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Surgical and oncological outcomes after hindquarter amputation for pelvic sarcoma

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Abstract

Aims. Survival rates and local control of pelvic sarcoma is poor compared to extremity locations, with a high incidence of complications. Outcomes for patients requiring hindquarter amputation (HQA) as treatment for pelvic sarcoma patients in an era of limb-salvage is poor. Our aim was to evaluate the patient, tumour and reconstructive factors affecting the survival of the patients who underwent HQA for primary or recurrent pelvic sarcoma.

Patients and Methods. The study comprised a retrospective review of all sarcoma patients who required HQA from 1996 to 2018 in a tertiary, supra regional sarcoma unit. Outcomes included oncological, surgical and survival characteristics.

Results. 136 patients, with a mean age of 51 (range 12-83) were operated. The overall survival (OS) for bone sarcoma was 90.7 months (95%CI 64.1-117.2) in patients with primary HQA and 90.3 months (95%CI 58.1-122.5) in patients undergoing secondary salvage HQA (p=0.727). For those treated for a soft-tissue sarcoma (STS), the mean OS was 59.3 months (95%CI 31.1-88.6) in patients with primary HQA, and 12.5 months (95%CI 9.4-15.5) in patients undergoing secondary salvage HQA (p=0.038). In multivariate analysis, high grade (HR 2.033; 95%CI 1.127-3.676, p=0.018) and STS diagnoses (HR 1.653; 95%CI 1.027-2.660, p=0.039) were associated with a poor prognosis. The 30-day mortality for patients with curative and palliative intent was 0.8% and

33.3% respectively (p=0.001). 53.7% of the patients had at least one complication with 23.5% requiring at least one further operation. Direct closure was inferior to flap reconstruction in terms of complete primary wound healing (60.0% vs. 80.6, p=0.023).

Conclusions. In carefully selected patients HQA is associated with a satisfactory overall survival, with a low risk of peri-operative mortality, but considerable morbidity. However, caution must be exercised when considering the procedure for palliation due to the high incidence of early post-operative mortality.

Key words: Hindquarter amputation, hemipelvectomy, survival, complications, sarcoma

Introduction

Sarcomas are rare malignant mesenchymal tumours, that constitute approximately 1% of all malignant tumours (1). The pelvis is a rare location for sarcomas accounting for only 5-15% of all tumours (2-4). The pelvis represents a unique challenge to oncological orthopaedic surgeons due to the absence of natural anatomical barriers, the close proximity of vital neurovascular structures, and the high mechanical demands placed on pelvic reconstruction following tumour excision, essential to maintain function.

Due to advances in imaging, diagnostic accuracy, a greater understanding of the pathology, as well advances in both the oncological and surgical management of pelvic sarcomas, the majority of osseous and soft tissue sarcomas (STS) of the pelvis are now managed by limb salvage surgery, through internal pelvic resection (5-9). However, in cases of advanced disease or where the potential to achieve clear margins at resection are compromised by limb salvage surgery, hindquarter amputation (HQA) may be considered. Hindquarter amputation (HQA) may also be considered in cases where the extremity would be rendered non-functional following tumour resection, or in the case of palliative resections for the treatment of intractable pain or to aid nursing care in the case of advanced disease. Whilst no absolute definitions exist, the commonly regarded criteria of orthopaedic oncology surgeons is that tumour involvement of two of the three critical structures around the pelvis, the iliac vessels, the hip joint, and the sciatic nerve, warrants consideration of ablative surgery in the form of HQA (10). These anatomical considerations should not be considered in isolation, and consideration should also be given to the patients age, comorbidities and their willingness to undergo life changing ablative surgery (10, 11).

Although considerable advances have been made in the treatment of sarcoma, the prognosis for patients with primary pelvic sarcomas continues to be inferior to sarcomas of the extremities, as tumours often present late, by which time, they have achieved a significant size, and have often metastasized at the time of presentation(12-14). Poor prognostic factors for patients undergoing pelvic resection for primary malignancies include age, tumour volume, surgical margin, and metastasis at presentation (6, 15). Results are more often based on limb salving procedures, and cohorts reporting outcomes of HQA are often relatively small (16-18), or due to rarity of the procedure, they include benign conditions such as infection, or include patients treated over long observational period, over which time pelvic imaging, whole-body staging or the indications for internal pelvic resection may have changed (17, 19, 20). Thus, the factors affecting disease specific and overall survival following HQA are not clearly described.

