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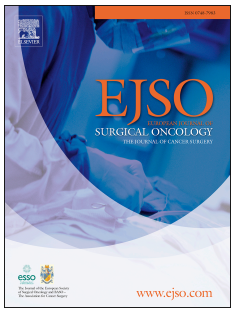

Surgical outcomes and prognostic factors of non-metastatic radiation-induced sarcoma of bone

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Original article

Surgical outcomes and prognostic factors of non-metastatic radiation-induced sarcoma of bone

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Original articles

Surgical outcomes and prognostic factors of non-metastatic radiation-induced sarcoma of bone

Abstract:

Background: The survival and prognostic factors in non-metastatic, radiation-induced bone sarcomas of bone have not been described. Moreover, the quantitative data about surgical outcomes and complications after limb-salvage surgery versus amputation are quite limited.

Methods: Twenty-five patients with non-metastatic, radiation-induced sarcoma of bone who underwent definitive surgery were analysed. Histological diagnosis was osteosarcoma in 19 and undifferentiated pleomorphic sarcoma in six. The definitive surgery was limb-salvage surgery in 15 patients and an amputation in 10.

Results: The 5-year overall survival rate (OS) and the 5-year event-free survival rate (EFS) were 53% (95% CI 31% to 70%) and 40% (21% to 59%), respectively. Patients with wide or radical surgical margins (n = 13) showed significantly better OS compared with those with marginal (n = 8) or intralesional (n = 2) margins (5-year OS, radical or wide = 74%, marginal = 17%, intralesional = 0%, p = 0.044). The risk of local recurrence was significantly higher in the limb-salvage group compared to the amputation group (49% vs 0%, p = 0.011). OS and EFS were not significantly different between limb-salvage group and an amputation group (p = 0.188 and 0.912, respectively).

Conclusions: We believe non-metastatic, radiation-induced sarcoma of bone should be

resected with the aim of achieving wide or radical margins. Although limb-salvage surgery was related to higher rates of local recurrence compared with those of the amputation group, OS and EFS were not different among two groups. Surgeons need to discuss the higher risk of local recurrence in limb-salvage surgery.

Keywords: Radiation-induced sarcoma of bone, Surgical outcomes, Prognosis

1. Introduction

Radiation-induced sarcoma of bone is a rare sarcoma that develops in a previously irradiated field after median latency of 10 years [1-5]. The link between radiation and bone sarcomas was first established by Martland et al. [6] in 1929.

We have previously reported a poor prognosis in radiation-induced bone sarcomas, especially for patients with metastasis at presentation [7], which has been substantiated by several authors [3, 8]. However, the survival and prognostic factors in non-metastatic, radiation-induced bone sarcomas of bone have not been described.

It has been suggested that pre-operative chemotherapy followed by surgery may improve survival [9-11]. Surgery for these patients is frequently challenging due to the effects of previous irradiation on surrounding tissues causing, a loss of clear distinction between anatomical planes, which can compromise cross sectional imaging and complicate surgical margins [12, 13]. Irradiation also reduces the proliferative capacity of normal tissues leading to poor wound healing and wound site infection [14, 15]. As a result, primary amputation was favoured for patients with radiation-induced bone sarcoma in several reports [3,4,13,16,17]. However, the quantitative data about surgical outcomes and complications after limb-salvage surgery versus amputation are quite limited.

We therefore aimed to determine surgical and oncological outcomes and prognostic factors of non-metastatic, radiation-induced sarcoma of bone. Surgical and oncological outcomes were also compared between those patients that underwent limb-salvage and amputation. This data can guide clinicians when deciding on an optimal surgical treatment strategy in non-metastatic, resectable, radiation-induced sarcoma.

