

ORIGINAL ARTICLE

Factors associated with reduced functional outcome and quality of life in patients having limb-sparing surgery for soft tissue sarcomas – a national multicenter study of 128 patients

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ABSTRACT

Background: Limb-sparing surgery for sarcomas has become possible in most cases. However, the impact of the procedure on the functional outcome has only been investigated in a few studies. The aim of this study has been to identify tumor- and patient-related factors associated with reduced functional outcome and quality of life after limb-sparing surgery in soft tissue sarcoma patients.

Material and methods: In total, 128 patients (mean age = 58, female/male = 54/74) who were treated with limb-sparing surgery without bone resection for soft tissue sarcomas in Denmark during the period 1 January 2009 to 31 December 2011 were included. Patients were asked to participate at least one year after surgery, and patients who had experienced local recurrence or metastatic disease were excluded. The Toronto Extremity Salvage Score (TESS) measured functional disability, while the Musculoskeletal Tumor Society Score (MSTS) measured functional impairment. European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 measured quality of life. Tumor- and patient-related factors (age, gender, tumor depth, tumor size, malignancy, comorbidity, location, and radiotherapy) were extracted from the Danish National Sarcoma Database. Wilcoxon rank-sum test and Kruskal-Wallis were used for univariable analysis. Adjusted odds ratios were estimated by using multiple logistic regression models.

Results: In the multiple regression analysis, it was found that female gender ($p = 0.03$), lower extremity tumors ($p < 0.01$) and radiotherapy ($p = 0.02$) resulted in an increased risk of a lower TESS score. Initial reduced postoperative function was found to be associated with a lower functional outcome. Patients with reduced functional outcome have increased risk for reduced quality of life ($p < 0.01$).

Conclusion: The results of this study show that patient- and tumor-related factors have an important role in the functional outcome.

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Approximately 1% of incident cancers in Denmark are soft tissue sarcomas. These tumors represent a heterogeneous group of neoplasms which are almost equally distributed in gender and arise in all age groups, however, the risk increases with age [1]. Amputation was once the standard treatment of sarcomas in the extremities, however, due to the advances in diagnostics and adjuvant therapies, limb-sparing surgery for soft tissue sarcomas is now state-of-the-art for the majority of patients leading to unchanged local control of disease and survival [2]. Limb-sparing surgery in the extremities includes resection of structures in the extremities and may entail risks of reduced functional outcome and quality of life.

Only few studies have addressed functional outcome in sarcoma patients. Davis et al. [3] have reported significant prognostic factors for functional outcome to be tumor size, bone resection, motor nerve resection, complications, and malignancy in 172 patients with lower limb soft tissue sarcomas.

In a study, by Heaver et al. [4], including 198 patients operated with limb-sparing surgery for sarcomas or giant cell tumors, female gender, increasing age, increasing BMI, smoking, and bone resection were associated with functional outcome. Also, in a study of 172 patients by Davidge et al. [5] it was found that patients' expectations on the postoperative functional outcome significantly influenced the functional outcome obtained after surgery. Amputation of the extremities impaired functional outcome as opposed to limb-sparing surgery, whereas quality of life did not seem to be impaired [6–8].

In a small study ($n = 36$) by Paredes et al. [9] no significant prognostic factors for quality of life in sarcoma patients were found. In contrast to this, Schreiber et al. [10] found in a study including 100 soft tissue sarcoma patients that functional outcome was significantly associated quality of life.

Nevertheless, all the above-mentioned studies concerning functional outcome and quality of life either included

patients with primary and local recurrence sarcomas and/or bone and soft tissue sarcomas. This increases the heterogeneity of an already widely heterogenic population.

In order to minimize heterogeneity, we only included patients treated with initial limb-sparing surgery for soft tissue sarcomas in the extremities without bone resection/amputation. We investigated whether patients' age, gender, comorbidity, radiotherapy, tumor location, tumor depth, tumor size, tumor grade, and postoperative physiotherapy have an impact on functional outcome and quality of life.

Material and methods

This is a cross-sectional study including all soft tissue sarcoma patients treated with first-time limb-sparing surgery without bone resection in Denmark from 1 January 2009 to 31 December 2011. All patients with at least one-year follow-up after surgery were invited to participate in the study when visiting the outpatient clinic in the period 1 April 2012 to 28 February 2013.