Therefore, the aims of this study were to firstly, evaluate specific patient and tumour characteristics that correlate with the most significant benefit from HQA, in the era of limb salvage surgery, taking into consideration advances in treatment, diagnostics and multidisciplinary management. Secondly, we aimed to evaluate if the method of reconstruction following HQA had any effect on overall or disease specific survival, or the incidence of complications.

Materials and methods

Following institutional review board approval, the study comprised a retrospective review of all patients undergoing HQA between January 1996 and August 2018 in a single tertiary referral sarcoma centre. Patients were identified from a prospectively maintained database which records all patient contacts as well as demographic, tumour and treatment related details. The period of

inclusion for the study was selected as during this time, all patients with the most common indications for HQA (primary malignant tumour of bone and soft tissue sarcoma) were managed in a comparable way through multidisciplinary team discussion and the use of modern chemotherapy and radiotherapy regimens, where indicated. A minimum 12 months' follow-up and complete histopathology records was required for all patients alive. Patients who underwent HQA for non-sarcoma diagnoses were excluded.

Patient demographics, tumoral characteristics, details of surgical resection and reconstruction, as well as post operative complications, were recorded. Hindquarter amputation was classified as extensile if the bone resection extended medial to the sacroiliac joint, to include the sacral ala, sacral vertebrae or lumber vertebrae, or resection of the abdominal wall. Primary curative surgery was defined as treatment to patients in whom the operation was aimed at cure (for example, the absence of metastatic disease without any previous surgery to the primary tumour), and secondary salvage surgery was defined as treatment to patients where prior limb salvage surgery had failed due to local recurrence. Palliative indication was considered only in cases when surgery would not effect cure, such as those presenting with inoperable metastatic disease. Patients who presented with synchronous metastases, but whose metastases were resected prior to or after hindquarter amputation, were considered be of curative intent. Primary healing was defined as no need for any revision surgery and no need for any local wound therapy over a one month period following the index procedure. Partial flap loss was defined as the need for any surgical debridement of the wound due to partial or total necrosis of the flap.

During the study period all patients underwent pelvic MRI and CT scanning for local disease evaluation, as well as systemic staging dependant on the primary tumour histology. The histology

and imaging studies were reviewed in a supra regional sarcoma MDT meeting at which point the tumour type, staging, indication for neo adjuvant therapy and operative management were discussed (Figure 1). The decision to undertake HQA was based on the underlying diagnosis, the staging of the patient, the volume of the tumour, particularly the projected margin achievable had limb salvage been contemplated, and the wishes of the patient and their family. Patients received counselling by special limb fitting services prior to amputation.

Statistical analysis

Median and mean values and ranges were calculated for continuous variables. Overall survival (OS) was measured from the date of HQA to the date of death or date of last follow-up. Local recurrence free survival (LRFS) was measured from the date of the HQA to the date of local recurrence (LR), date of death or date of last follow-up. Kaplan-Meier curves were constructed to assess OS and LRFS and Log rank test was used to test the statistical significance. Cox proportional hazard model was used to assess factors affecting the OS. We calculated the 95% confidence interval (95%CI) for relative risks. The Mann-Whitney U-test and chi-squared test were used to test the statistical significance for continues and categorical variables, respectively. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics 24.0 (IBM Armonk, NY, USA).

Results:

The study population comprised 136 patients, with mean age of 51 (range 12-83) years who underwent HQA during the study period. 59% (n=80) of the patients were male. The majority of patients underwent HQA as treatment for a sarcoma of bone (66.9%, n=91). 61% (n=83)

underwent HQA as primary curative surgery whilst 39% (n=53) underwent HQA as secondary salvage surgery following tumour recurrence or failed limb salvage surgery. Patients were operated for curative and palliative intent in 94.1% (n=128) and 4.4% (n=6), respectively. The initial treatment intent was missing for two patients. Patient demographics are summarized in table 1.

