■ ONCOLOGY

A comparison of clinical outcomes between additional excision after unplanned and planned excisions in patients with soft-tissue sarcoma of the limb

A PROPENSITY MATCHING COHORT STUDY

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Aims

Patients with soft-tissue sarcoma (STS) who undergo unplanned excision (UE) are reported to have worse outcomes than those who undergo planned excision (PE). However, others have reported that patients who undergo UE may have similar or improved outcomes. These discrepancies are likely to be due to differences in characteristics between the two groups of patients. The aim of the study is to compare patients who underwent UE and PE using propensity score matching, by analyzing data from the Japanese Bone and Soft Tissue Tumor (BSTT) registry.

Methods

Data from 2006 to 2016 was obtained from the BSTT registry. Only patients with STS of the limb were included in the study. Patients with distant metastasis at the initial presentation and patients with dermatofibrosarcoma protuberans and well-differentiated liposarcoma were excluded from the study.

Results

A total of 4,483 patients with STS of the limb were identified before propensity score matching. There were 355 patients who underwent UE and 4,128 patients who underwent PE. The five-year disease-specific survival (DSS) rate was significantly better in the patients who received additional excision after UE than in those who underwent PE. There was no significant difference in local recurrence-free survival (LRFS) between the two groups. After propensity score matching, a new cohort of 355 patients was created for both PE and UE groups, in which baseline covariates were appropriately balanced. Reconstruction after tumour excision was frequently performed in patients who underwent additional excision after UE. There were no significant differences in DSS and LRFS between the patients who underwent PE and those who had an additional excision after UE.

Conclusion

Using propensity score matching, patients with STS of the limb who underwent additional excision after UE did not experience higher mortality and local failure than those who underwent PE. Reconstruction may be necessary when additional excision is performed.

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Introduction

Soft-tissue sarcoma (STS) is a rare and heterogeneous tumour,[1] of which approximately 50% are located in the limbs.[2] Owing to its scarcity, however, there is a lack of awareness about the natural history of STS and unfortunately, unplanned excision (UE) occurs in some patients when treated by untrained surgeons, primarily because they may not have considered STS in the differential diagnosis.[3] In a UE, omission of a radiological examination is also not uncommon. Furthermore, there may be no intent to achieve surgical tumour-free margins, and the direction of the skin incision may not be taken into consideration. To reduce the possibility of recurrence, the mainstay of additional treatment is wide

Table I. Patient's background depending on surgical type.

Variable	PE (n = 4,128)	UE (n = 355)	p-value
Age, yrs			
Mean (SD)	60.3 (18.3)	58.3 (18.5)	0.075*
> 60, n (%)	2,444 (59)	200 (56)	
< 60, n (%)	1,684 (41)	155 (44)	0.311*
Sex, n (%)			
Male	2,225 (54)	175 (49)	
Female	1,903 (46)	180 (51)	0.097†
Depth, n (%)			
s.c	1,030 (25)	211 (59)	
Deep	3,098 (75)	144 (41)	< 0.001†
Limb, n (%)			
Upper	756 (18)	99 (28)	
Lower	3,372 (82)	256 (72)	< 0.001†
Grade, n (%)			
Low	848 (21)	75 (21)	
High	3,280 (79)	280 (79)	0.785†
Size, cm			
Mean (SD)	9 (5.7)	4.2 (4.1)	< 0.001*
> 5, n (%)	2,940 (71)	96 (27)	
< 5, n (%)	1,188 (29)	259 (73)	< 0.001†
Adjuvant Rx, n (%)			
Yes	742 (18)	36 (10)	
No	3,386 (82)	319 (90)	< 0.001†
Adjuvant Cx, n (%)			
Yes	961 (23)	50 (14)	
No	3,167 (77)	305 (86)	< 0.001†

*Mann-Whitney U test.
†Chi-squared test.
Cx, chemotherapy; PE, planned excision; Rx, radiotherapy; s.c, superficial; SD, standard deviation; UE, unplanned excision.

re-excision, taking generous margins around the previous excision cavity, and removing the tumour bed with wide, or at least negative, margins.[3–6]

Patients who undergo UE have been reported to have worse outcomes than those who undergo planned excision (PE),[7,8] on the other hand some authors have shown that patients who undergo UE have similar or improved outcomes.[4,6,9,10] These discrepancies are likely due to different characteristics between the patients who had UE and those who underwent PE. Patients with large and deep STSs are also more likely to be referred to a sarcoma-specific centre. On the other hand, patients with small and superficial STSs are likely to undergo UE by non-specialized surgeons.[3,11] The aim of this study is to compare patients who underwent UE and PE using propensity score matching, reviewing data from the Japanese nationwide Bone and Soft Tissue Tumor (BSTT) registry.

