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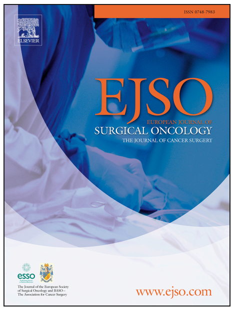

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Navigation-Assisted Pelvic Resections and Reconstructions for Periacetabular Chondrosarcomas

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Running title: Navigated Surgery for Periacetabular Chondrosarcoma

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Abstract

Objectives: Survival in patients with chondrosarcomas has not improved over 40 years. Although emerging evidence has documented the efficacy of navigation-assisted surgery, the prognostic significance in chondrosarcomas remains unknown. We aimed to assess the clinical benefit of navigation-assisted surgery for pelvic chondrosarcomas involving the peri-acetabulum.

Methods: We studied 50 patients who underwent limb-sparing surgery for periacetabular chondrosarcomas performed with navigation (n=13) without it (n=37) at a referral musculoskeletal oncology centre between 2000 and 2015.

Results: The intralesional resection rates in the navigated and non-navigated groups were 8% (n=1) and 19% (n=7), respectively; all bone resection margins were clear in the navigated group. The 5-year cumulative risk of local recurrence was 23% and 56% in the navigated and non-navigated groups, respectively (p=0.037). There were no intra-operative complications related to use of navigation. There was a trend toward better functional outcomes in the navigated group (mean MSTS score, 67%; range, 30 to 97%) than the non-navigated group (mean MSTS score, 60%; range, 17 to 93%; p=0.412). At a mean follow-up of 63 months (range, 5 to 154 months), the 5-year disease-specific survival was 76% and 53% in the navigated and non-navigated group, respectively (p=0.085), whilst the 5-year progression-free survival was 62% and 28% in the navigated and non-navigated group, respectively (p=0.032).

Conclusion: This study confirmed improved local control and progression-free survival with the use of computer navigation in patients with limb-salvage surgery for periacetabular chondrosarcomas, although the advancement in other treatment modalities is required for improvement of disease-specific survival.

Introduction

Chondrosarcomas are the second common primary malignant bone tumours, characterised by the production of the cartilaginous matrix [1]. Disappointingly, several studies have highlighted the lack of remarkable improvement in the survival of patients over the last 40 years [2, 3]. Previous investigations have determined that the poor prognostic factors for patients with chondrosarcoma are high-grade tumours and axial/pelvic tumour location [3-5]. In pelvic chondrosarcomas, intralesional/marginal margins, high-grade tumours, and larger tumours are negative prognostic factors for patient survival [6]. Intralesional/marginal margins and high-grade tumours are also associated with an increased risk of local failure [7, 8]. Of these, the only surgically modifiable factor for pelvic chondrosarcomas is the resection margin since chondrosarcomas are highly resistant to other treatment modalities, such as chemotherapy and radiotherapy [3, 5, 9-11]. However, achieving adequate resection margins in pelvic chondrosarcomas remains a major challenge for orthopaedic oncologists [6, 7, 12].

Recent evidence has highlighted the advantages of computer navigation in orthopaedic oncology [13-19]. We have previously reported a reduced intralesional resection rate following navigated resection of pelvic and sacral tumours, in which clear bone resection margins were obtained in all cases [15]. In primary bone sarcomas of the posterior ilium and sacrum navigated-assisted resection resulted in no intralesional resection margins and improved disease-free survival than the non-navigated resection group [19]. However, the efficacy of computer navigation, for peri-acetabular chondrosarcomas, with no adjuvant therapy, is limited to case reports and small series [13, 20, 21].

The aim of this study was to evaluate the efficacy of the navigation-assisted surgery of chondrosarcomas involving the peri-acetabulum to address the following research questions: (1) Does the computer navigation improve local control? (2) Does the use of navigation affect the complication rate and functional outcome? (3) Does the navigation-assisted surgery exert any effects on the survival of patients?

Patients and Methods

Eligibility

We conducted a retrospective comparative study of patients who underwent limb-sparing surgery for chondrosarcomas involving the acetabulum at a single referral musculoskeletal oncology centre between November 2000 and August 2015. From a total of 98 patients eligible patients seen during the study period, patients who underwent excision for tumour localized to only ilium (PI, n = 20), pubis/ischium (PIII, n = 5), and sacrum (PIV, n= 4) were excluded. Patients who underwent curettage as definitive treatment or those who required primary hindquarter amputation were also excluded from the analysis, because the navigation was not used for them (**Supplementary Figure 1**). A total of 50 patients matched after exclusion criteria. Tumour resection was performed with navigation assistance in 13 patients, whose early results were, in part, reported in a previous study [15]. We compared this group of patients with a group of 37 patients who underwent tumour resection without the navigation assistance.