Patient related outcomes

According to univariate analysis, for patients with a primary bone sarcoma, the mean OS was 90.7 months (95%CI 64.1-117.2) in patients with primary curative surgery, and 90.3 months (95%CI 58.1-122.5) in patients with secondary salvage surgery (p=0.727) (Figure 2A). The tumour volume for primary and salvage groups were 3748 cm^3 and 1519 cm^3, respectively (p<0.001). For patients undergoing HQA as treatment of STS with primary curative intent, the mean OS was 59.3 months (95%CI 31.1-88.6), which compared with 12.5 months (95%CI 9.4-15.5) for patients undergoing secondary salvage surgery (p=0.038) (Figure 2B). The tumour volume for primary and salvage groups were 3318 cm^3 and 2227 cm^3, respectively (p=0.162). The 1-, 3- and 5-year OS is presented in table 2. According to multivariate analysis, factors associated with a poor prognosis for overall survival included HQA as treatment for STS (HR 1.653; 95%CI 1.027-2.660, p=0.039) and high grade histological subtypes, including both bone and soft tissue (HR 2.033; 95%CI 1.127-3.676, p=0.018).

The incidence of LR in patients undergoing HQA as treatment for sarcomas of bone was 12.7% (95%CI 5.6-19.8) and 15.5% (95%CI 3.9-27.1) in those undergoing HQA as treatment for STS. LRFS was 96.5% (95% CI 93-100) at 1-year and 61.5% (48-75) at 5-years for bone sarcoma patients, and 87.5% (77-98) at 1-year and 43.1% (19-67) at 5-years for STS patients (p=0.216). None of the

variables investigated, including tumour grade, extent of the HQA, margin or tumour volume, had a significant effect on LRFS.

In six patients, the indication for HQA was palliative. Three patients underwent HQA for treatment of a bone sarcoma and three patients for treatment of an STS. The median tumour volume was 5600 cm^3, which was significantly larger when compared to patients undergoing HQA with curative intent (2830 cm^3) (p=0.019). The margins achieved at HQA were significantly closer (p=0.020) and four patients had intralesional margins. The median OS was 2.4 months (95%CI 0.0-6.1) and two out of six (33.3%) died whilst still in-hospital, within two weeks of surgery. The 30-day mortality for patients undergoing surgery with curative intent and those for palliative intent was 0.8% and 33.3% respectively (p=0.001).

Flap related outcomes

The soft tissue reconstruction in the majority of patients was by means of a local posterior gluteal flap (PTF) or by means of the anterior thigh flap (ATF). The contralateral vertical rectus abdominis musculocutaneous (VRAM) flap was used in two patients (1.5%). 4.4% of patients had massive soft tissue defect following HQA necessitating a free flap reconstruction. All free flaps were microvascular fillet flaps from amputated extremities. Flap description was insufficient in 22.8% (n=31) of the cases. Direct wound closure was used in five patients. The incidence of complete wound healing was lower in those who underwent direct wound closure when compared to those in whom the defect was reconstructed using either a local or free flap (60.0% vs. 80.6%, p=0.023). In two cases (1.5%), flap loss required a secondary flap reconstruction. There were no other significant differences between the method of local or free flap used for reconstruction in terms of flap related complications, flap survival, re-operation or primary healing rate (Table 3).

The majority of patients (53.7%) had at least one complication with 23.5% requiring re-operations for complication management. Tumour origin (soft-tissue vs. bone), pre-operative radiotherapy, chemotherapy, the chosen reconstructive flap and the treatment intent did not affect the rate of complications. The results for flap survival and complications are summarized in Tables 3 and 4.

Discussion

Hindquarter amputation remains a mainstay of treatment for locally advanced sarcomas arising from, or involving the pelvis, despite advances in the management of pelvic tumours and the increasing use of limb salvage surgery. We have demonstrated that despite the relatively high incidence of post-operative complications, HQA remains a safe surgical option in terms of post-operative mortality with a 30-day mortality less than 1%.