Study population

Postoperatively, all soft tissue sarcoma patients received individual instructions for physical training and restrictions for daily activities after surgery. In addition, the surgeon assessed whether the patient needed further rehabilitation. Most of

the patients were expected to complete physical rehabilitation without further help. A smaller group of the patients with major physical impairments were referred, by the surgeon, to individual training by a physical therapist. Some of the patients were referred to radiotherapy based on a multidisciplinary conference. All patients returned to the outpatient clinic every 3–6 months in order to be examined for recurrent disease.

Patients in the study were identified in the Danish Sarcoma Database (DSD) established in January 2009 as a nationwide and population-based clinical database. The DSD contains data concerning treatment, tumor topography, and morphology data. The DSD has almost 100% data completeness for incident sarcomas with topography in the extremities [11].

Patient inclusion criteria for the study were initial limb-sparing surgery for soft tissue sarcoma in the extremities without bone resection, aged 16 or more at the date of diagnosis and Danish speaking. A total of 311 patients were identified meeting the inclusion criteria. Exclusion criteria were competitive disease affecting function, recurrence, metastasis from the sarcoma, second active malignant disease, and replacement surgery in the extremity, where the sarcoma was located. Competitive diseases were defined as severe neurological diseases (dementia, ICD-10 code: DF039, Parkinson DG209) severe arthritis (DM199), pseudo arthrosis (DM841) and severe cardiopulmonary diseases (DI519 and DJ894). A flowchart (Figure 1) describes the final sample of 128 patients included in the study.