The acetabular lesions were excised using a variety of resection types according to Enneking and Dunham's classification system [22, 23]; iliac (PI), acetabular (PII), pubis or ischium (PIII), and sacral (PIV). Combinations of these resections were also performed, as follows: PI-II, resection of the iliac and acetabular regions; PII-III, resection of the acetabular and pubic/ischial regions; PI-II-III, resection of the iliac, acetabular, and pubic/ischial regions; PI-II-IV, resection of the iliac, acetabular, and sacral regions. After tumour resection, the closest resection margin was evaluated by pathologists, who were highly experienced in bone and soft-tissue sarcomas, according to gross and microscopic examinations of the specimen. Regardless of whether navigation was used, the extent of margin width was evaluated at the bony and soft-tissue resection margins. Bony margins were determined as the closest longitudinal distance between the tumour and the cut surface of the bone. Similarly, soft-tissue margins were determined as the closest distance between the tumour that had extended to soft tissues and the cut surface of the soft-tissue. The resection margins were considered clear when no tumour cells were observed microscopically at the resection margins, while the margins were determined to be intralesional when tumour cells were observed at the resection margins. Clear margins were further classified as marginal margins (dissection through the pseudocapsule or reactive zone) or wide margins (dissection entirely through the surrounding normal tissue) according to Enneking's system [24]. Function was assessed using the Musculoskeletal Tumour Society (MSTS) system developed by Enneking et al. [25]. This system is based on the analysis of factors pertinent to the patient as a whole (pain, restriction in activities and/or occupation, and emotional acceptance) and factors specific to the affected limb (use of walking supports, walking ability, and gait) [25]. Each parameter is given a value, ranging from 0 to 5, according to specific criteria. The overall result is expressed as a total score of each parameter, which was then converted into a percentage of the maximum possible score. Following the institutional ethical approval, all patients provided appropriate consent, and all data were collected from the clinical records and imaging systems as part of the routine patient follow-up.

Surgical Procedures

Preoperatively, computed tomography (CT) and magnetic resonance (MR) images, which were taken as routine staging studies, were fused in the oncology-specific navigation system (Stryker Orthomap 3D Navigation System II; Stryker, Kalamazoo, MI). The plane of the surgical resection margins was determined in the workstation before undertaking tumour resection (**Figure 1**). Intraoperatively, a reference tracker was inserted into a stable portion of the pelvis, away from the tumour and the planned resection margin, regardless of tumour size and extraosseous growth into the intra- or extra-pelvic lesion. For tumours that required PII or PII+PIII (PI-uninvolved) resection, the tracker was placed onto the iliac crest, following surgical exposure of the iliac crest for its insertion. For tumours that required PI+II or PI+II+PIII (PI-involved) resection, the tracker was placed onto the iliac bone, at or close to the posterior superior iliac spine, following extensive exposure posteriorly using the extended ilioinguinal approach. Then, a paired-point and surface-point matching were performed. An overall registration error of < 1 mm was considered as acceptable, which was achieved for all patients. Next, the planned resection margins were marked on the bone under the navigation, and the osteotomy was performed with navigated surgical tools. Subsequently, the resected specimens were sent for histopathological analysis to confirm the diagnosis and evaluate the resection margins.

After tumour resection, patients underwent reconstruction with custom-made prostheses (Stanmore Implants, London, United Kingdom), ice-cream cone prostheses (Coned Hemi-Pelvis;

Stanmore Implants), irradiated autografts, or cemented total hip replacement (THR), which was selected according to the extent of the resection required and the types of reconstruction available. In cases where reconstruction required a custom-made implant, the planned resection margins were determined according to the implant (**Figure 1**), which was discussed with engineers beforehand. In cases where an ice-cream cone prosthesis was used, the location and direction of the hole for a coned stem, depth of insertion, and abduction angle and anteversion of the acetabular component, were planned with navigation. In the non-navigated group, tumour resection and reconstruction was performed by measurements from pelvic landmarks according to pre-operative planning. Surgeries were performed by a single surgical team, consisting of the senior authors (LJ and RG). Surgical navigation was performed by the lead author (LJ) after appropriate training on the navigation equipment, and all surgeons' skills were at a stable level.

Statistical Analysis

Analyses for local recurrence (LR) were completed with a competing risks framework. Analyses for local recurrence (LR) were completed with a competing risks framework. The LR at a given time was defined as the cumulative incidence of LR, with death regarded as the competing event, and the differences were calculated by Gray's test. The progression-free survival (PFS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier analysis and a log-rank test. PFS was defined as the period from surgical resection to local recurrence or distant metastasis and was censored at the date of the latest follow-up or death due to other causes. DSS was defined as the period from the date of surgical resection to the last date when the patient was recorded to be alive or the date of tumour-related death. Univariate and multivariate analyses were performed using the and Cox regression model. Both the navigated and non-navigated groups were compared with regard to the presence of complication and functional outcome using Fisher's exact test or Mann-Whitney U test. Differences were considered to be statistically significant at $p<0.05$. All statistical analyses were performed using the R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) and the SPSS software (version 23; IBM, Armonk, NY, USA).