Methods

Data source. This study was approved by the institutional review boards of the authors' affiliated institutions. Informed consent was waived because of the nature of the study, and an "opt-out" option was permitted, where the patients had an opportunity to deny participation in the study. Data from 2006 to 2016 were obtained from the BSTT registry, and patients with STS of the limb were included. In this study, STSs at the shoulder and buttocks were considered as truncal tumours because they are registered as truncal tumours in the BSTT registry. We excluded patients with distant metastasis at initial presentation. We also excluded dermatofibrosarcoma protuberans and well-differentiated liposarcoma. Overall, 4,483 patients were included in this study and all patients underwent PE or additional excision after UE.

Statistical analysis. Statistical associations between the clinicopathological variables were evaluated using the Mann-Whitney U test for quantitative data and the chi-squared test for qualitative data. Survival time was measured from the date of surgery of the primary tumour to the date of sarcoma-related death or last follow-up. Local recurrence was measured from the date of surgery of the primary tumour to the date of local recurrence. When patients underwent additional excision after UE, the date of surgery was defined as the date of additional excision. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses were performed using Cox proportional hazards regression models. Variables with a p-value < 0.05 in the univariate analyses were included in the multivariate analysis.

To adjust for bias, we used logistic regression, including the following variables for the propensity score calculation: age (≥ 60 years vs < 60 years), sex (male vs female), tumour location (upper vs lower limb), and tumour size. We selected these variables because they could be identified before biopsy and/or surgery. Using callipers (0.2) of the standard deviation (SD) of the logit of the propensity score, we performed propensity score analysis with 1:1 matching using the nearest neighbour matching method.

All statistical analyses were performed with the EZR graphical user interface (Saitama Medical Centre, Jichi Medical University, Japan) for R (R Foundation for Statistical Computing, Austria), which is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.

Results

Unmatched cohort. Our study comprised 4,483 patients with STS of the limb. Primary tumour sites included the lower limbs (3,628) and upper limbs (855). Superficial tumours were found in 1,241 patients and deep tumours in 3,242 patients. The mean size of STSs was 8.7 cm (SD 5.7). The tumours were histologically classified as undifferentiated pleomorphic sarcoma (UPS; 1,289), liposarcoma (LPS; 1,157), myxofibrosarcoma (MFS; 601), leiomyosarcoma (LMS; 398), synovial sarcoma (309), malignant peripheral nerve sheath tumour (MPNST; 175), and others (554). Of the 4,483 patients included, 4,128 received PE at the primary site and 355 received additional excision after UE. Tumour site, size, and depth were associated with the incidence of UE (Table I). Of 1,241 patients with superficial sarcomas, 211 patients (17%) underwent UE, while 144 (4.4%) of 3,242 deep sarcomas underwent UE.

The mean follow-up duration was 36 months. At the time of the last follow-up, 440 patients had died of the disease and 356 reported local recurrence. The five-year disease-specific survival (DSS) rate was 84.6% (95% confidence interval (CI)

Table II. Patient's background after propensity score matching.

Variable	PE (n = 355)	UE (n = 355)	p-value
Age, yrs			
Mean (SD)	58.6 (18.1)	58.3 (18.5)	0.619*
> 60, n (%)	207 (58)	200 (56)	
< 60, n (%)	148 (42)	155 (44)	0.649†
Sex, n (%)			
Male	185 (52)	175 (49)	
Female	170 (48)	180 (51)	0.499†
Depth, n (%)			
s.c	217 (61)	211 (59)	
Deep	138 (39)	144 (41)	0.646†
Limb, n (%)			
Upper	112 (32)	99 (28)	
Lower	243 (68)	256 (72)	0.324†
Grade, n (%)			
Low	75 (21)	75 (21)	
High	280 (79)	280 (79)	1.000†
Size, cm			
Mean (SD)	4.1 (4.0)	4.2 (4.1)	0.515*
> 5, n (%)	104 (29)	96 (27)	
< 5, n (%)	251 (71)	259 (73)	0.559†
Adjuvant Rx, n (%)			
Yes	36 (10)	36 (10)	
No	319 (90)	319 (90)	1.000†
Adjuvant Cx, n (%)			
Yes	48 (14)	50 (14)	
No	307 (86)	305 (86)	0.913†
Histology, n (%)			
UPS	109 (31)	103 (29)	
MFS	52 (15)	56 (16)	
LPS	47 (13)	57 (16)	
LMS	44 (12)	46 (13)	
SS	34 (10)	25 (7)	
MPNST	10 (3)	18 (5)	
Others	59 (17)	50 (14)	