We have demonstrated that histological diagnosis and tissue of origin has an effect on the overall survival following HQA with those with soft tissue tumours origin faring worse than with bone sarcoma. The five year OS of bone tumour patients was higher compared to STS patients, 47.2% vs. 24.0%, respectively. This reinforces the findings of others in the literature who have demonstrated that HQA as treatment for a sarcoma of bone can offer a long term cure (21, 22). This may reflect the variations in histological diagnoses seen in the pelvis. The pelvis is a common site for chondrosarcomas, whose treatment is almost entirely surgical. When considering STS, for tumours to have grown to such a volume where HQA would be required, itself an independent factor relating to a poor outcome, the presence of as yet undetected metastases is extremely likely. Therefore, this in part explains the poor survival characteristics for patients undergoing HQA as treatment for a STS involving the pelvis.

Secondary salvage surgery for bone sarcomas had a similar survival to patients who underwent HQA as a primary surgical intervention. In contrast, in patients undergoing salvage HQA following recurrence of a STS, the overall survival was especially poor with a mean OS of only 12.5 months. This is significantly worse when compared to the OS seen in recurrent extremity STS (23) and may be explained by the difficulty in attaining clear margins of the recurrent disease even with ablative surgery (24). Tumour volume itself did not have a significant effect on overall survival, but may have an effect on the margins achieved at the time of HQA. For sarcomas of bone, the smaller tumour volume in the salvage surgery group may partly explain the favourable outcomes seen in this group. The same of course is not true for the salvage STS group and may represent the poor prognosis conferred by advanced recurrence in STS.

The relatively large number of patients with a diagnosis of chondrosarcoma, osteosarcoma and undifferentiated pleomorphic sarcoma (UPS) allowed a subset analysis of OS in these tumour types. Chondrosarcoma patients had better 5-year OS compared to osteosarcoma patients, that is also evident from previous publications (25, 26).In addition to STS, only margin $\leq$1mm and grade 3 were prognostic for unfavourable OS in univariate model. In multivariate model only grade 3 histology and STS location of the tumour remained poor prognostic factors.

In our series, the indication for HQA was palliation in 6 patients. Though there exists anecdotal evidence that in selected cases, patients benefit from this massive palliative surgery (19), the outcome of these patients remain poor. Our 30-day mortality of 0.8% for curatively indicated patients is lower than previously published (19, 20, 27-29). However, 33% of patients undergoing palliative HQA died within two weeks of the operation. The median survival in this group was only

2.4 months. As the likelihood of achieving any benefit following such radical surgery is likely to come within months of the procedure, the indication for HQA as palliation must be called into question. It appears from the results presented here, that none of the patients who underwent palliative HQA survived long enough to truly benefit from the sacrifice of the operation. There is no clear evidence that palliative major proximal amputation reduces pain, though in selected cases, it has been reported that palliative amputation can improve patients' quality of life (30). There are not comparative studies of major proximal amputation vs. surveillance or other means for palliation in the literature. Therefore, on the basis of these results, HQA solely for palliation should be considered with extreme caution and only considered when all other, lower morbid interventions are deficient and patient is suffering intolerably. Patients and their families should be carefully counselled on the nature and the outcomes of the planned procedure.

The majority of patients (53.7%) included in this study suffered at least one complication following HQA, with nearly one third requiring secondary operations. The incidence of complications has remained unchanged over time and is comparable to our own previous studies and those of others (19, 20, 29). It was noteworthy however, that only 1.5% (n=2) of patients suffered failure of the flap reconstruction requiring secondary flap surgery for wound closure, which is lower than that reported elsewhere (31). We have demonstrated that direct closure of the defect following HQA is associated with a high chance of secondary wound complications and on the basis of this, we would advocate local or free flap reconstruction wherever possible. Extended HQA has been shown to increase complications, while age, sex, histology, grade or intent of the operation has not been associated to wound complication (29). However, in our study, we were unable to identify any of these factors in relation to the risk of flap failure.