2. Patients and Methods

We identified 47 patients with a radiation-induced bone sarcoma from our oncology database between 1987 and 2017. Inclusion criteria required patients to be free of metastatic disease at initial presentation and to have undergone definitive surgery. Twenty-two patients were excluded due to: metastasis at diagnosis (n = 8), received only chemotherapy because of local tumour progression (n = 5), treatments at other hospitals (n = 5), only palliative care (n = 2), died during pre-operative chemotherapy (n = 1) or follow-up elsewhere (n = 1). The remaining 25 patients were included. We retrospectively reviewed the clinical records and imaging for these patients. The diagnosis was made following a review of the histopathology and radiology at the multidisciplinary discussion. The diagnostic criteria for radiation-induced sarcoma of

bone was according to previous reports by Arlen et al. [1] and Cahan et al. [2]. All tumours were resected with the aim of achieving clear margins. An amputation was performed if it was not possible to obtain clear margins with limb-salvage surgery after careful review of the pre-operative imaging. The decision for pre-operative chemotherapy was made in consultation with medical oncologists and patients, taking into account the chemotherapy previously received and patients' comorbidities. Margins were evaluated according to Enneking's criteria [18]. Any patient with intralesional/marginal margins were assessed for further radiotherapy based on local tissue toxicities from previous radiotherapy doses on a case-by-case basis following discussion with clinical oncologists as part of the multidisciplinary team. Currently we a use a 3 Tesla MRI scanner as our cross-sectional imaging of choice.

Kaplan-Meier analysis was used to estimate overall survival (OS), event-free survival (EFS), metastasis-free survival (MFS) and local recurrence-free survival (LRFS). OS was defined as the time from the diagnosis to death by any cause and was censored at the date of the latest follow-up. EFS was defined as the time from diagnosis to either the date of the death or recurrence (local or distant) and was censored at the date of the latest follow-up. LRFS and MFS were defined as the time from the surgical procedure to local recurrence or metastasis and were censored at the date of the latest

follow-up or death. Prognostic factors were assessed using log-rank test. Categorical variables were compared between groups using chi-square tests; numerical variables were compared using Mann-Whitney U tests. A two-tailed probability (P) value of <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY).

3. Results

3.1 Patient demographics

Table 1 shows patients' previous tumours for which radiation therapy was performed. The most frequent previous tumour in this series was Ewing's sarcoma (n = 5, 20%). Radiation-induced sarcoma of bone occurred after a median 16 years (interquartile range [IQR], 11 to 20 years) following radiation therapy for previous tumours. Radiation doses were not available because of the length of the study period. There were 10 males and 15 females (Table 2). The median age at diagnosis of a radiation-induced sarcoma of bone was 42 years (IQR, 23 to 63 years). The most common site was the pelvis (n = 7, 28%). Histological diagnoses were osteosarcoma in 19 patients and undifferentiated pleomorphic sarcoma in six, all categorized as high grade. Definitive surgical resection achieved limb-salvage surgery in 15 patients and

103 necessitated amputation in ten. The surgical margins achieved were radical in three
104 patients, wide in ten, marginal in eight, intralesional in two patients and unavailable in
105 two patients.

106 Fourteen patients received (neo-)adjuvant chemotherapy. The
107 chemotherapy-induced necrosis was ≥90% in three patients, <90% in eight and
108 unavailable in three. The regimens varied: doxorubicin and cisplatin (n = 3), high dose
109 methotrexate (HD-MTX), ifosfamide and etoposide (n = 2), HD-MTX, doxorubicin and
110 cisplatin (n = 1), doxorubicin and ifosfamide (n = 1), vincristine, ifosfamide,
111 doxorubicin and etoposide (n = 1) or no information (n = 6). Predisposing genetic
112 diseases, such as Li-Fraumeni syndrome or bilateral retinoblastoma, were not detected
113 in this study group. No patient underwent further radiation therapy after surgery.

114

115 **3.2 Oncological outcomes**

116 The median follow-up time for all patients was 40 months (IQR, 14 to 192 months). The
117 5-year OS, 5-year EFS and 5-year LRFS for all patients were 53% (95% CI 31% to
118 70%), 40% (95% CI 21% to 59%) and 68% (95% CI 45% to 84%), respectively.
119 Fourteen (56%) of 25 patients died at last follow-up.

120 Eleven patients (44%) developed distant metastases after surgery with the most

121 frequent location being lung (82%). Of the 11 patients, nine died from metastases, one
122 patient was alive with disease at final follow-up, while one patient underwent excision
123 of two lung metastases after two months from initial definitive surgery and survived for
124 218 months.