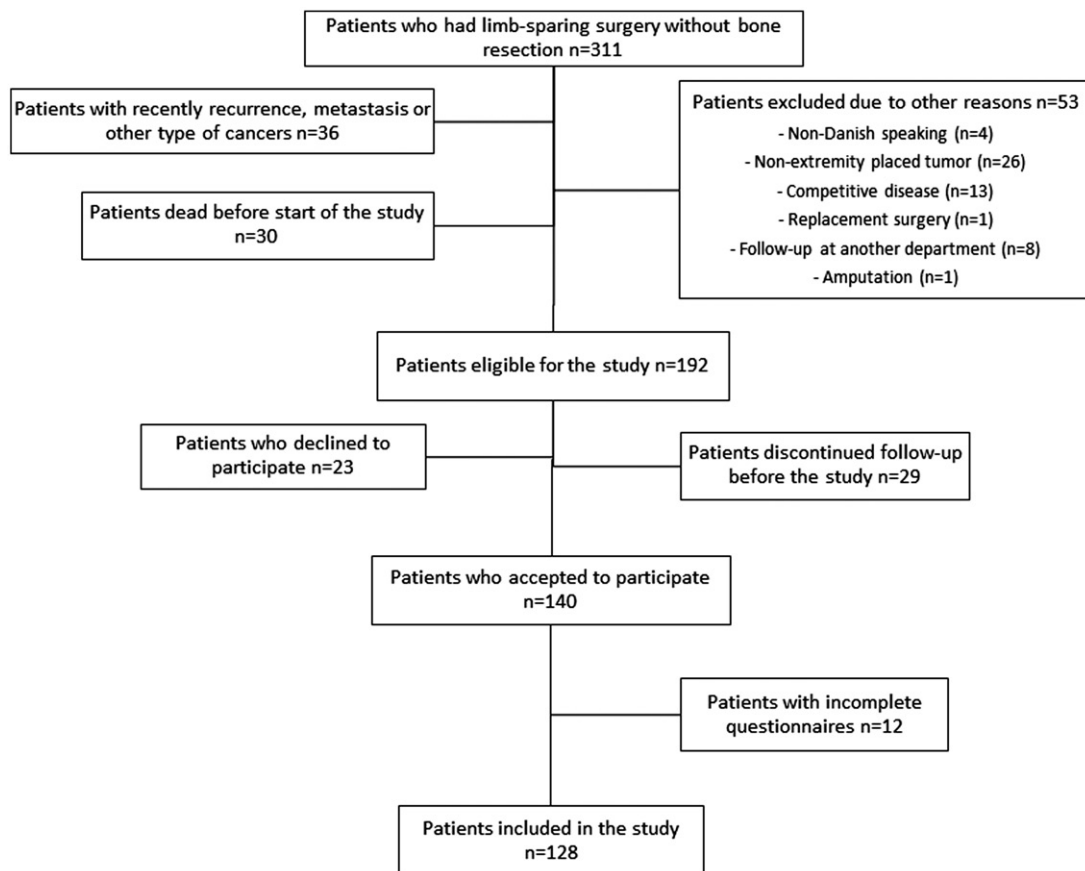


Figure 1. Flowchart for patients (age ≥ 16) operated 1–5 years after limb-sparing surgery for soft tissue sarcomas in the period, Denmark, 2009–2012.

Outcome measurement

The patients were asked to complete three questionnaires in the outpatient clinic.

The Toronto Extremity Salvage Score (TESS) questionnaire is a sarcoma-specific Patient Report Outcome Measurement (PROM) for patients with sarcomas in the extremities. The TESS has been designed and validated to assess the physical function in musculoskeletal tumor patients aged 12–85 years [12]. The TESS has been translated into Danish and validated for sarcoma patients [13].

The Musculoskeletal Tumor Society Score (MSTS) is a six-item questionnaire with three overall items and three extremity-specific items. The MSTS was the first disease-specific measurement for the patients with sarcomas in the extremities. It was revised several times, and though its properties have never been fully tested in terms of reliability or validity it is a widely used functional outcome questionnaire in the sarcoma research community [14].

The QLQ-C30 questionnaire was used to measure the global quality of life. QLQ-C30 is a 30-item PROM based on cancer patients' experience in the previous week [15]. The QLQ-C30 has been validated in the Danish population [16].

Each of the above-mentioned measurements ranged from zero to 100, where higher scores indicate higher level of functional outcome or quality of life.

Patient- and tumor-related factors

Patient- and tumor-related data was gathered from DSD. The patients were asked if they had received physical therapy after the limb-sparing surgery. Possible factors associated with functional outcome and quality of life were the age of the patient when completing the questionnaires (young vs. old with the median age set as the dividing point), gender (male vs. female), tumor depth (subcutaneous vs. subfascial), tumor size (≤ 5 cm vs. > 5 cm), malignancy [low malignant (grade 1) vs. high malignant (grade 2 and 3)], comorbidity (presence or absence of any comorbidity according to the Charlson Comorbidity Index), anatomical location (upper vs. lower extremities), radiotherapy (yes or no) and physiotherapy (no therapy vs. restricted amount vs. several fully guided physiotherapy sessions). Functional outcome was also considered to possibly be associated with quality of life.

Statistics

Data was analyzed in Stata, version 12.1. Student's *t*-test was used to measure any differences in age between the two groups, and a χ^2 -test was used to test for distribution of gender between the two groups. The patient's age in the excluded group is defined as the age of the patient, when the list of eligible patients was extracted from the DSD. The data from the TESS, MSTS and QLQ-C30 questionnaires was found to be non-normally distributed. The patient- and tumor-related variables were all evaluated by non-parametric tests (Wilcoxon rank-sum test or Kruskal-Wallis test) for univariable analysis as independent factors for each outcome and the median and interquartile range

(IQR) calculated for each of them. Spearman's correlation coefficient was used to describe the relation between functional outcome and quality of life. Multiple logistic regressions were used for the multivariable analysis, as the data did not meet the requirements for normal distribution. It was necessary to convert the TESS, MSTS, and QLQ-C30 scores to binomial outcome (high and low scores) by using the median score as a dividing point for each score. Multiple logistic regressions were done to identify the functional outcome for possible influence on quality of life when the other factors were included. Each multiple logistic analysis generated an odds ratio (OR) with a 95% CI. *p* Values below 0.05 were considered significant.

Ethical considerations

This study was reported to and approved by the Danish Data Protection Agency (file no. 1-16-02-108-12). In compliance with ethical practices, we developed information material concerning participation in the study, which was handed out to patients concurrently with an oral information procedure. Patients were asked for written informed consent in order to review patient records, if deemed necessary following assessment of records in the DSD.