The retrospective design of this study presents unavoidable limitations. We were not able to evaluate the functional outcome or health-related quality of life of these patients. The database used for the study does not include systematically collected patient reported outcome measures or functional status. Complications were not prospectively collected and as a result, it was not possible to reliably classify them according to the Clavien-Dindo classification (32). However, due to the comprehensive nature of the database utilised in the institution, it was possible to reliably identify complications requiring secondary surgical procedures. This study does, however, have several strengths. Firstly, this cohort comprises all sarcoma patients who underwent HQA performed by specialist orthopaedic oncologists in a high volume supra-regional sarcoma unit over a 21 year study period. Secondly, outcome data were present for all patients and no patients were lost to follow-up. Thirdly, this patient cohort was relatively homogenous when compared to the available literature, as the study population excluded all non-sarcoma related diagnoses. All patients included in this study were managed through a single MDT, therefore there was consistency in the pre-operative assessment and post-operative evaluation of patient and tumour related factors. Imaging and histology were reviewed in an MDT meeting and the indications for limb-salvaging pelvic resection remained consistent throughout the study period.

In conclusion, therefore, whilst HQA is a drastic, disfiguring and life changing procedure, it offers reasonable survival for patients undergoing primary treatment of a pelvic sarcoma, especially those of bony origin, and for those with recurrent disease, has a role in selected patients for improving overall survival. However, caution must be exercised when considering HQA for recurrent STS involving the pelvis as the overall survival is significantly worse than that seen for osseous pelvic sarcomas. The notion held by the surgeon that there is nothing else that can be done apart from a drastic limb sacrificing procedure, must be tempered against the poor overall

survival seen in specific subgroups. Indeed, when considering HQA in the case of palliation, the survival following the procedure is so poor that one must question the role of HQA for palliation of recurrent, disseminated pelvic sarcoma. However, in carefully selected patients, particularly those with a primary, localised sarcoma of bone, HQA where indicated, is associated with a satisfactory overall survival, with a low risk of peri-operative mortality. The incidence of post-operative wound complications is high but the incidence of flap failure requiring secondary flap reconstruction is low.

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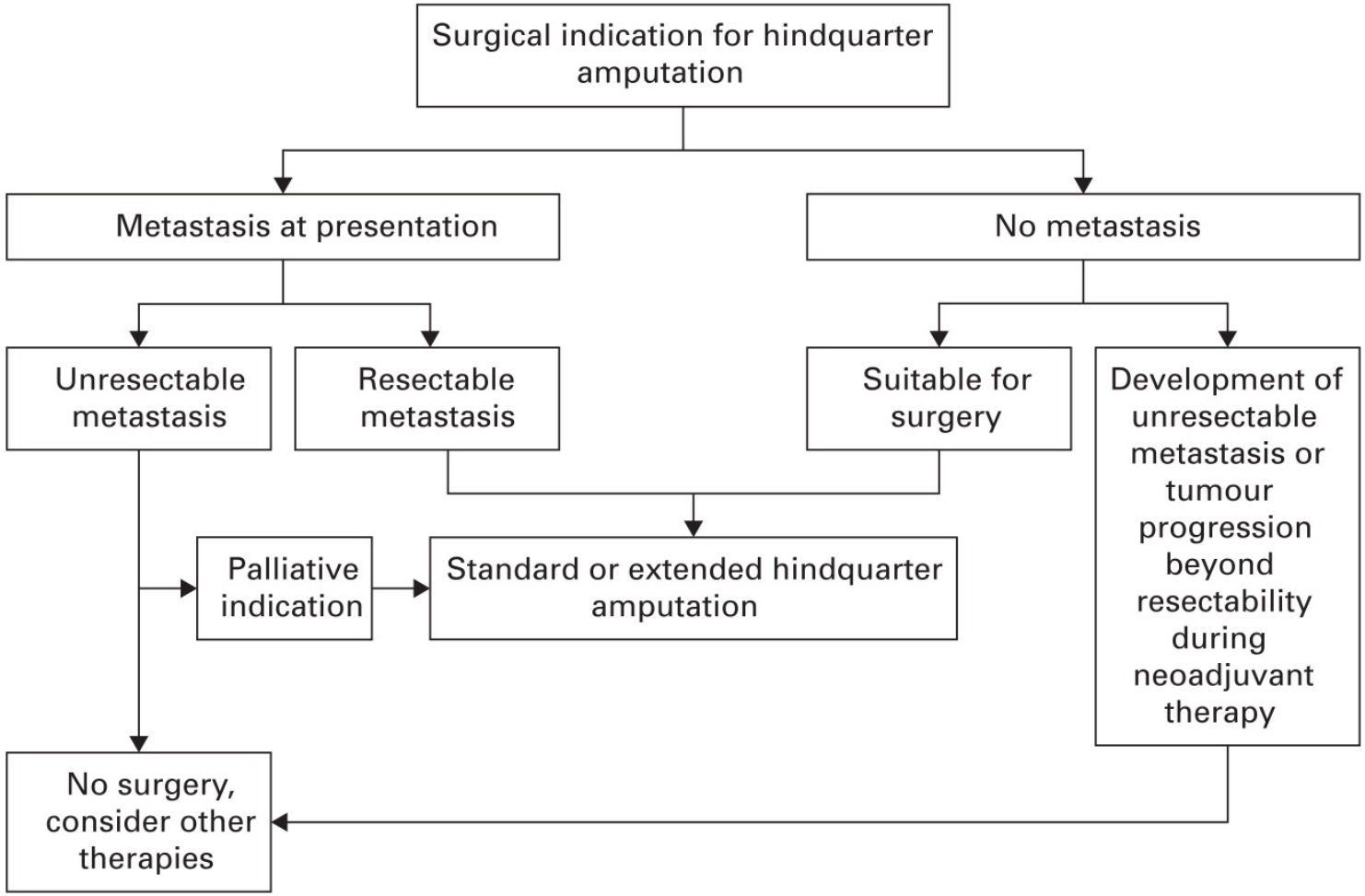