Results

Patients' characteristics

The study cohort comprised of 36 males and 14 females, and the mean age at the time of resection was 53 years (range, 20 to 77 years). The mean tumour size was 10 cm (range, 5 to 20 cm) and the tumour grade based on the resected specimen was grade 1 in 7 (14%), grade 2 in 23 (46%), grade 3 in 12 (24%), and dedifferentiated in 8 (16%). A discrepancy in 25 patients (50%) regarding the diagnosis between biopsy and resected specimens was observed; these patients were all upgraded in the resected specimens compared with the biopsy specimens (grade 2 to 3 in 8; grade 1 to 2 in 8; grade 1 to 3 in 2; grade 1 to dedifferentiated in 3; benign to grade 1 in 2; and benign to grade 2 in 2). The resected acetabular lesions according to the classification system of Enneking and Dunham [22, 23] were type PII in 8 (16%), type PI–II resection in 14 patients (28%), type PII–III resection in 18 (36%), and type PI–II–III in 8 (16%). Reconstructions after tumour resection were performed using custom-made prostheses in 23 patients (46%), ice-cream cone prostheses in 15 (30%), irradiated autografts in 7 (14%), and the other procedures in 5 (10%) (cemented THR and hip transposition, respectively). Three patients (6%) with dedifferentiated chondrosarcoma received adjuvant chemotherapy, and 2 patients (4%) received adjuvant radiotherapy. The mean follow-up was 63 months (range, 5 to 154 months). The difference in the baseline characteristics between patients treated with and without navigation was not statistically significant in all variables (**Table 1**).

Local control

In the navigated group, a clear margin was obtained in 12 patients (92%; wide, 61% and marginal, 31%), and tumour contamination at the soft-tissue margins was observed in only a single patient (**Table 1**). No intralesional bony margins were observed in the navigated group. In the non-navigated group, the margin was clear in 30 patients (81%; wide, 24% and marginal, 57%) and intralesional in 7 (19%); tumour contamination was identified at the bone resection margin in 6 patients (superior pubic ramus in 4 patients and ilium in 2) and at the soft-tissue margin in 1 patient. In a comparison of the two groups, the rate of wide resection margins was significantly higher in the navigated group than in the non-navigated group (62% versus 24%; $p = 0.019$).

Local recurrence (LR) occurred in 24 patients (48%); 7 LRs with intralesional margins, 13 LRs with marginal margins and 4 LRs with wide margins were observed ($p = 0.010$; chi-square test). The competing risk analysis revealed that the 5-year cumulative incidence of LR was 45% in the entire cohort, whereas it was 88% in those with intralesional margins, 48% in those with marginal margins and 24% in those with wide margins ($p = 0.007$; Gray's test; **Figure 2A, Table 2**). In a comparison according to the use of navigation, the 5-year cumulative LR incidence was 23% and 56% in the navigated and non-navigated groups, respectively ($p = 0.035$; Gray's test; **Figure 2B**, **Table 2**). The Cox regression hazard model revealed that the risk of local failure was significantly low in patients with wide margins (wide margins: HR, 0.184 [95% CI, 0.053–0.630] versus intralesional margins: HR, 1; $p = 0.007$) and in those in whom navigation was used (navigated: HR, 0.269 [95% CI, 0.080–0.903] versus non-navigated; HR, 1; $p = 0.034$; **Table 2**). Among 22 patients with LR, 9 patients (41%) were determined to have a higher tumour grade than their primary tumour was at diagnosis, as follows; grade 2 versus 3 in 4 patients, grade 2 versus dedifferentiated in 3 patients, grade 1 versus 2 in 1 patient and grade 1 versus dedifferentiated in 1 patient.

Complication

There was no intra-operative complication related to the navigation procedure. Complications related to surgery were seen in 34 patients (68%), with 9 (69%) in the navigation-assisted group and 25 (68%) in the non-navigation-assisted group (p = 0.600). These complications included dislocation in 16 patients (32%), loosening in 4 (8%), implant/bone fracture in 4 (8%), deep/superficial infection in 19 (38%), deep-vein thrombosis in 4 (8%), neurological complication in 4 (8%), wound necrosis in 2 (4%), leg-length discrepancy in 2 (4%), pulmonary embolism in 2 (4%), lymphoedema in 2 (4%), visceral complication in 2 (4%) and heterotopic ossification in 1 (2%) (**Table 3**). The rate of major complications, which required at least one surgical intervention, was 31% and 46% in the navigated and non-navigated groups, respectively (p = 0.268). Except for tumour-related complications, we identified no statistical difference in the occurrence of surgical complications (**Table 3**).

Functional outcome

Among patients who were followed up for more than 12 months after surgery, the median MSTS score in the navigated group was 66% (range, 30 to 97), whereas that of the non-navigated group was 60% (range, 17 to 93; *p* = 0.412). The median MSTS score by custom-made prosthesis was 63% (range, 47 to 90) and 50% (range, 17 to 93) in the navigated and non-navigated groups, respectively (*p* = 0.285). Among patients who underwent reconstruction with ice-cream cone prostheses, the median MSTS scores were 74% (range, 50 to 97) and 70% (range, 40 to 90) in the navigated and non-navigated groups, respectively (*p* = 0.872). Overall, patients with a major complication or LR, which was a major cause of additional surgical interventions, had significantly poorer scores than those without a major complication or LR; the median score was 55% and 72% in patients with and without a major complication, respectively (*p* = 0.025), and 57% and 70% in patients with and without LR, respectively (*p* = 0.007).