*Mann-Whitney U test.
†Chi-squared test.
Cx, chemotherapy; LMS, leiomyosarcoma; LPS, liposarcoma; MFS, myxofibrosarcoma; MPNS, malignant peripheral nerve sheath tumour; PE, planned excision; Rx, radiotherapy; s.c, superficial; SD, standard deviation; SS, synovial sarcoma; UE, unplanned excision; UPS, undifferentiated pleomorphic sarcoma.

Table III. Predictive factors for reconstruction after tumour excision after propensity score matching.

Variable	Reconstruction		p-value
	Yes (n = 344)	No (n = 366)	
Age, yrs			
Mean (SD)	59.2 (18.0)	57.8 (17.8)	0.318*
> 60, n (%)	207 (60)	200 (55)	
< 60, n (%)	137 (40)	166 (45)	0.149*
Sex, n (%)			
Male	178 (52)	182 (50)	
Female	166 (48)	184 (50)	0.600†
Depth, n (%)			
s.c	243 (73)	186 (51)	
Deep	101 (27)	180 (49)	< 0.001†
Limb, n (%)			
Upper	103 (30)	108 (30)	
Lower	241 (70)	258 (70)	0.935†
Grade, n (%)			
Low	57 (17)	93 (25)	
High	287 (83)	273 (75)	0.004†
Size, cm			
Mean (SD)	4.6 (2.9)	5.5 (5.0)	< 0.001*
> 5, n (%)	269 (78)	125 (34)	
< 5, n (%)	75 (22)	241 (66)	< 0.001†
Surgical type, n (%)			
PE	153 (44)	202 (55)	
UE	191 (56)	164 (45)	0.005†

*Mann-Whitney U test.
†Chi-squared test.
PE, planned excision; s.c, superficial; SD, standard deviation; UE, unplanned excision.

Table IV. Logistic regression model for predicting the necessity of reconstruction after tumour excision.

Variable	Odds ratio (95% CI)	p-value
Depth (s.c vs deep)	2.34 (1.68 to 3.25)	< 0.001
Grade (low vs high)	0.529 (0.361 to 0.774)	0.001
Size, cm	0.978 (0.939 to 1.02)	0.271
Surgical type (UE vs PE)	1.6 (1.18 to 2.18)	0.003

CI, confidence interval; PE, planned excision; s.c, superficial; UE, unplanned excision.

83 to 86.1), and the five-year local recurrence-free survival (LRFS) rate was 88.5% (95% CI 87.1 to 89.7). The five-year DSS rate was significantly higher in the patients who underwent additional excision after UE (90.7% (95% CI 85.1 to 94.2)) than in those who underwent PE (84.1% (95% CI 82.4 to 85.6); p = 0.002; Figure 1). There was no significant difference in five-year LFRS between the two groups (PE, 88.3%; UE, 89.7%; Figure 2).

Propensity-scored weighted cohort. After propensity score matching, a new cohort of 355 patients in each group was created for both the PE and UE, with appropriately balanced baseline covariates. There was no difference in patient characteristics between the two groups (Table II). First, we compared the rate of reconstruction following additional excision after UE and PE. Of the 710 patients, 344 underwent reconstruction using a skin graft and/or flap after tumour excision. Tumour depth, grade, size, and surgical type (UE vs PE) were related to the need for reconstruction (Table III). In the logistic regression model, tumour depth, grade, and surgical type remained significant (Table IV). There was no relationship between limb salvage and surgical type.

