)	0.623	N.E.	N.E.	17.1 (3.4–39.8)	0.915	N.E.	N.E.
	Female (11)	51.9 (19.8–76.7)				31.8 (7.8–59.8)			
Year of first R/P	2000–2009 (10)	27.0 (4.1–58.4)	0.294	N.E.	N.E.	40.0 (12.3–67.0)	0.536	N.E.	N.E.
	2010–2019 (20)	62.9 (32.7–82.5)				15.7 (3.1–37.2)			

Time of R/P	RFI ≥ 18 months (19)	64.8 (34.0–84.0)	0.001	Reference		29.2 (10.1–51.6)	0.001	Reference	
	RFI < 18 months (11)	20.8 (1.4–56.1)		1.51 (0.19–12.24)	0.697	NA (NA–NA)		1.58 (0.40–6.23)	0.514
Primary tumor site	Extremity (27)	56.4 (33.6–74.1)	0.259	N.E.	N.E.	23.2 (8.6–41.9)	0.923	N.E.	N.E.
	Axial (3)	NA (NA–NA)				NA (NA–NA)			
R/P site	Lung alone (21)	62.7 (37.0–80.3)	0.007	Reference		24.4 (8.4–44.8)	0.027	Reference	
	Local (3)	NA (NA–NA)		1.29 (0.11–15.40)	0.840	NA (NA–NA)		0.33 (0.04–2.67)	0.297
	Bone and lung (5)	NA (NA–NA)		0.36 (0.04–2.95)	0.342	NA (NA–NA)		0.51 (0.08–3.25)	0.477
	Extra (1)	NA (NA–NA)		1.15 (0.03–39.20)	0.939	NA (NA–NA)		13.71 (0.45–420.0)	0.134
Number of lesions	One (13)	56.1 (19.5–81.5)	0.146	N.E.	N.E.	33.6 (10.4–59.1)	0.113	N.E.	N.E.

	Two or more (17)	46.6 (20.5–69.3)				16.3 (2.9–39.5)			
Histological subtype	Osteoblastic (16)	66.8 (32.9–86.4)	0.029	Reference		NA (NA–NA)	0.013	Reference	
	Fibroblastic (6)	62.5 (14.2–89.3)		0.45 (0.04–4.52)	0.497	66.7 (19.5–90.4)		0.08 (0.01–0.95)	0.045
	Chondroblastic (7)	14.3 (0.7–46.5)		1.77 (0.32–9.77)	0.511	NA (NA–NA)		2.03 (0.60–6.90)	0.255
	Telangiectatic (1)	NA (NA–NA)		2.91e-9 (0–Inf)	0.999	NA (NA–NA)		2.07 (0.17–24.91)	0.568
Type of first-line chemotherapy	Type A (13)	38.4 (12.2–64.6)	0.609	N.E.	N.E.	36.9 (12.5–62.0)	0.415	N.E.	N.E.
	Type B (17)	60.1 (24.2–83.3)				NA (NA–NA)			
Degree of necrosis	Grade 1 (4)	NA (NA–NA)	0.218	N.E.	N.E.	NA (NA–NA)	0.37	N.E.	N.E.

	Grade 2 (12)	56.6 (20.1–81.7)				37.0 (11.5–63.4)			
	Grade 3 (6)	80.0 (20.4–96.9)				20.0 (0.8–58.2)			
	NA (8)	23.4 (1.3–61.6)				NA (NA–NA)			
Salvage chemotherapy after first R/P	Yes (27)	52.6 (28.2–72.2)	0.630	N.E.	N.E.	25.3 (9.5–44.8)	0.487	N.E.	N.E.
	No (3)	33.3 (0.9–77.4)				NA (NA–NA)			
Curative local surgery after first R/P	Yes (22)	63.6 (35.4–82.1)	<0.001	Reference		28.3 (10.4–49.5)	<0.001	Reference	
	No (8)	NA (NA–NA)		1.51e-08 (0–Inf)	0.995	NA (NA–NA)		26.54 (1.50–468.4)	0.025

R/P, relapse or progression; OS, overall survival; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; N.E., not evaluated; RFI, relapse-free interval.