Results

There was no significant difference between the excluded and included patients in the distribution of age and gender. The participation rate was 66% (128 included patients of 192 eligible patients). Median age of the 128 participating patients was 61 years (IQR 47–70), with slightly more men enrolled (58%). The median tumor diameter was 6 cm (IQR 3–13), the majority of tumors were deeply located (59%), highly malignant (57%), and in the lower extremities (70%). Comorbidity was observed in one of four patients (24%). Most patients received neither radiotherapy (71%) nor physiotherapy (62%). The median follow-up time was 727 days (IQR 492–978).

The results of the univariable analysis of the tumor- and patient-related factors' influence on the TESS, MSTS, and QLQ-C30 showed that the overall median TESS score was 98 (IQR 85–100), the overall median MSTS score was 97 (IQR 82–100) and the overall median QLQ-C30 score was 88 (IQR 75–100) (Table 1).

For the TESS score, in the multiple logistic regression analysis we found female gender, anatomical location in the lower limb, radiotherapy, and physiotherapy to be significantly associated with reduced outcome. For the MSTS score we found physiotherapy to be significantly associated with reduced outcome. We did not find any significant association with the QLQ-C30 score (Table 2).

We found a significant Spearman's rank correlation coefficient of 0.62 ($p < 0.01$) between functional outcome, measured by TESS, and quality of life, measured by QLQ-C30. The Spearman's rank correlation coefficient between functional outcome, measured by MSTS, and quality of life was 0.60 ($p < 0.01$).

Table 1. The Median outcome score in a univariable analysis.

	No.	TESS: Median (IQR)	<i>p</i> Value	MSTS: Median (IQR)	<i>p</i> Value	QLQ-C30: Median (IQR)	<i>p</i> Value
Age							
Young (≤ 61 years)	68	98 (86–100)		93 (78–100)		83 (67–100)	
Old (> 61 years)	60	98 (84–100)	0.93	97 (83–100)	0.18	92 (75–100)	0.47
Gender							
Male	74	100 (88–100)		97 (87–100)		92 (83–100)	
Female	54	93 (81–99)	0.01*	90 (77–97)	0.03*	83 (67–100)	0.03*
Depth							
Subcutaneous	53	100 (92–100)		97 (90–100)		92 (83–100)	
Subfascial	75	94 (78–100)	0.01*	90 (70–97)	$< 0.01^*$	83 (67–100)	0.17
Size							
≤ 5 cm	62	100 (90–100)		97 (87–100)		92 (75–100)	
> 5 cm	66	93.5 (78–100)	0.01*	93 (77–97)	0.02*	83 (67–100)	0.17
Malignancy							
Low malignancy	55	99 (90–100)		97 (87–100)		92 (75–100)	
High malignancy	73	98 (77–100)	0.03*	93 (70–100)	0.09	83 (67–100)	0.30
Radiotherapy							
No Comorbidity	97	99 (88–100)		97 (83–100)		92 (75–100)	
Comorbidity	31	89 (73–99)	0.01*	90 (70–100)	0.32	83 (58–100)	0.04*
Radiotherapy							
Upper extremity	38	100 (99–100)		97 (90–100)		100 (83–100)	
Lower extremity	90	94 (81–99)	$< 0.01^*$	93 (77–100)	0.01*	83 (67–100)	0.10
Radiotherapy							
No radiotherapy	91	99 (91–100)		97 (87–100)		92 (75–100)	
Radiotherapy	37	81 (68–98)	$< 0.01^*$	87 (67–97)	0.01*	83 (67–100)	0.07
Physiotherapy							
None	79	99 (91–100)		97 (88–100)		92 (75–100)	
Instructions	26	94 (73–100)	0.01*	93 (80–100)	0.01*	83 (67–100)	0.08
Physiotherapy	23	86 (78–98)		87 (67–90)		83 (67–92)	

IQR: Interquartile range.

*: statistical significance ($p < 0.05$).**Table 2.** Multiple logistic regression analysis for patient- and tumor-related factors influence on the TESS, MSTS and QLQ-C30 score.