Figure 1. Algorithm diagram for hindquarter amputation.

Table 1. Patient demographics

Characteristics	Number	%
Eligible patients	136	
Male gender	80	58.8
Age in years, mean (range)	51 (12-83)	
Bone sarcoma	91	66.9
Total hemipelvis	30	22.1
Ilium	17	12.5
Acetabulum	17	12.5
Public or ischial bone	3	2.2
Proximal femur	24	17.6
Soft tissue sarcoma	45	33.0
Thigh	24	17.6
Gluteal	17	12.5
Groin	4	2.9
Histology		
Chondrosarcoma	56	41.2
Osteosarcoma	28	20.6
Ewing's sarcoma	2	1.5
Parosteal osteosarcoma	1	0.7
Periosteal osteosarcoma	1	0.7
Undifferentiated pleomorphic sarcoma	23	16.9
Leiomyosarcoma	6	4.4
Angiosarcoma	2	1.5
Myxoid liposarcoma	4	2.9
Synovial sarcoma	4	2.9
Malignant peripheral nerve sheet tumour	3	2.2
Triton tumour	2	1.5
Fibrosarcoma	2	1.5
Extraskeletal chondrosarcoma	1	0.7
Liposarcoma	1	0.7
Size in cm, mean (range)	16.2 (5-49)	
Tumour volume in cm^3, mean (range)	2944 (100-39 700)	
Closest margin in mm, mean (range)	8.5 (0-120)	
Positive surgical margin (R1/2)		
Bone	17	18.7
STS	14	31.1
Surgical attempt		
Primary surgical procedure	83	61.0
Secondary surgical procedure	53	39.0
Extent of amputation		
Standard	92	67.6
Extended	40	29.4

Missing	4	2.9
Preoperative chemotherapy		
Bone	15	16.9
STS	7	16.3
Preoperative radiotherapy		
Bone	2	2.3
STS	14	27.3
Indication for surgery		
Curative	128	94.1
Palliative	6	4.4
Missing	2	1.5
Alive at latest follow-up	57	41.9
Local recurrence	36	26.5
Metastasis	67	49.3