Supplementary Table 1. First and subsequent lines of chemotherapy for R/P

Regimen	First-line chemotherapy			≥2nd-line chemotherapy		
	Neoadjuvant	Adjuvant	Total	Neoadjuvant	Adjuvant	Total
IFM-based	7	10	17	4	3	7
GEM-based	3	4	7	6	8	14
TMZ-based	0	1	1	6	5	11
CDDP+DXR-based	1	0	1	2	1	3
IRI-based	0	0	0	4	0	4
Pazopanib	0	0	0	4	3	7
Regorafenib	0	0	0	3	0	3
Others	0	1	1	2	1	3

R/P, relapse or progression; IFM, ifosfamide; GEM, gemcitabine; TMZ, temozolomide; CDDP, cisplatin; DXR, doxorubicin; IRI, irinotecan.

Fig. 1

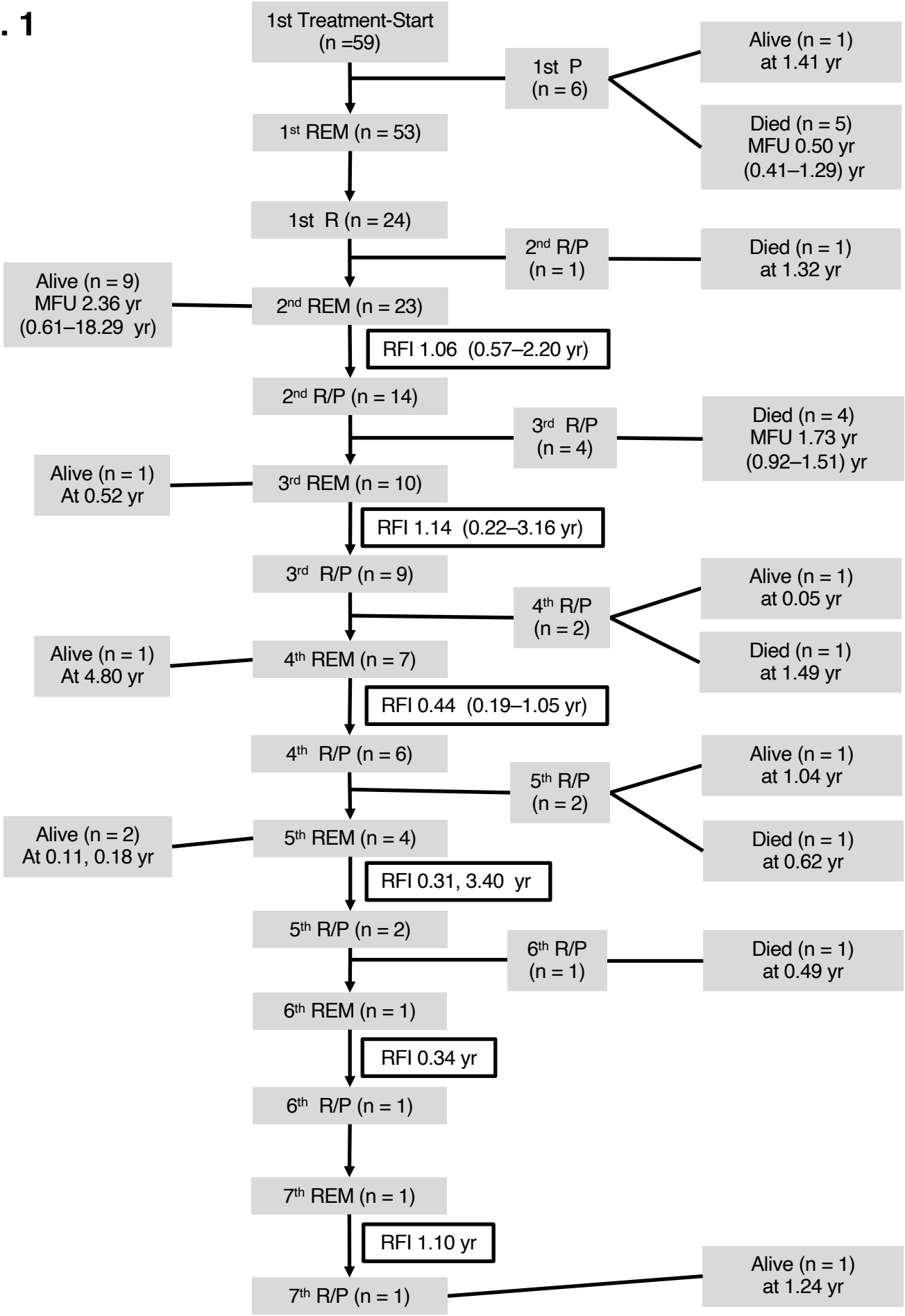
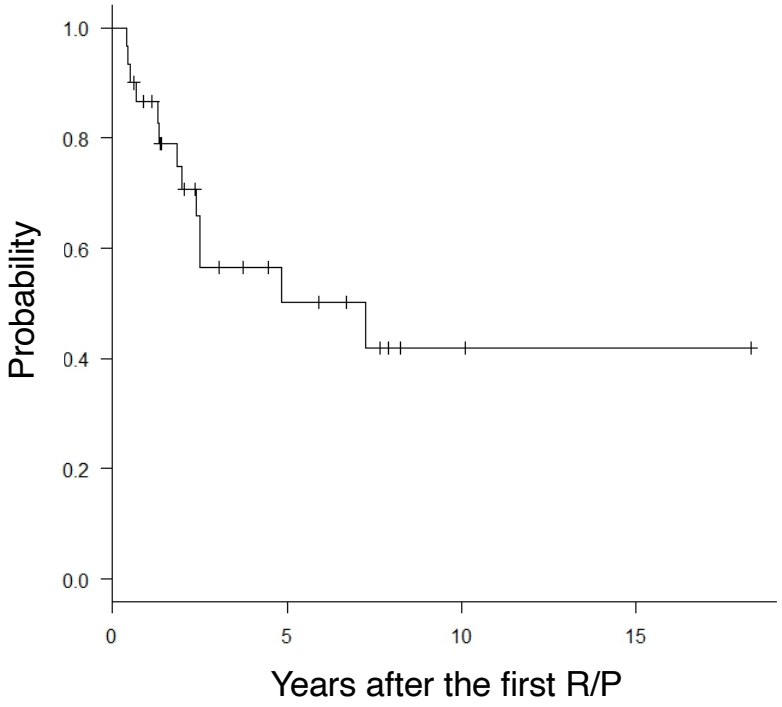