	TESS score			MSTS score			QLQ-C30 score		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age									
Young	1			1			1		
Old	1.1	0.4–3.4	0.82	0.6	0.2–1.5	0.25	0.9	0.4–2.0	0.73
Gender									
Male	1			1			1		
Female	3.0	1.1–8.0	0.03*	2.1	0.9–4.8	0.09	1.8	0.8–3.9	0.13
Tumor depth									
Subcutaneous	1			1			1		
Subfascial	0.8	0.3–2.3	0.66	1.6	0.6–4.2	0.30	0.7	0.3–1.8	0.47
Tumor size									
≤ 5 cm	1			1			1		
> 5 cm	2.1	0.7–6.0	0.18	1.1	0.4–2.9	0.79	1.4	0.6–3.4	0.45
Malignancy									
Low malignancy	1			1			1		
High malignancy	0.4	0.1–1.3	0.13	1.0	0.4–2.6	0.99	0.8	0.3–1.8	0.57
Comorbidity									
No	1			1			1		
Yes	3.0	0.9–9.9	0.08	1.5	0.6–4.3	0.42	2.0	0.8–5.3	0.14
Anatomical location									
Upper extremity	1			1			1		
Lower extremity	13.4	4.0–43.4	$< 0.01^*$	1.9	0.8–4.7	0.16	1.4	0.6–3.2	0.43
Radiotherapy									
No	1			1			1		
Yes	4.9	1.2–19.5	0.02*	2.2	0.8–6.7	0.15	1.8	0.7–4.8	0.26
Physiotherapy									
Instructions vs. None	1.6	0.5–5.2	0.42	1.4	0.5–3.9	0.51	1.3	0.5–3.6	0.57
Physiotherapy vs. None	9.0	1.9–42.7	0.01*	5.2	1.5–18.6	0.01*	2.1	0.7–5.9	0.19
Physiotherapy vs. Instructions	5.6	1.0–32.5	0.06	3.7	0.9–16.4	0.08	1.5	0.4–5.5	0.51

OR: Odds ratio; 95% CI: 95% confidence interval. *: statistical significance ($p < 0.05$).

Table 3. Multiple logistic regression analysis for functional outcomes influence on the quality of life measured by QLQ-C30.

	Odds ratio (OR)	95% Confidence interval (95% CI)	p Value
TESS score			
High score	1		
Low score	14.3	4.6–45.1	<0.01*
MSTS score			
High score	1		
Low score	8.8	3.5–22.1	<0.01*

*: statistical significance ($p < 0.05$).

Multiple logistic regression analysis for the functional outcomes' influence on quality of life showed that a low TESS or MSTS score is most likely to result in a significantly lower quality of life (Table 3).

Discussion

The results of this study suggest that the initial postoperative functional outcome is the best indicator for the final functional outcome. Furthermore, we found gender, radiotherapy, and anatomical location to be significantly associated with functional outcome expressed by the TESS score. Functional outcome was associated with quality of life.

Our finding that female gender is associated with a lower TESS score after limb-sparing surgery correlate with a newer finding [4], but is in contrast to an older study [3]. In a normal population it has been ascertained that the TESS is not sensitive to gender [17], indicating female gender to be a true negative prognostic factor for lower TESS score on soft tissue sarcoma patients. It is interesting that females seem to have a decreased functional outcome measured by the TESS, while there is no difference between male and female in functional outcome measured by the MSTS. The study by Heaver et al. [4] argues that females compared to males have less muscle mass and strength, which can have an effect on the rehabilitation process due to difficulties in compensating.

We have found radiotherapy to be significantly associated with reduced functional outcome measured by the TESS. This has not previously been ascertained in other studies [3,18]. Furthermore, pre- or postoperative radiotherapy had no significant difference in effect on functional outcome in a randomized study of 190 soft tissue sarcoma patients [19]. Although, different effects of radiotherapy may be caused by diverse indications for giving radiotherapy, or it could be related to the radiation dose. However, radiotherapy is typically given to patients having subfascial tumors and tumors located close to vital structures such as vessels or nerves, where the surgical procedure itself may have a negative impact on the functional outcome.

Patients with lower extremity tumors have been shown to have a reduced functional outcome compared to patients with upper extremity tumors [19]. We found similar results for functional outcome measured by the TESS, although we did not find any difference between upper and lower extremity tumors' effect on functional outcome measured by the MSTS.