125 Seven patients (28%) developed a local recurrence. Four of these patients had
126 multiple lung metastases at the time of local recurrence and therefore did not undergo
127 local treatments. Three patients did not have distant metastasis at the time of local
128 recurrence and underwent a re-excision. The risk of local recurrence was 0% (0 of 3)
129 with radical margins, 30% with wide margins (3 of 10), 38% with marginal margins (3
130 of 8) and 50% (1 of 2) in intralesional margins.

131

132 **3.3 Prognostic factors**

133 Patients with wide or radical surgical margins (n = 13) showed significantly better OS
134 compared with those with marginal (n = 8) or intralesional (n = 2) margins (5-year OS,
135 radical or wide = 74%, marginal = 17%, intralesional = 0%, p = 0.044, Table 3 and Fig.
136 1a). Local recurrences were significantly associated with worse OS (p = 0.006). Patients
137 who received neo-adjuvant chemotherapy showed significantly better MFS (p = 0.040).
138 However, preoperative chemotherapy or chemotherapy-induced necrosis of ≥90% was

not significantly associated with better OS (p = 0.747, p = 0.659, respectively).

3.4 Comparison of surgical and oncological outcomes between the limb-salvage group and the amputation group

Table 4 shows patients demographics and outcomes in the limb-salvage group and the amputation group.

Local recurrence:

Local recurrence was the most common complication. Of the 15 patients who underwent limb-salvage surgery, seven (47%) patients developed local recurrence. Local recurrence occurred in 60% (3 of 5) of the pelvic cases, 75% (3 of 4) of the scapula cases and 17% (1 of 6) in long bone cases. The risk of local recurrence in the limb-salvage group was significantly higher compared to that of the amputation group (47% vs 0%, p = 0.011). The LRFS was significantly better in the amputation group compared to that of the limb-salvage group (5-year = 100% vs 49%, p = 0.017, Fig. 1b). In the limb-salvage group, risk of local recurrence was 50% (3 of 6) in patients with wide margin, 43% (3 of 7) in patients with marginal margin and 100% (1 of 1) in a patient with an intralesional margin. For local recurrence without distant metastasis, two

157 pelvic recurrences underwent secondary hindquarter amputation; one scapula recurrence
158 underwent re-excision. Four patients with pulmonary metastases at restaging with local
159 recurrence received palliative chemotherapy without local control after MDT
160 discussion.

161

162 ***Surgical site infection:***

163 No patients who underwent a primary amputation suffered surgical site infection. Three
164 patients developed infection after limb-salvage surgery: one distal tibial endoprosthetic
165 replacement was successfully treated with debridement and implant retention. One
166 scapulectomy patient developed chronic infection necessitating secondary forequarter
167 amputation. One distal femoral endoprosthetic replacement developed a superficial
168 infection and was successfully treated with antibiotics alone.

169

170 ***Overall complications and additional surgeries for complications:***

171 Of the 15 patients who underwent limb-salvage surgery, 11 (73%) developed at least
172 one complication, which was significantly higher than the amputation group (10%, p =
173 0.002). Similarly, the risk of additional surgeries for the management of complications
174 was significantly higher in the limb-salvage group than that of the amputation group

(33% vs 0%, p = 0.041).

Oncological outcomes:

The 5-year OS and EFS were 37% and 37% in the limb-salvage group and 78% and 45% in the amputation group, respectively. These were not significantly different (p = 0.188 and p = 0.912, respectively). The 5-year MFS was 56% in the limb-salvage group and 45% in the amputation group (p = 0.452).

4. Discussion

We have reported the surgical and oncological outcomes and prognostic factors for non-metastatic, radiation-induced sarcoma of bone. Because many previous reports concerning radiation-induced sarcoma of bone are small case series often combined with radiation-induced soft-tissue sarcomas, it is difficult to compare our results [1-5,19-23]. There are three reports that mainly focused on radiation-induced sarcoma of bone (Table 5). Tabone et al. [9] and Shaheen et al. [10] reported five-year OS as between 50% and 69% respectively, which is similar to our result (five-year OS, 53%). By contrast, Lewis et al. [11] reported very poor five-year OS (24%) with high rate of metastatic recurrences (73%).

In our analysis, wide or radical surgical margins were associated with improved survival outcomes. However, multivariate analyses were not performed because of the limited number in our study. Confounding factors as well as selection bias might have an effect on our results. Larger studies are needed to possibly gain a more valid conclusion. Our study also showed local recurrence was significantly associated with worse OS. Like other reports on conventional osteosarcoma [24-26], it is difficult to determine whether local recurrence causes a poor outcome or is simply an indicator of aggressive tumour biology. In our experience, 57% of patients had synchronous distant metastases at the time of restaging after local recurrence.