Second, we analyzed oncological outcomes. The five-year DSS rate was 90.6% (95% CI 87.1 to 93.2). In univariate analysis, tumour depth, grade, and size were prognostic factors for survival and showed statistical significance in the multivariate analysis (Table V). There was no significant difference in five-year DSS between the patients who received PE (87.8% (95% CI 82.1 to 91.7)) and those who received additional excision after UE (90.7 (95% CI 85.1 to 94.2); Figure 3). The five-year LRFS rate was 89.3% (95% CI 85.6 to 92). Concerning local control, tumour size, surgical margin, and perioperative radiotherapy were related to the development of local recurrence (Table VI). Tumour size and surgical margins remained

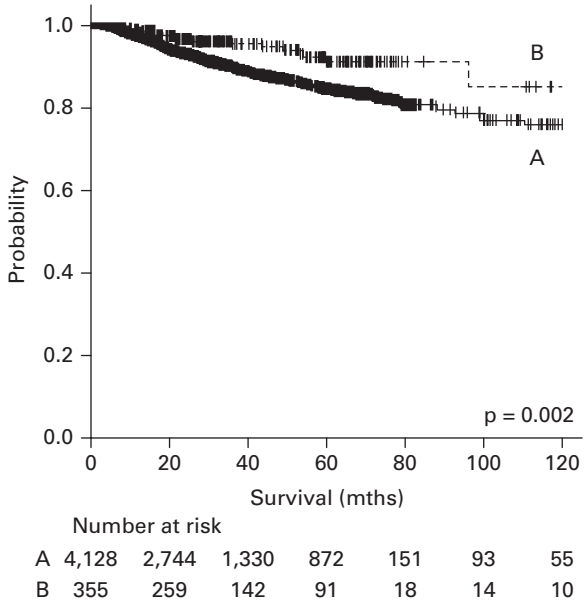

Fig. 1

Kaplan-Meier curve showing the disease-specific survival before propensity score matching (A: patients who underwent an additional excision after an unplanned excision; B: patients who underwent a planned excision).

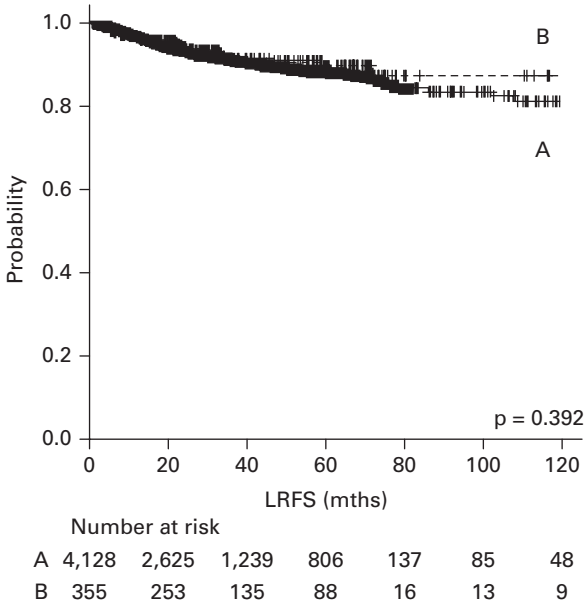

Fig. 2

Kaplan-Meier curve showing local recurrence-free survival before propensity score matching (A: patients who underwent an additional excision after an unplanned excision; B: patients who underwent a planned excision). LRFS, local recurrence-free survival.

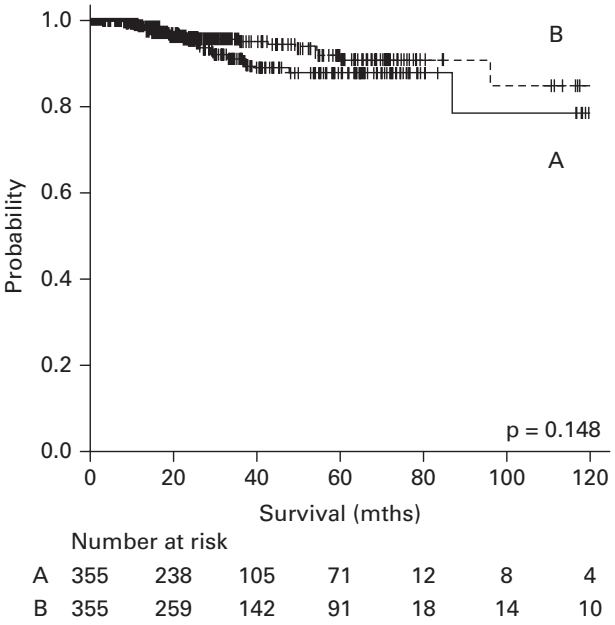

Fig. 3

Kaplan-Meier curve showing disease-specific survival after propensity score matching (A: patients who underwent an additional excision after an unplanned excision, B: patients who underwent a planned excision).