Survival outcome

A total of 23 patients (46%) had distant metastasis with a median period of 15 months postoperatively. Distant metastasis was observed in 4 patients (31%) in the navigated group and 19 patients (51%) in the non-navigated group, but this difference was not statistically significant (*p* = 0.170). The 5-year progression-free survival was 37% in the entire cohort; 62% and 28% in the navigated and non-navigated group, respectively (*p* = 0.032; **Figure 3**). The Cox regression hazard model revealed that the histological grade, resection margin, and the use of navigation was significantly associated with progression-free survival (**Table 4**).

The 5-year disease-specific survival was 57% in the entire cohort; 76% and 53% in the navigated and non-navigated group, respectively (p = 0.085; **Figure 4**). The Cox regression hazard model revealed that histological grade, tumour size, and LR were significantly associated with disease-specific survival (**Table 4**). When adjusted with these factors, histological grade and LR were independent prognostic predictors for disease-specific survival (**Supplementary Table 1**).

Discussion

Local control of pelvic chondrosarcomas involving the acetabulum is challenging. Puri *et al.* has reported that 18 of 21 LRs (85%) were chondrosarcomas among 91 patients with primary malignant bone tumours of the pelvis treated with limb-sparing resection [26]. Since surgical margin is a prognostic factor for LR, and LR has been proven to be a negative prognostic factor for survival, precise surgical management is crucial for improving outcomes. Since the surgical margin status is associated not only with LR [9, 27] but also survival [4] in the management of pelvic chondrosarcomas, precise surgical management is crucial to improve outcomes. Mavrogenis et al. stated that patients with any surgical margins other than wide margins had a 1.75× higher risk of LR (odds ratio, 1.754 [95% CI, 1.035–2.974]; $p = 0.0378$) compared with those with wide margins [28], while Bus et al. reported that patients with intralesional margins had a 2.36× higher risk of disease-specific death (hazard ratio, 3.56 [95% CI, 1.80–7.02]; $p < 0.001$) compared with those with wide margins [6]. We have introduced navigated resection for pelvic sarcomas since 2010, which significantly decreased the incidence rate of intralesional margin and contributed better outcome in local control [15]. In this study, we confirmed the significantly better outcome in local control and progression-free status by the navigation-assisted surgery. Overall, these findings validated the advantages of navigation in not only tumour resections but also reconstructions.

Although bony clear margin was achieved in all cases with navigated resection, the incidence of intralesional margin was observed in 1 patient in soft tissue despite the assistance of navigation. In this patient, the original tumour showed substantial involvement to soft tissue inward to the abdominal cavity, where the tumour contamination was observed. Among 3 patients with LR in the navigated group, 2 had soft tissue involvement in the preoperative images. Nandra et al. recently reported that, among 23 patients with a primary pelvic or sacral tumour who underwent navigated resection, no bony recurrences were observed but 8 patients (35%) developed soft-tissue LR [29]. Owning to the limitation of the computer navigation for soft tissues, surgeons should be cautious in the management of soft tissue margins regardless of the use of the computer navigation.

In this study, the difference in disease-specific survival between the groups did not reach statistical significance despite the introduction of computer navigation. Although some studies have suggested that wide resection margins are associated with a significant survival advantage [6], wide margins do not eliminate the possibility of metastatic disease and disease-specific death in patients with high-grade chondrosarcomas [7, 30, 31]. In this study, 24 of 26 patients (92%) with distant metastasis died of the disease. We realise that advancements in other treatment modalities, especially systemic treatment, for high-grade chondrosarcomas are crucial for improving disease-specific survival. Although literatures has shown the clinical benefit for the use of conventional chemotherapy [32-34] or targeted therapy [35], the efficacy has been limited to the dedifferentiated and mesehchymal subtypes or advanced/palliative settings.

Recent studies have indicated that patient-specific instrumentation (PSI) can be used for bone resection with the same accuracy as computer navigation [36-38]. In addition, less resection time was required for PSI than for navigation in these reports [37, 38], although these investigations were cadaveric studies. At our institute, we do not use PSI for tumour resection. However, this new technology would not only improve accurate tumour resection but also reduce surgical time.

We acknowledge several limitations to this study. First, this study is a retrospective study conducted at a single referral centre without randomization. Although the study number is limited, no significant differences were found in tumour- and treatment-related variables between the navigated and non-navigated groups. The treatment strategy and surgical technique did not change throughout the study period except for the use of navigation. Second, the surgeon's technical bias may have existed. All cases were performed by a single surgical team, consisting of the senior authors (LJ and RG), of which the navigated surgeries were carried out by the lead author (LJ) who received appropriate training on the navigation equipment before performing those resections. Third, a comparison of the navigated and non-navigated groups included a time effect based on the introduction of computer navigation in 2010. However, this bias would be minimal because no major difference was observed in the follow-up period between the navigated (mean, 65 months) and non-navigated groups (mean, 62 months). Finally, this study includes some bias based on technical factors and imaging studies, which improved over time. Improvements in surgical margins, in turn, might be achieved as a result of better imaging. Despite these limitations, this is the first study, to the best of our knowledge, reporting the outcomes of navigated resection focussing on the periacetabular chondrosarcomas, providing the useful information to patients and treating surgeons.

In conclusion, the navigation-assisted surgery for pelvic chondrosarcomas involving the acetabulum significantly decreased the intralesional margin rate and the risk of LR, and improved the progression-free survival with favourable functional outcome. We believe that these findings are encouraging to orthopaedic oncologists for better management against chondrosarcomas whose outcome has been plateaued for more than 40 years.