The main surgical challenge in radiation-induced sarcoma of bone is the difficulty of obtaining a clear margin. Our experience showed that the local recurrence rate was 47% in the limb-salvage group, which was higher than that previously report by Shaheen et al [10] (25%). Local recurrence in our study occurred in 60% (3 of 5) in pelvic cases, 75% (3 of 4) in scapula cases and 17% (1 of 6) in long bone cases. This high local recurrence rate in our analysis is presumably related to the location of the tumours. Indeed, 60% of tumours are located in the pelvis and scapula in our series, while only 35% of tumours were located in the axial skeleton in the study by Shaheen et al. [10] Thijssens et al [16] also reported a high local recurrence rate (54%) after surgery,

including amputation and excision, for radiation-induced bone or soft tissue sarcomas. These high rates of local recurrence are possibly explained by the difficulty of identifying tumour planes using MRI due to tissue alteration following radiotherapy [27]. In our experience, MRI highlighted the difficulty of detecting clear tumour margins due to the combination of scarring and radiotherapy changes. Although we evaluated the tumours using a combination of MRI, CT and PET, there remains an inherent difficulty to detect clear tumour margins in tissues following radiation therapy. It is hoped that advancement in imaging modalities may provide clearer anatomical relationships in tissues exposed to radiotherapy. Radiation-induced fibrosis also makes it difficult for surgeons to palpably detect the true tumour margin. Furthermore, dissection of normal vessels and/or nerves away from the tumour during resection is also challenging post radiotherapy.

Our experience showed that 20% of patients in the limb-salvage group developed infection, while no patients developed an infection in the amputation group. The wound complication rate, including infection, has been reported to be 17% (2 of 12) after limb-salvage surgery for radiation-induced sarcoma of bone [10]. High rates (30%) of wound problems associated with excisions of soft tissue sarcomas after preoperative radiation therapy are well documented [28]. Radiation damage leads to

229 defective collagen deposition by the irradiated fibroblasts [12-14], which hinders repair
230 of the wound. Moreover, the resection of normal fat or muscle, to obtain a margin,
231 during surgery can impair the blood supply of skin over the surgical site. This would
232 explain the high risk of infection in the limb-salvage group, compared to the amputation
233 group where skin closure uses normal tissue with an abundant blood supply.

234 Surgeons and patients need to make complex decisions in the surgical
235 treatment of non-metastatic radiation-induced sarcoma of bone. Although limb-salvage
236 surgery was significantly associated with high rates of local recurrence and
237 postoperative complications, OS and EFS were not significantly different between the
238 limb-salvage group and the amputation group. However, even if a wide margin was
239 obtained, 50% of the patients subsequently developed local recurrence after
240 limb-salvage surgery. We recommend careful discussion about the high risks of local
241 recurrence and complications when choosing limb-salvage surgery. This study is the
242 first to report comparative, quantitate data about the rates of local recurrence,
243 postoperative complications, including additional surgeries for complications, between
244 limb-salvage and amputation in this subset of patients. Our data can help the surgeon
245 and patient to select a surgical procedure based on predicted risks for non-metastatic,
246 radiation-induced sarcoma of bone.

It is difficult to discuss the benefit of preoperative chemotherapy because a variety of regimens were used in our study. This is because chemotherapy protocols for radiation-induced sarcoma of bone are not standardized and are affected by previous chemotherapy treatment. Tabone et al [9] concluded patients with resectable radiation-induced osteosarcoma can be cured with surgery and intensive neo-adjuvant chemotherapy based on their experience in 16 patients. Bielack et al [23] also reported that the treatment of secondary osteosarcoma, including radiation-induced osteosarcoma, with neoadjuvant chemotherapy and surgery had a prognosis which approaches that of primary osteosarcoma. In our study, preoperative chemotherapy was related to better MFS. However, chemotherapy-induced necrosis did not have a significant correlation with OS and MFS, which is comparable with the previous report by Lewis et al [11]. Our current first choice of chemotherapeutic drugs for patients with radiation-induced sarcoma of bone is methotrexate, doxorubicin and cisplatin (MAP) neo-adjuvant/adjuvant chemotherapy. However, each patient needs to be assessed carefully by a specialist oncologist within a multidisciplinary team to determine the potential risks and benefits of neo-adjuvant/adjuvant chemotherapy, paying particular attention to the previous treatment regimes used to manage past malignancies.

