

Clinical Outcomes of Unplanned Soft Tissue Sarcoma excision in Comparison with Primary Planned Excision at Sarcoma Center; The Impact of Residual Tumor in Re-Excision Specimen

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Abstract (723 words):

Background:

Unplanned excision (UPE) is a common issue in soft tissue sarcoma treatment, but controversy still remains concerning its adverse effects on clinical outcomes. Some papers have reported even favorable patient survivals for UPE. However, different backgrounds should be considered because UPE tends to occur more often in superficial and small lesions. Residual tumor (ReT) after UPE has been revealed as an independent risk factor for local recurrence, but its correlation with mortality is uncertain. As such, further investigation is required regarding the effect of ReT after UPE on clinical outcomes.

Questions/Purposes:

The aims of this study are to report clinical outcomes of UPE for soft tissue sarcomas in comparison with planned excision (PE) at specialized sarcoma center in similar patient background, and to clarify clinical impacts of UPE itself and ReT after UPE.

Patients and Methods:

Soft tissue sarcoma patients who underwent definitive surgery at our institution in 1996–2012 were reviewed. Our standard treatment for soft tissue sarcomas has been wide resection following pre-operative radiotherapy of 50.4Gy/28Fr with adjuvant chemotherapy for specific subtypes such as Ewing's sarcoma, extra-osseous osteosarcoma and rhabdomyosarcoma; however, amputation was performed if limb-sparing surgery is unfeasible.

The inclusion criteria of this study were non-metastasis at the first presentation and at least 2 years of follow-up. A total of 451 eligible cases (median follow-up for survivors: 72.6 months) were divided into UPE and PE groups, and Kaplan-Meier survivals, including disease-specific survival (DSS), metastasis-free survival (MFS), and local-recurrence-free survival (LRFS), for all cases and accumulative amputation rate for extremity cases, were compared between these two groups using log-rank test and Fisher's exact test, respectively. For patient background standardization, American Joint Committee on Cancer (AJCC) TNM staging version 7 was used. Then, Cox regression analysis using backward elimination method was

performed to identify risk factors for lower DSS, MFS, and LRFS in the cohort of all the 451 patients. In this Cox analysis, the age and gender of patients, size, location, depth, and FNCLCC grade of tumors, reception of pre- or post-operative radiotherapy and neo-adjuvant or adjuvant chemotherapy, and UPE itself were thought possible factors.

UPE cases were further classified into two subgroups regarding ReT in re-excision specimen. The survivals and amputation rate were compared between these two subgroups. Then, instead of UPE itself in the aforementioned Cox analysis, ReT status (UPE with ReT, UPE without ReT, or PE) was included to evaluate the impact of ReT after UPE.

All statistic analyses were conducted using SPSS® version 17 (SPSS Inc., Chicago, IL, USA). A p -value of 0.05 or less was regarded as significant.

Results:

Clinical outcomes of UPE compared to PE

One-hundred-and-sixty-one UPE cases were identified. The AJCC stages for UPE and PE were significantly different, with 47 and 56 cases (stage IA+IB), 80 and 110 cases (stage IIA+IIB), and 34 and 124 cases (stage III), respectively ($p < 0.001$). Although there was no significant difference, UPE tended to have lower disease-specific survival (DSS) than PE (5-year DSS: 80.3% vs. 84.2% at stage II, 57.5% vs. 67.7% at stage III; **Figure 1b**). The local-recurrence-free survivals (LRFSS) were significantly different at stage I ($p = 0.037$, 84.2% vs. 98.2% at 5 years; **Figure 1d**). The amputation rate was slightly higher for UPE than PE in each stage. Cox analysis revealed UPE as an independent risk factor for poorer DSS with hazard ratio (HR) of 1.66 (reference: PE, 95%CI: 1.07–2.58), along with size, age, and FNCLCC grading.