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Figure Legends

Figure 1. (A) Preoperative planning. The tumour is highlighted in yellow. The resection line is marked in light blue. In this case, resection for anterior pelvis was planned at the symphysis pubis, in which the resection line was unnecessary. The custom-made implant is marked in green. (B) Postoperative radiograph. Custom-made implant was completely fitted to the osteotomy line.

Figure 2. Competing analysis showing the cumulative incidence of local recurrence according to the surgical margin (A; $p = 0.007$; Gray's test) and the use of navigation (B; $p = 0.037$; Gray's test).

Figure 3. Kaplan-Meier curve showing progression-free survival according to the use of navigation. $p = 0.032$; log-rank test.

Figure 4. Kaplan-Meier curve showing disease-specific survival according to the use of navigation. $p = 0.085$; log-rank test.

Table 1. Patient characteristics

Variable	Total		Navigated		Non-navigated		*p* value
	Number	Range, %	Number	Range, %	Number	Range, %	
No. of patients	50	–	13	–	37	–	
Age (mean, years)	53	20–77	55	20–77	53	31–75	0.750
Gender							0.529
Male	36	72%	9	69%	27	73%	
Female	14	28%	4	31%	10	27%	
Size (mean, cm)	10	5–20	10	5–20	10	5–20	0.752
Grade							0.463
Grade 1	7	14%	3	23%	4	11%	
Grade 2	23	46%	7	54%	17	46%	
Grade 3	12	24%	2	15%	9	24%	
Dedifferentiated	8	16%	1	8%	7	19%	
Adjuvant therapy							
Chemotherapy	3	6%	1	8%	2	5%	0.604
Radiotherapy	2	4%	1	8%	1	3%	0.456
Type of surgery							0.889
Custom-made EPR	23	46%	7	54%	16	43%	
Ice-cream cone EPR	15	30%	3	23%	12	32%	
Irradiated autograft	7	14%	2	15%	5	14%	
Others (cemented THR, hip transposition)	5	10%	1	8%	4	11%	
Resected area							0.374
PI uninvolved (PII, PII-III)	26	52%	5	46%	21	57%	
PII	8	16%	2	15%	6	16%	
PII–III	18	36%	3	23%	15	41%	
PI involved (PI-II, PI-II-III)	24	48%	7	54%	16	43%	
PI–II	16	32%	7	54%	9	25%	
PI–II–III	8	16%	1	8%	7	19%	
Type of resection							0.301
Extra-articular	11	22%	4	31%	7	19%	
Intra-articular	39	78%	9	69%	30	81%	
Surgical margin							0.050

Wide	17	34%	8	61%	9	24%	
Marginal	25	50%	4	31%	21	57%	
Intralesional	8	16%	0: bone 1: soft tissue	8%	6: bone 1: soft tissue	19%	
Follow-up (mean, months)	63	5–154	65	15–107	62	5–154	0.837

Table 2. Results of the competing analysis using Gray's test and the Cox regression hazard model for LR

Variables	N	Cumulative LR incidence (%; 5-year)	Gray's test	Cox regression hazard model		
			p value	HR	95% CI	*p* value
Age			0.535			
≤ 60 years	35	44%		1	Reference	
> 60 years	15	56%		1.393	0.594–3.271	0.446
Sex			0.721			
Male	36	49%		1	Reference	
Female	14	43%		1.000	0.397–2.534	0.999
Size			0.496			
≤ 8 cm	16	52%		1	Reference	
> 8 cm	34	44%		1.029	0.440–2.408	0.947
Histological grade			0.502			
Grade 1	7	29%		1	Reference	
Grade 2	23	54%		2.720	0.610–12.127	0.190
Grade 3	12	42%		2.347	0.453–12.166	0.310
Dedifferentiated	8	50%		3.887	0.709–21.318	0.118
Chemotherapy			0.524			
Yes	3	67%		1	Reference	
No	47	46%		0.728	0.171–3.102	0.668
Radiotherapy			0.694			
Yes	2	50%		1	Reference	
No	48	47%		0.820	0.110–6.101	0.846
Resected area			0.153			
PI involved (PI-II, PI-II-III)	24	61%		1	Reference	
PI uninvolved (PII, PII-III)	26	33%		0.615	0.269–1.410	0.251
Margin			0.007			
Intralesional	8	88%		1	Reference	
Marginal	25	48%		0.486	0.193–1.222	0.125
Wide	17	24%		0.184	0.053–0.630	0.007
Navigation			0.035			
No	37	56%		1	Reference	
Yes	13	23%		0.269	0.080–0.903	0.034