1st Treatment-Start (n =59)
1st P (n = 6)
Alive (n = 1) at 1.41 yr
Died (n = 5) MFU 0.50 yr (0.41–1.29) yr
1st REM (n = 53)
1st R (n = 24)
2nd R/P (n = 1)
Died (n = 1) at 1.32 yr
Alive (n = 9) MFU 2.36 yr (0.61–18.29 yr)
2nd REM (n = 23)
RFI 1.06 (0.57–2.20 yr)
2nd R/P (n = 14)
3rd R/P (n = 4)
Died (n = 4) MFU 1.73 yr (0.92–1.51) yr
Alive (n = 1) At 0.52 yr
3rd REM (n = 10)
RFI 1.14 (0.22–3.16 yr)
3rd R/P (n = 9)
4th R/P (n = 2)
Alive (n = 1) at 0.05 yr
Died (n = 1) at 1.49 yr
Alive (n = 1) At 4.80 yr
4th REM (n = 7)
RFI 0.44 (0.19–1.05 yr)
4th R/P (n = 6)
5th R/P (n = 2)
Alive (n = 1) at 1.04 yr
Died (n = 1) at 0.62 yr
Alive (n = 2) At 0.11, 0.18 yr
5th REM (n = 4)
RFI 0.31, 3.40 yr
5th R/P (n = 2)
6th R/P (n = 1)
Died (n = 1) at 0.49 yr
6th REM (n = 1)
RFI 0.34 yr
6th R/P (n = 1)
7th REM (n = 1)
RFI 1.10 yr
7th R/P (n = 1)
Alive (n = 1) at 1.24 yr

Fig. 2

A


1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
5
10
15
Years after the first R/P