There are several limitations in our study including small sample size and

265 retrospective nature of the study. However this is one of the largest series to report
266 non-metastatic, radiation-induced sarcoma of bone.

267

268 **5. Conclusion**

269 We believe that non-metastatic, radiation-induced sarcoma of bone should be resected
270 aiming to achieve wide or radical surgical margins. Limb-salvage surgery showed
271 higher local recurrence and postoperative complication rates compared to amputation.
272 However, OS and EFS were not significantly different between two groups.

273

274 **Conflict of interest statement**

275 No conflicts of interest to declare.

276

277

278 **Figure legend**

279 **Figure 1.**

280 a) Kaplan-Meier curves of overall survival for all patients stratified by surgical

281 margins.

282 b) Kaplan-Meier curves of local recurrence-free survival comparing limb-salvage

283 group and an amputation group.

284

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363 Table 1. Previous tumours

Total	N	%
Ewing's sarcoma	5	20
Breast cancer	4	16
Non Hodgkin lymphoma	4	16
Rhabdomyosarcoma	3	12
Osteosarcoma	2	8
Cervix cancer	2	8
Prostate cancer	1	4
Undifferentiated pleomorphic sarcoma	1	4
Giant cell tumour of bone	1	4
Ovarian teratoma	1	4
Not available	1	4

364

365

366 Table 2. Patient demographics

		N	%
Total		25	
Median age (years, IQR)		42 (23 to 63)	
Sex	Male	10	40
	Female	15	60
Median size (cm, IQR)		11 (7.5 to 15)	
Pathological diagnosis	Osteosarcoma	19	76
	Undifferentiated pleomorphic sarcoma	6	24
Part of tumour	Pelvis	7	28
	Femur	5	20
	Humeurs	5	20
	Tibia	4	16
	Scapula	4	16
Procedure	Excision	7	28
	Excision + endoprosthesis	8	32
	Hindquarter amputation	3	12
	Above knee amputation	5	20
	Forequarter amputation	2	8
Margin	Radical	3	12
	Wide	10	40
	Marginal	8	32
	Intralesional	2	8
	Not available	2	8
Preoperative chemotherapy		14	56
Necrosis after chemotherapy	≥90%	3	21
	<90%	8	58
	Not available	3	21
Local recurrence		7	28
Status at last follow-up	Continuously disease-free	9	36
	No evidence of disease	1	4
	Alive with disease	1	4
	Death of sarcoma	11	44
	Death of unknown cause	2	8
	Death of heart disease	1	4
Median follow-up (months, IQR)		40 (14 to192)	

IQR, Interquartile range

367 Table 3. Prognostic factors for overall survival (OS) and local recurrence-free survival (LRFS)

		N	5-year OS (%)	p value	5-year LRFS (%)	p value
Age (years)	≤40	12	56	0.775	64	0.908
	>40	13	50		75	
Sex	Male	10	36	0.143	80	0.351
	Female	15	80		58	
Size (cm)	≤8	6	60	0.618	80	0.958
	>8	12	53		80	
	Not available	7				
Site	Pelvis	7	43	0.368	51	0.407
	Others	18	58		77	
Preoperative chemotherapy	Yes	14	57	0.747	70	0.802
	No	11	48		69	
Chemotherapy-induced necrosis (%)	<90	9	56	0.659	64	0.296
	≥90	3	67		100	
	Not available	13				
Limb salvage	No	10	69	0.188	100	0.017
	Yes	15	38		49	
Latency period (years)	<15	9	44	0.100	70	0.454
	≥15	11	80		90	
	Not available	5				
Local recurrence	Yes	7	0	0.006	Not available	
	No	18	71		Not available	
Margin	Radical or wide	13	74	0.044	75	0.707
	Marginal	8	38		60	
	Intralesional	2	0		0	
	Not available	2				