Table 3. Postoperative complications

Complication	Total		Navigated		Non-navigated		*p* value
	Number	%	Number	%	Number	%	
Mechanical complications							
Soft-tissue complication							
Dislocation	16	32%	4	31%	12	32%	0.600
Aseptic loosening							
Early (≤2 years)	3	6%	0	0%	3	8%	0.396
Late (>2 years)	1	2%	1	8%	0	0%	0.260
Structural complication							
Implant	1	2%	1	8%	0	0%	0.260
Bone	3	6%	0	0%	3	8%	0.396
Non-mechanical complications							
Infection							
Deep	15	30%	4	31%	11	30%	0.602
Superficial	4	8%	0	0%	4	11%	0.287
Tumour progression							
Local recurrence	24	48%	3	23%	21	57%	0.037
Distant metastasis	23	46%	4	31%	19	51%	0.170
Other complications							
Deep-vein thrombosis	4	8%	1	8%	3	8%	0.725
Nerve complication	4	8%	1	8%	3	8%	0.725
Wound necrosis	2	4%	1	8%	1	3%	0.456
Limb-length discrepancy	2	4%	1	8%	1	3%	0.456
Pulmonary embolism	2	4%	1	8%	1	3%	0.456
Lymphoedema	2	4%	0	0%	2	5%	0.544
Visceral complication	2	4%	0	0%	2	5%	0.544
Heterotopic ossification	1	2%	1	8%	0	0%	0.260

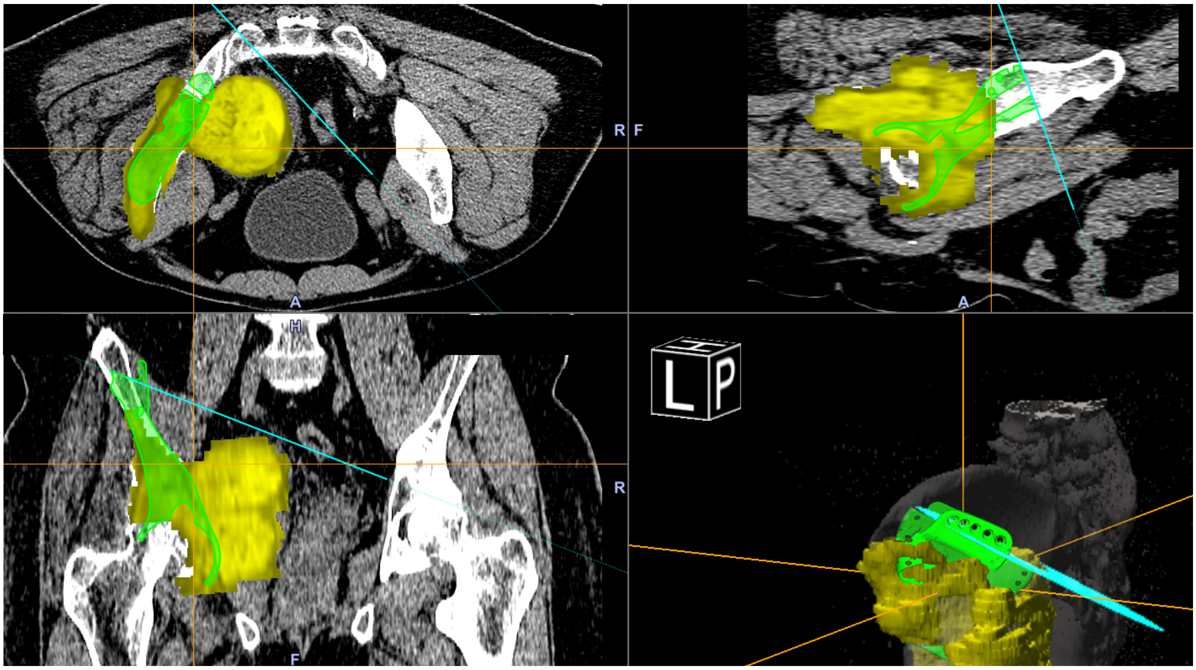
Table 4. Results of the Cox regression hazard model for PFS and DSS

Variables	N	PFS			DSS		
		HR	95%CI	*p* value	HR	95%CI	*p* value
Age							
≤ 60 years	35	1	Reference		1	Reference	
> 60 years	15	1.553	0.772–3.124	0.220	1.634	0.693–3.851	0.260
Sex							
Male	36	1	Reference		1	Reference	
Female	14	0.946	0.408–2.191	0.900	1.383	0.564–3.393	0.480
Size							
≤ 8 cm	16	1	Reference		1	Reference	
> 8 cm	34	1.223	0.589–2.536	0.590	4.148	1.280–13.440	0.018
Histological grade							
Grade 1	7	1	Reference		1	Reference	
Grade 2	23	2.851	0.645–12.602	0.167	26530	10100–69700	<0.001
Grade 3	12	4.838	1.054–22.195	0.043	49210	17880–135400	<0.001
Dedifferentiated	8	5.342	1.073–26.599	0.041	54960	14900–202800	<0.001
Chemotherapy							
Yes	3	1	Reference		1	Reference	
No	47	1.010	0.241–4.231	0.989	0.540	0.153–1.906	0.340
Radiotherapy							
Yes	2	1	Reference		1	Reference	
No	48	1.178	0.160–8.658	0.872	0.626	0.084–4.674	0.648
Resected area							
PI involved (PI-II, PI-II-III)	24	1	Reference		1	Reference	
PI uninvolved (PII, PII-III)	26	0.805	0.402–1.615	0.540	0.810	0.363–1.809	0.607
Margin							
Intralesional	8	1	Reference		1	Reference	
Marginal	25	0.704	0.293–1.692	0.433	0.683	0.262–1.783	0.436
Wide	17	0.336	0.117–0.964	0.042	0.303	0.086–1.075	0.065
Navigation							
No	37	1	Reference		1	Reference	
Yes	13	0.387	0.154–0.973	0.044	0.444	0.133–1.481	0.190
LR							
No	28	–	–	–	1	Reference	