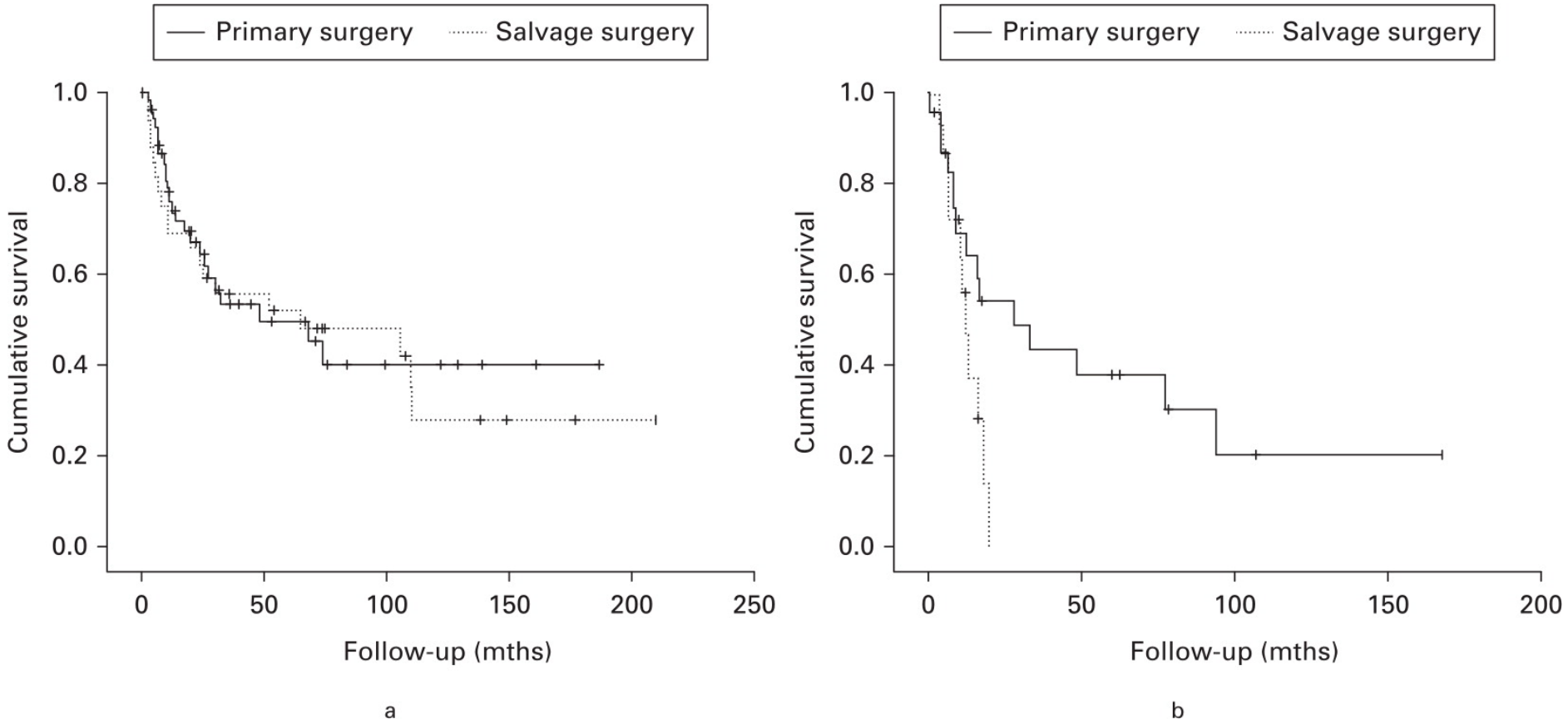

Figure 2. a) Survival after hindquarter amputation for bone sarcoma as a primary surgical procedure and salvage surgical procedure after local recurrence. b) Survival after hindquarter amputation as a primary surgical procedure and salvage surgical procedure for soft tissue sarcoma after local recurrence.

Table 2. 1-, 3- and 5-year OS. Log-rank test for mean survival time (p-value). UPS = undifferentiated pleomorphic sarcoma.