Comparison between UPE with ReT and UPE without ReT

Of 161 UPE cases, 88 cases (55%) had residual tumor in re-excision specimen. DSS, MFS, and LRFS for UPE with ReT were significantly worse than UPE without ReT at each stage (**Figure 2**).

Impact of ReT on DSS and LRFS

The HRs of UPE with ReT for lower DSS and LRFS were 2.20 (reference: PE, 95%CI: 1.39–3.46) and 2.15 (reference: PE, 95%CI: 1.23–3.77), respectively. The extremity amputation rate of UPE with ReT (13/68, 19.1%) was significantly higher than PE (17/232, 7.3%) according to Fisher's exact test ($p = 0.008$).

Conclusions:

- (1) Unplanned excision of soft tissue sarcomas can compromise not only local control but also patient survival.
- (2) The clinical impact of residual tumor after unplanned excision is significantly large. Approximately half of the unplanned resections fall into this category.
- (3) Therefore, sarcoma patients should be treated at specialized sarcoma centers without unplanned excision.

Figure 1. The comparison of disease-specific survivals (DSSs) and local-recurrence-free survivals (LRFs) between unplanned excision (UPE) and planned excision (PE). **a:** DSS of all the cases, **b:** DSS of AJCC stages IA+IB (**b1**), IIA+IIB (**b2**), and III (**b3**), **c:** LRFs of all the cases, and **d:** LRFs of AJCC stages IA+IB (**d1**), IIA+IIB (**d2**), and III (**d3**)

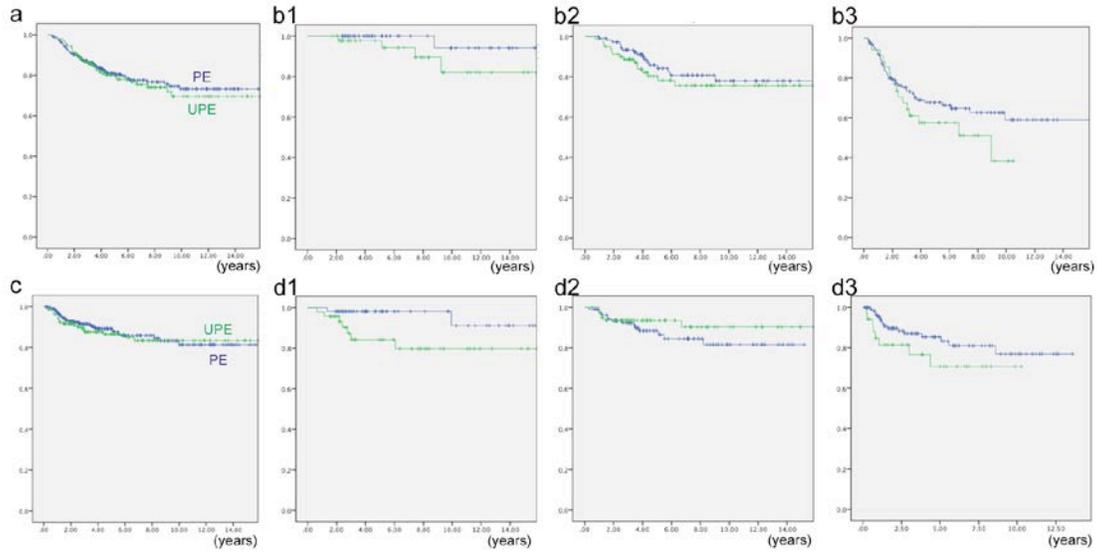


Figure 2. The comparison of DSSs and LRFs between UPE with residual tumor (ReT) and UPE without ReT. **a:** DSS of all the cases, **b:** DSS of AJCC stages IA+IB (**b1**), IIA+IIB (**b2**), and III (**b3**), **c:** LRFs of all the cases, and **d:** LRFs of AJCC stages IA+IB (**d1**), IIA+IIB (**d2**), and III (**d3**)