Yes	22	–	–	–	6.384	2.553–15.960	<0.001

Figure 1

A



B

Figure 2

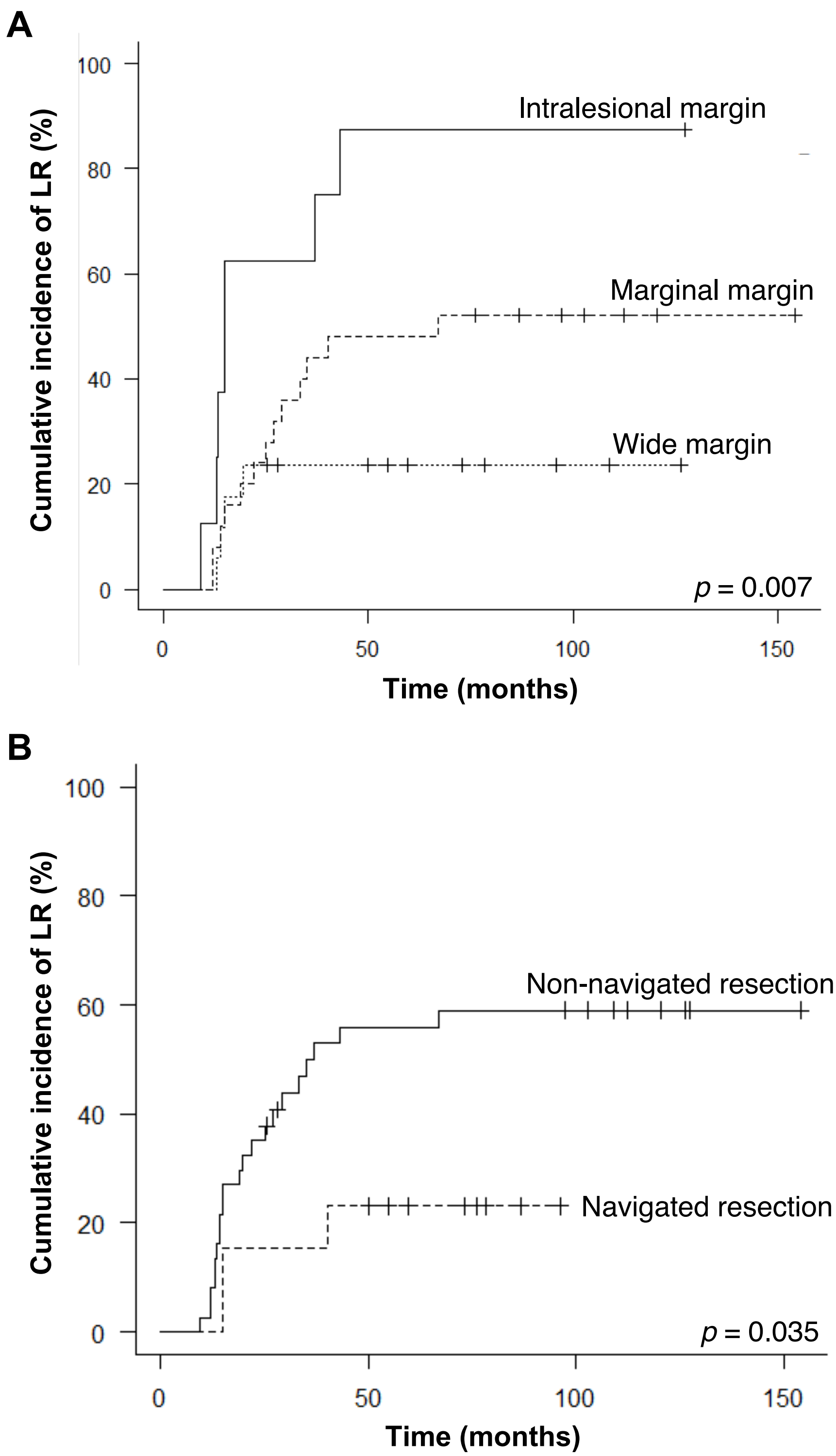

A
Cumulative incidence of LR (%)
100
80
60
40
20
0
Intralesional margin
Marginal margin
Wide margin
p = 0.007
0
50
100
150
Time (months)
B
Cumulative incidence of LR (%)
100
80
60
40
20
0
Non-navigated resection
Navigated resection
p = 0.035
0
50
100
150
Time (months)