B

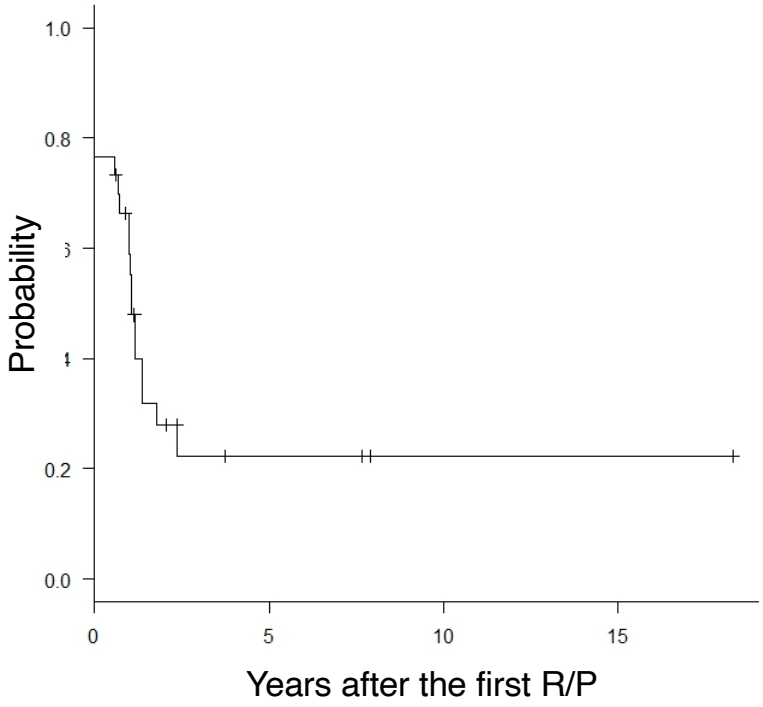

1.0
0.8
0.2
0.0
Probability
0
5
10
15
Years after the first R/P

Fig. 3

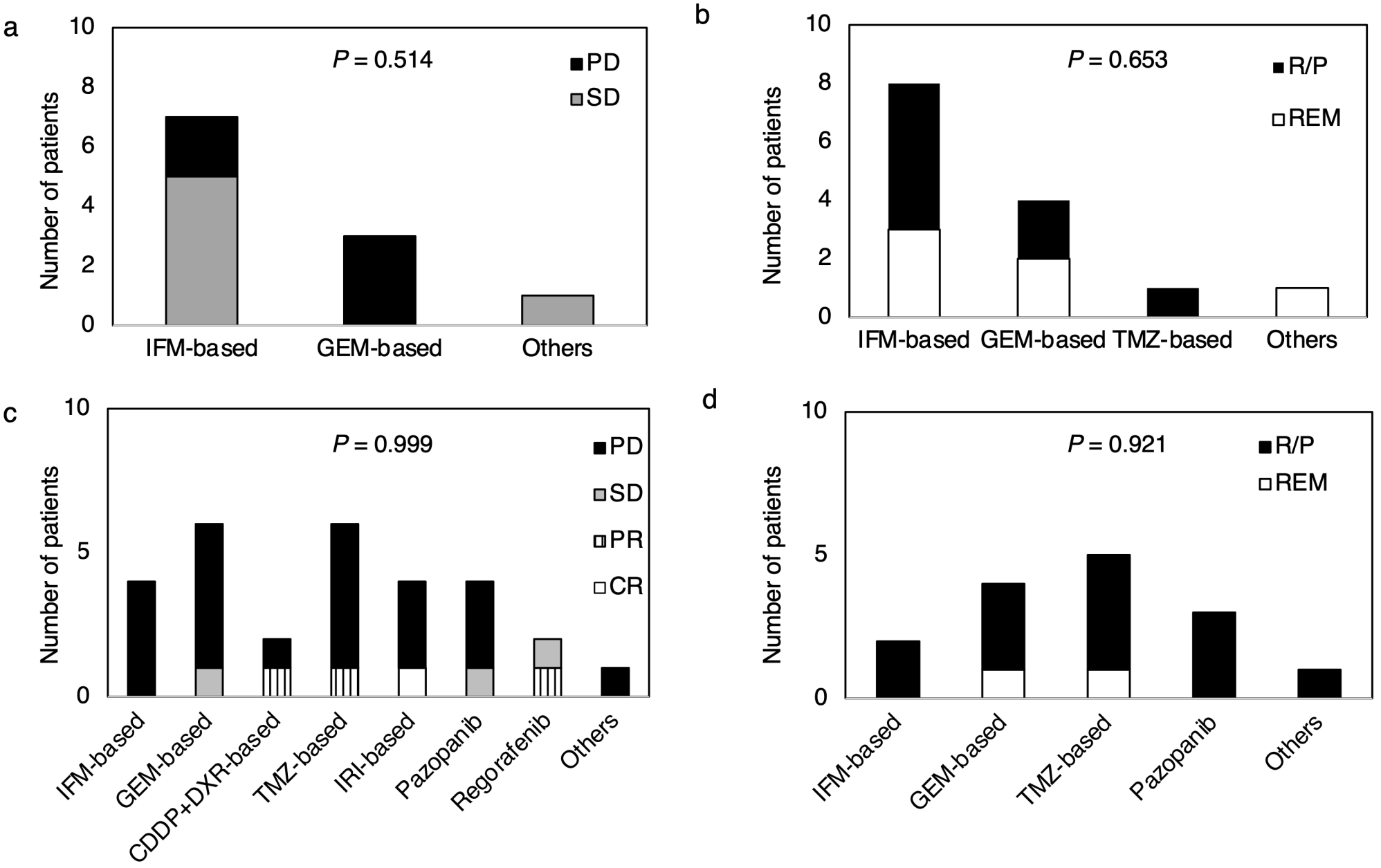
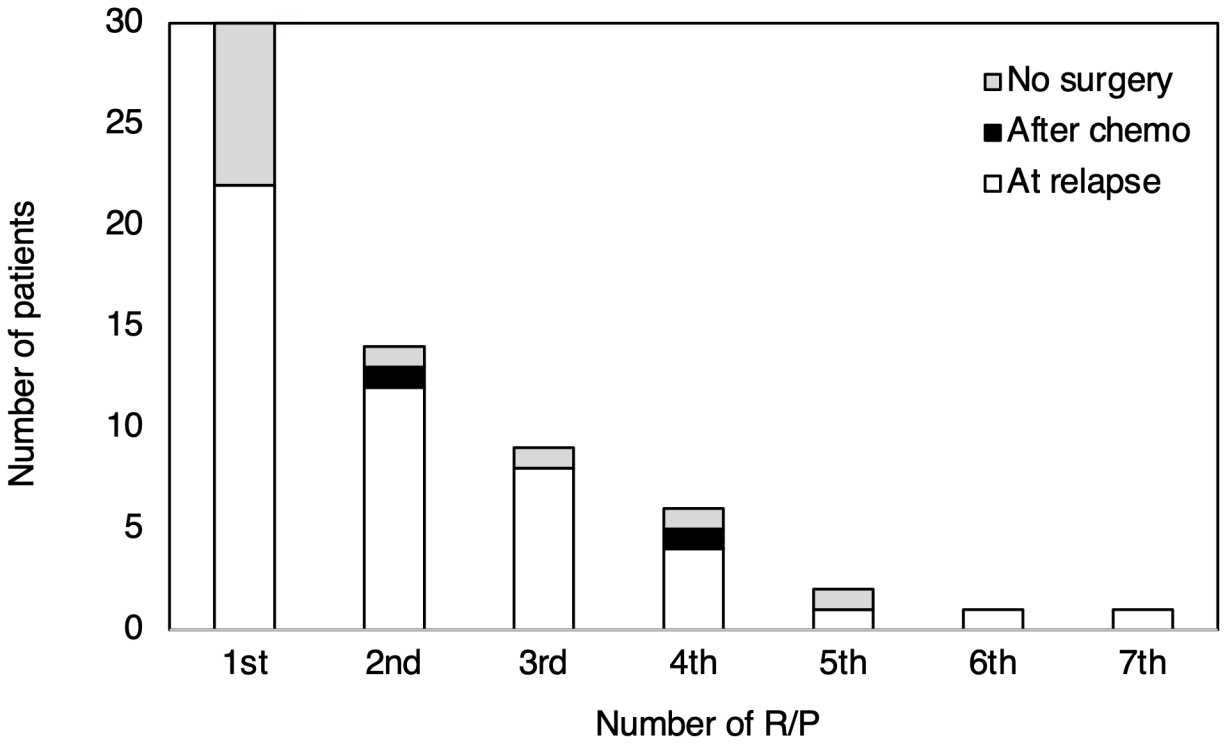

a
10
8
6
4
2
0
Number of patients
P = 0.514
PD
SD
IFM-based
GEM-based
Others
b
10
8
6
4
2
0
Number of patients
P = 0.653
R/P
REM
IFM-based
GEM-based
TMZ-based
Others
c
10
5
0
Number of patients
P = 0.999
PD
SD
PR
CR
IFM-based
GEM-based
CDDP+DXR-based
TMZ-based
IRI-based
Pazopanib
Regorafenib
Others
d
10
5
0
Number of patients
P = 0.921
R/P
REM
IFM-based
GEM-based
TMZ-based
Pazopanib
Others

Fig. S1


30
25
20
15
10
5
0
Number of patients
No surgery
After chemo
At relapse
1st
2nd
3rd
4th
5th
6th
7th
Number of R/P