Tumor size has been determined as a significant prognostic factor for functional outcome in previous studies, as an increase in tumor size is seen to result in a reduction of

functional outcome [3,18–20]. The absence of this impact in our study could be a result of dichotomizing the size into groups with smaller tumors (<5 cm) and larger tumors (>5 cm) [21].

We did not find age to be significantly associated with reduced functional outcome as previous studies did [4,18,19]. In one study the TESS questionnaire was found to be age sensitive in a healthy population, suggesting age to be considered as a confounder [17]. Further studies should investigate the relation between age and functional outcome.

Tumor depth (subcutaneous/subfascial) was determined not to be related to functional outcome in this study, however, previous studies have shown that it could be a significant prognostic factor for functional outcome measured by the TESS [18,22]. However, some patients included in these studies had undergone bone resection, and thus the possibility of more extensive surgery compared to only soft tissue resection. Therefore, our results are more reflective of the functional outcome for sarcomas exclusively involving soft tissue in the extremities.

In this study, we used the referral to physiotherapy as a surrogate for the initial postoperative functional outcome, as surgeons only referred to physiotherapy if they found it necessary. Our results indicate that the initial postoperative functional outcome is an indicator of the final functional outcome, which correlates with a previous study that found baseline function to be significant prognostic factor [18]. It is, however, evident that patients, even though they have received physiotherapy, have not gained the same level of function as the patients who did not need any physiotherapy. A study compared a small group of patients who had limb-sparing surgery in the lower extremities with normal subjects, and found that even though the restoration of gait after surgery is impressive, it is not complete and can break down under visual and cognitive impairment [23]. We know from other cancer patients that progressive resistance training has a significant effect on functional outcome and quality of life [24].

Our finding of low functional outcome as having a negative influence on quality of life was in agreement with previous studies [3,7,10]. This indicates that preservation of functional outcome without compromising survivability should be of vital concern for the treating physician or surgeon when treating a patient for soft tissue sarcomas. The finding that reduced function after amputation was not associated with quality of life indicates that the feeling of getting rid of the sarcoma makes it easier to cope with the function deficit [7,8,25].

The TESS and MSTS were found to result in different functional outcomes. A study comparing TESS with SF-36 and the 1987 and 1993 versions of the MSTS concluded that when choosing a functional outcome measurement for extremity sarcoma patients, the TESS has superior measurement properties compared to the other questionnaires [12]. However, others have argued that the TESS measures the patients' ability to cope, whereas the MSTS estimates the impairment of function and thus measures different aspects of the functional outcome [25]. Consequently, the TESS is superior at measuring physical disability. The MSTS also measures other aspects

such as pain and acceptance of treatment and is partially patient- and physician-reported. Therefore, the utilization of the TESS does not exclude the use of the MSTs. The even stronger relation between the TESS and quality of life could possibly be an expression of the patients' inability to cope.

One of the strengths in this study is the attempt to minimize the heterogeneity in soft tissue sarcoma patients by excluding bone resection and competitive diseases which may affect the function.

This study has some limitations, first the fact that some of the data is gathered retrospectively. Second, the relatively high number of non-participating patients is a potential bias, particularly as no reasons were given by patients who declined to participate and patients who discontinued follow-up. It can be contemplated patients that were not affected by their surgery did not see the need to participate, or that patients who were severely affected did not have the energy to participate. In addition to this, several patients were excluded by preset exclusion criteria, which could be a potential bias; however, none of the exclusion criteria (except other cancers) has a causal relation to soft tissue sarcomas. Finally, we have to address the issues with including radiotherapy as an independent variable. The indication of radiotherapy in the treatment strategy is determined by the individual sarcoma center, therefore the radiotherapy variable may not be entirely independent and there is a potential bias issue. However, in order to compare with other studies [3,18], we chose to include radiotherapy as an independent variable. It is also important to consider a difference in surgical procedures between different sarcoma center analyzing data.

This study has found significant associations between functional outcome and factors such as gender, anatomical location (upper vs. lower extremity), and radiotherapy. It is, however, important to further investigate the possible causal relation between prognostic factors and functional outcome. This knowledge can be used when assessing the postoperative rehabilitation needs and the possibility of individualizing the rehabilitation of soft tissue sarcoma patients.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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