368 Table 4. Comparison of patient demographics and outcomes between the limb-salvage group and the amputation group

		Total	Limb salvage	%	Amputation	%	p value
Total		25	15		10		
Gender	Male	10	5	33	5	50	0.405
	Female	15	10	67	5	50	
Median size (cm)		11	10		15		0.139
Site	Pelvis	7	5	33	2	20	0.162
	Femur	5	1	7	4	40	
	Humeurs	5	3	20	2	20	
	Tibia	4	2	13	2	20	
	Scapula	4	4	27	0	0	
Margin	Radical	3	0	0	3	30	0.067
	Wide	10	6	40	4	40	
	Marginal	8	7	46	1	10	
	Intralesional	2	1	7	1	10	
	Not available	2	1	7	1	10	
Complications	Local recurrence	7	7	47	0	0	0.011
	Infection	3	3	20	0	0	0.132
	Dislocation	1	1	7	0	0	0.405
	Delayed wound healing	1	0	0	1	10	0.211
	Aseptic loosening	1	1	7	0	0	0.405
	At least one complication	12	11	73	1	10	0.002

Surgery for complication	Secondary amputation	3	3	20	0	0	0.132
	Debridement	1	1	7	0	0	0.405
	Revision for aseptic loosening	1	1	7	0	0	0.405
	At least one surgery for complication	5	5	33	0	0	0.041
5-year overall survival (%)			37		78		0.188
5-year event-free survival (%)			37		45		0.912
5-year metastasis-free survival (%)			56		45		0.452
5-year local recurrence-free survival (%)			49		100		0.017

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371 Table 5. Summary of the comparative literature

Authors	Years	N	Histology (N)	Non-metastatic cases (%)	Received surgery (%)	Preoperative chemotherapy (%)	LSS (%)	LR after LSS (%)	SSI (%)	Metastatic recurrence	Overall survival	Prognostic factors
Tabone et al[9]	1999	23	OS (23)	20 (87)	16 (70)	14 (61)	14 (61)	NA	NA	NA	8yr, 50%	NA
Shaheen et al[10]	2006	24	OS (17), UPS (4), CS (1), FS (1), LMS (1)	18 (75)	20 (83)	14 (58)	12 (50)	3 (25)	2 (10)	50%	5yr, 69%*	NA
Lewis et al[11]	2006	27	OS (27)	26 (96)	27 (100)	22 (81)	21 (78)	NA	NA	73%	5yr, 24%	Long latency period
Current paper	2018	25	OS (19), UPS (6)	25 (100)	25 (100)	14 (56)	15 (60)	7 (47)	3 (12)	44%	5yr, 53%	Wide or radical margin

* Ten patients with non-metastatic tumour who received chemotherapy and surgery

OS, osteosarcoma; UPS, undifferentiated pleomorphic sarcoma; CS, Chondrosarcoma; FS, fibrosarcoma; LMS, leiomyosarcoma; LSS, limb-salvage surgery; LR, local recurrence; SSI, surgical site infection; NA, not available

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Fig. 1

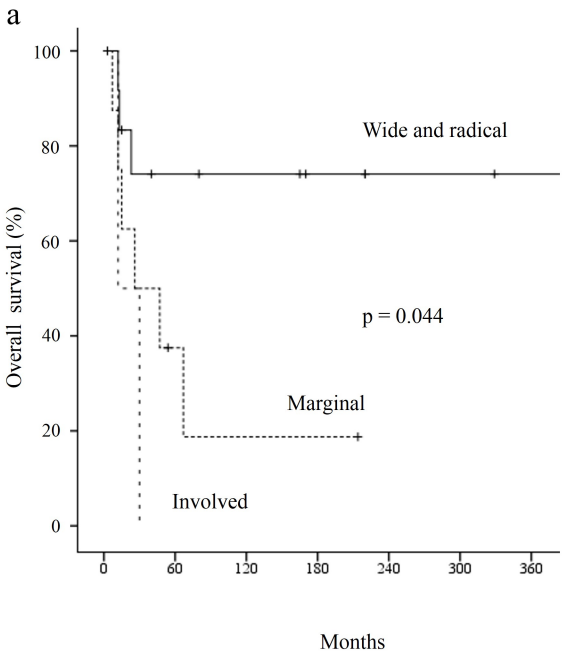

Fig. 1