	1-year OS(95%CI)	3-year OS (95%CI)	5-year OS (95%CI)	p-value
Tumour location				
- Bone	71.5(62.0-80.8)%	52.5(41.5-63.5)%	47.2(35.6-58.8)%	
- Soft-tissue	62.1(31.9-62.5)%	27.5(12.0-43.0)%	24.0(9.1-38.9)%	.008
Histology				
- Chondrosarcoma (CS)	77.8(66.6-89.9)%	64.0(50.3-77.7)%	57.8(43.1-72.5)%	
- Osteosarcoma	64.3(45.9-82.7)%	36.7(18.1-55.3)%	32.1(13.7-50.5)%	.017 vs CS
- UPS	66.6(46.2-87.0)%	41.6(15.9-67.3)%	31.2(4.9-57.5)%	.100 vs CS
- Other	56.4(37.0-75.8)%	20.2(4.5-35.9)%	20.2(4.5-35.9)%	<.001 vs CS
Grade				
- Grade 1	100%	100%	100%	.010 vs gr3
- Grade 2	94.7(84.7-100)%	66.0(43.9-88.1)%	52.0(27.3-76.7)%	.018 vs gr3
- Grade 3	60.3(50.5-70.1)%	38.0(27.4-48.6)%	34.6(24.0-45.2)%	
Closest margin				
- >1mm	79.4(69.8-89.0)%	48.8(36.1-61.5)%	46.2(33.3-59.1)%	
- ≤1mm	55.9(43.2-68.6)%	41.4(28.1-54.7)%	34.1(20.8-47.4)%	.017
Gender				
- Female	69.0(56.7-81.3)%	52.3(38.6-66.0)%	49.5(35.4-63.6)%	
- Male	68.3(57.5-79.1)%	39.4(27.1-51.7)%	32.9(20.6-45.2)%	.183
Timing of the surgery				
- Primary	72.6(62.6-82.6)%	48.9(36.9-60.9)%	42.5(30.0-55.0)%	
- Salvage	62.1(48.6-75.6)%	39.5(25.4-53.6)%	36.8(22.7-50.9)%	.257
Extent of the surgery				
- Standard	67.7(58.3-77.1)%	39.6(28.0-51.2)%	35.9(24.3-47.5)%	
- Extended	69.9(55.6-84.2)%	61.9(46.6-77.2)%	52.0(35.5-68.5)%	.302
Tumour volume				
- <1000 cm^3	70.3(54.8-85.8)%	51.4(34.2-68.6)%	41.7(24.6-58.8)%	
- 1000-1999 cm^3	69.4(51.8-87.0)%	44.9(22.0-67.8)%	33.7(8.0-59.4)%	.453 vs <1000cc
- 2000-3999 cm^3	64.3(46.5-82.1)%	41.5(22.7-60.3)%	41.5(22.7-60.3)%	.649 vs <1000cc
- >4000 cm^3	66.6(48.6-84.6)%	35.7(14.7-56.7)%	35.7(14.7-56.7)%	.379 vs <1000cc

Table 3. Number (%) of flaps used, flap loss rate and primary healing rate. Complete flap survival was defined as complete flap survival without any need for flap revision or wound necrosis. Primary healing was defined as no need for any takeback to theatre and no prolonged local wound therapy. *p<.05. VRAM = Vertical rectus abdominis flap.

	n (%)	Complete flap survival	Re-operation	Primary healing
Posterior gluteal flap	50 (36,8)	85.7%	22.0%	64.0%
Anterior thigh flap	42 (30,9)	78.0%	21.4%	73.8%
Fillet flap	6 (4,4)	83.3%	33.3%	66.7%
Direct closure / skin only	5 (3,7)	60%*	40.0%	60.0%
VRAM flap	2 (1,5)	100%	0%	50.0%
Unknown reconstruction	31 (22,8)	75.9%	27.6%	58.6%
Total	136 (100)	79.9%	23.9%	65.7%

Table 4. Number (%) of complications.

	Bone	STS	Total	p-value
Wound dehiscence	29 (32,6)	8 (17,8)	37 (27,6)	.082
Infection	21 (23,6)	9 (20)	30 (22,1)	.916
Pulmonary embolism	2 (2,2)	1 (2,2)	3 (2,2)	1.00
In-hospital death	1 (1,1)	2 (4,4)	3 (2,2)	.211
Clostridium Difficile infection	2 (2,2)	0 (0)	2 (1,5)	.316
Other medical complication	2 (2,2)	0 (0)	2 (1,5)	.316
Ureter injury	1 (1,1)	0 (0)	1 (0,7)	.480
Retained foreign body	1 (1,1)	0 (0)	1 (0,7)	.480