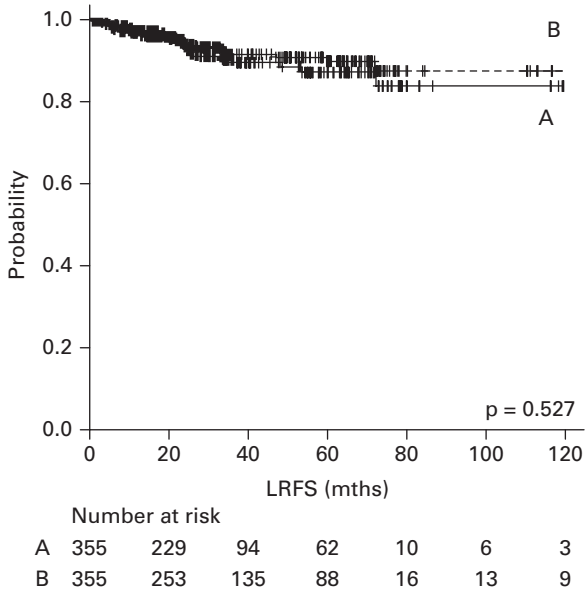

Fig. 4

Kaplan-Meier curve showing local recurrence-free survival (LRFS) after propensity score matching (A: patients who underwent an additional excision after an unplanned excision; B: patients who underwent a planned excision).

significant in multivariate analysis. There was no significant relationship between the surgical margin and surgical type. Wide surgical margins were achieved in 307 of 355 patients who underwent additional excision after UE and 312 of 355 patients who underwent PE. There was no significant difference in five-year LRFS between patients who had PE (87.2% (95% CI 81.1 to 91.4)) and those who had additional excision after UE (89.7% (95% CI 84.6 to 93.2); Figure 4).

Table V. Univariate analysis for predicting survival after propensity score matching.

Variable	n	5 yr-DSS, % (95% CI)	p-value*
Age, yrs			
> 60	407	88.5 (83.3 to 92.2)	
< 60	303	90.3 (84.1 to 94.1)	0.181
Depth			
s.c	429	93.9 (89.7 to 96.4)	< 0.001
Deep	281	82.5 (75.1 to 87.9)	
Grade			
Low	160	98.1 (92.6 to 99.5)	0.006
High	560	86.4 (81.5 to 90.1)	
Location			
Upper	211	94.1 (88.8 to 97)	0.086
Lower	499	87.1 (82 to 90.8)	
Sex			
Male	360	88.3 (82.4 to 92.3)	0.462
Female	350	90.1 (84.6 to 93.7)	
Size, cm			
< 5	510	93.7 (89.4 to 96.3)	
> 5	200	78.3 (69.3 to 84.9)	< 0.001

*Log-rank test.
CI, confidence interval; DSS, disease-specific survival; s.c, superficial.

Table VI. Univariate analysis for predicting local recurrence.

Variable	n	5 yr-LRFS, % (95% CI)	p-value*
Age, yrs			
> 60	407	86.7 (81.5 to 90.6)	
< 60	303	91.1 (85.5 to 94.7)	0.097
Depth			
s.c	429	88.8 (83.5 to 92.5)	
Deep	281	88.1 (82.4 to 92.0)	0.302
Grade			
Low	160	90.8 (82.3 to 95.3)	
High	560	88 (83.7 to 91.2)	0.242
Location			
Upper	211	89.2 (82.1 to 93.6)	
Lower	499	88.3 (83.6 to 91.7)	0.813
Sex			
Male	360	88.5 (82.9 to 92.3)	
Female	350	88.6 (83.1 to 92.4)	0.981
Size, cm			
< 5	510	93.6 (89.7 to 96.1)	
> 5	200	75.8 (66.7 to 82.8)	< 0.001
Margin			
Intralesional	30	68.8 (46.5 to 83.3)	
Marginal	57	88.2 (69.8 to 95.7)	
Wide	623	89.7 (85.7 to 92.5)	< 0.001
Rx			
Yes	72	81.1 (67.4 to 89.5)	
No	638	89.4 (85.6 to 92.3)	0.041

*Log-rank test.
CI, confidence interval; LRFS, local recurrence-free survival; Rx, radiotherapy; s.c, superficial.