Figure 3

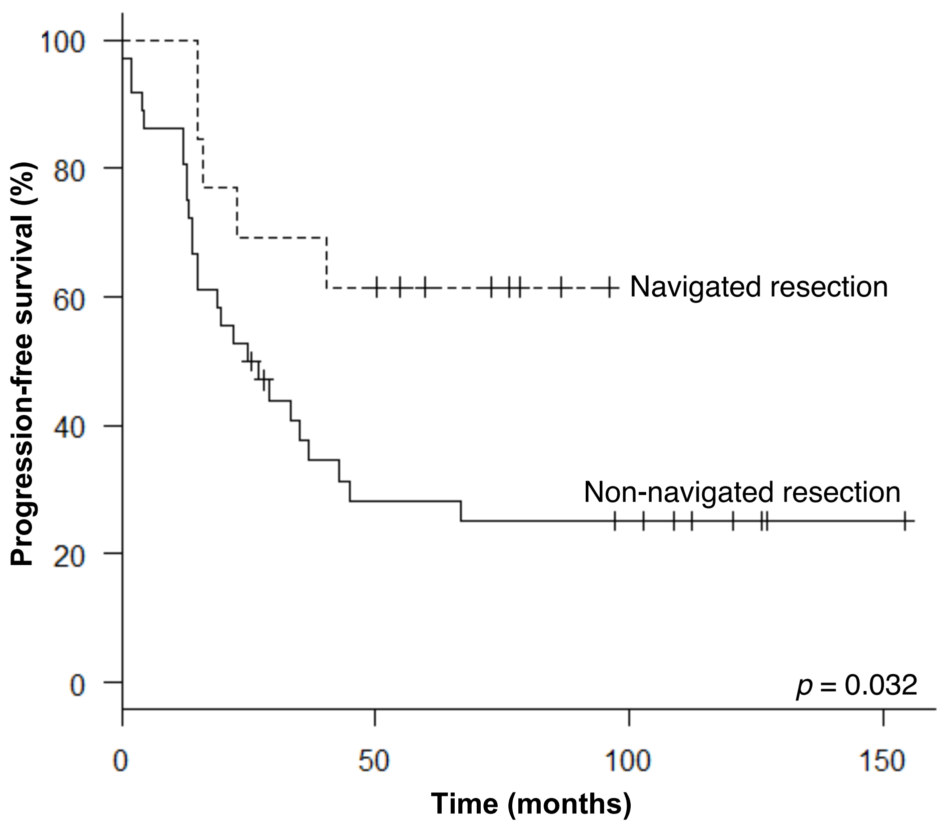
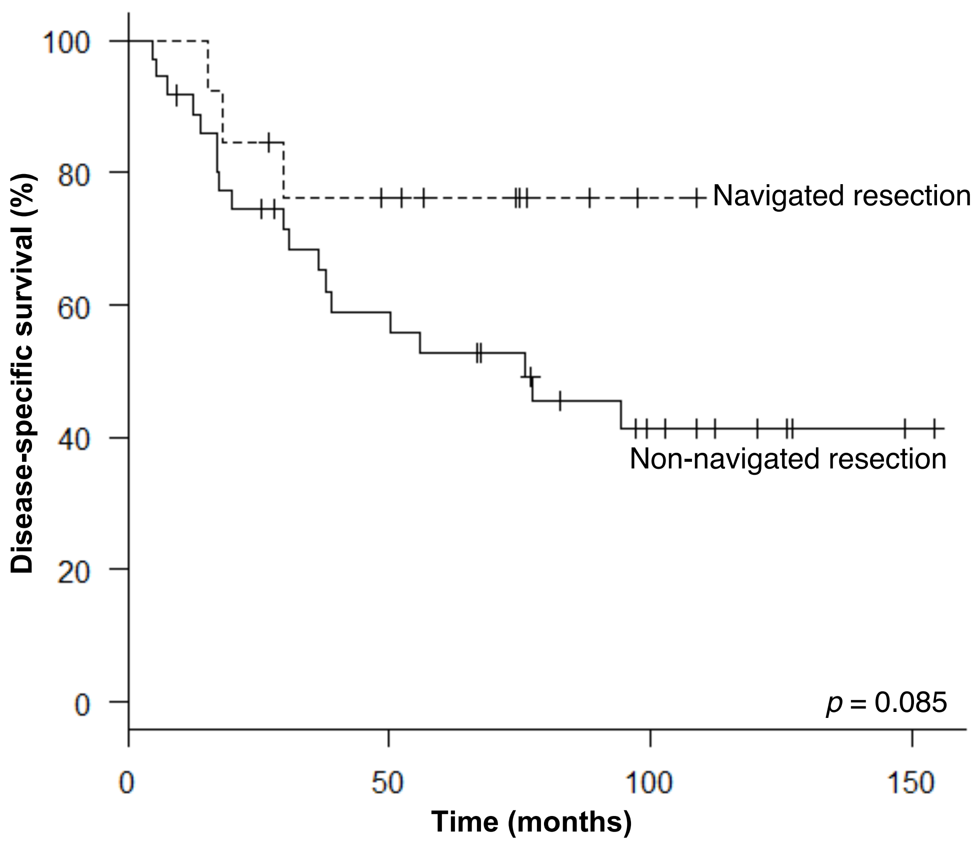

Progression-free survival (%)
100
80
60
40
20
0
Navigated resection
Non-navigated resection
p = 0.032
0
50
100
150
Time (months)

Figure 4



Disease-specific survival (%)
100
80
60
40
20
0
Navigated resection
Non-navigated resection
p = 0.085
0
50
100
150
Time (months)

Conflict of interest statement

The authors have no conflicts of interest to declare.