Discussion

In this study, we found that UE often required reconstruction. We found no significant difference in survival and local control in the propensity score weighted cohort, although before propensity score matching, the patients who underwent additional excision after UE had better DSS than those who underwent PE. Generally, UE occurs in small and superficial STSs.[3,11] In fact, tumour size and depth were related to the incidence of UE before propensity score matching in our study. Several authors have commented on the high rates of limb reconstruction needed after additional excision, although there are few reports comparing the reconstruction rate between patients who underwent additional excision after UE and PE.[12,13] In our study, the patients who underwent additional excision after UE had a higher risk of reconstruction (odds ratio 1.6; 95% CI 1.180 to 2.180). In many situations, the mainstay of further treatment will be a wide re-excision, taking generous margins around the previous excision cavity and often removing the deep fascia as a relatively impermeable deep barrier.[2–5] Another problem with UE is that they are often carried out through inappropriate approaches (e.g. transverse incisions), and may be accompanied by the insertion of a drain, which further extends the field of contamination,[3] and may well lead to plastic surgical reconstruction.

It is generally accepted that the main risk factors for survival in STSs are tumour grade, size, depth, and patient age.[14,15] There are several papers which have compared outcomes in patients who underwent UEs.[4,9,13] The general consensus from these papers is that, compared to age and matched case controls, there is little difference overall, as patients with UEs tend to have smaller and more superficial tumours, which are known to have a better prognosis.[3] Smolle et al,[9] in a large study using propensity scores, showed that UE did not seem to adversely affect prognosis. Zaidi et al[4] also reported that UE was not associated with worse prognoses compared with PE. We also found that after propensity score matching, there was no difference in survival between the patients who underwent additional excision after UE and PE. Clearly, the aim of wide re-excision is to eventually obtain clear margins to minimize the risk of local recurrence. Numerous authors have reported the rate of local recurrence after wide re-excision, with results ranging from 5% to 45% at five years.[3–10,12,13]

In our study, we found that the five-year LRFS rate was 89.3%. A wide surgical margin was acquired in 307 (86.5%) out of 355 patients who underwent additional excision after UE. Therefore, additional excision played an important role in local control. In Japan, it is not common to consider adjuvant radiotherapy when the wide surgical margin is acquired and 10.1% of our patients who had undergone additional excision received adjuvant radiotherapy. Zaidi et al[4] performed propensity score matching and reported that UE was associated with earlier local recurrence in patients with high-grade STSs. However, patient characteristics such as age and tumour size and depth were not described. We believe that the additional excision with a wide margin played an important role in local control.

There were limitations to our study. First, it was a retrospective study. Second, a large number of patients who underwent PE were excluded after propensity matching due to the small number of patients who had had additional excision after UE. Furthermore, the follow-up period was short, only 36 months. However, to our knowledge, this is the largest series of UE and PE reported in the literature.

In conclusion, patients with STS of the limb who had additional excision after UE did not experience either a higher mortality or local failure compared to those who underwent PE. However, reconstruction needs to be considered when additional excision is performed. From the patient's point of view, a planned excision was better than undergoing two operations (UE and additional excision) because of less time in hospital and away from work, and was overall more cost-effective.[16] Therefore, we suggest that education of medical students and surgeons concerning STSs during training is essential to ensure awareness and for the correct diagnostic procedures to be performed.

Take home message

- The patients with soft-tissue sarcomas of the limb who underwent additional excision after unplanned excision (UE) did not experience higher mortality and local failure than those who underwent planned excision (PE).
- However, reconstruction may be required when additional excision is performed; furthermore, from the patient's point of view, PE is better than UE and additonal excision.

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This study was approved by the Clinical Research Ethics Review Committee of Mie University Hospital (H2020-144).

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