Effect of surgical margins on prognosis in aggressive fibromatosis: A single-institutional analysis of 90 patients

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Abstract. The treatment of aggressive fibromatosis poses a therapeutic challenge in an interdisciplinary setting. The extent of surgical resection is still discussed controversially. The present retrospective analysis aimed to determine prognostic factors leading to recurrence. Between 2000 and 2014, 114 patients with aggressive fibromatosis were treated surgically at BG-University Hospital Bergmannsheil (Bochum, Germany). Univariate and multivariate analyses were restricted to 90 participants with information available on surgical margins at the initial procedure. The median follow-up time was 7.7 years. A total of 45 patients (50%) developed recurrence during follow-up. Primary tumors were resected with negative margins (R0) in 50 patients (68%) and with microscopically positive margins (R1) in 28 patients (25%). In addition, tumors in 12 patients (7%) were resected with macroscopically positive margins at the initial surgical procedure. The rates of recurrence-free survival (RFS) after 5 years were 68.8% [95% confidence interval (CI), 53.5-79.9%] in patients with R0-resected primary tumors and 34.1% (95% CI, 19.9-48.9%) in patients with R1/R2-status (P=0.001). Narrow and wide clear margins within the R0-group were not associated with significantly different outcomes. Adjuvant radiation, tumor site and patient age were not associated with a significant alteration of RFS. The current results suggest that the attainment of microscopically negative surgical margins at the initial surgical treatment is associated with a significantly improved prognosis. A conservative surgical approach involving the attainment of narrow negative margins while preserving function should be sought in patients in whom tumor resection is indicated. The decision for resection should be made interdisciplinary in each case based on tumor progression, available treatment alternatives and the decision of the informed patient.

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Introduction

Aggressive fibromatosis, also known as desmoid tumor, is a semi-malignant soft tissue neoplasm of clonal myofibroblastic origin that arises from the musculoaponeurotic structures, fascial planes and ligaments throughout the body. The incidence is estimated to be 3-4 cases/million people/year in Europe and the USA, accounting for ~3% of all soft-tissue tumors analyzed by biopsy (1,2). Aggressive fibromatosis can occur sporadically or be associated with familial adenomatous polyposis in Gardner syndrome. Among all cases of sporadic aggressive fibromatosis, >70% are associated with β-catenin mutations; however, the clinical implication of this finding has not been determined completely (3-5). Although aggressive fibromatosis does not have the ability to metastasize, it is characterized by locally aggressive growth with destructive infiltration of the surrounding tissues and high rates of local recurrence despite surgical resection, leading to significant functional impairments and morbidity.

Numerous analyses have been conducted to assess the prognostic factors that affect recurrence-free survival (RFS) in patients with aggressive fibromatosis (1,2,6-16). Among these factors, anatomical site, tumor size and patient age are considered to be the most significant for RFS (10,11). Notably, the prognostic significance of negative surgical margins on RFS remains a subject of debate, and inconsistent results have been presented in published studies investigating the clinical significance of surgical margins in aggressive fibromatosis, questioning the impact of curative surgical resection in general.

Prior to 1999, limb-sparing surgical resection with clear margins was considered the therapy of choice in the vast majority of cases, reflecting the standard approach for the treatment of soft tissue sarcomas. In 1998 and 1999, the Massachusetts General Hospital and the M.D. Anderson Cancer Center (MDACC) reported improved RFS rates for patients with negative margins, following analyses of 92 and 168 patients, respectively (6,7). Shortly afterwards, Merchant *et al* (8) analyzed the outcomes of a series of 105 surgically treated patients with primary disease at the Memorial Sloan-Kettering Cancer Center (MSKCC), and were

unable to detect any significant effect of positive margins on RFS. In 2003, Gronchi *et al* (10) from the Instituto Nazionale Tumori (INT) in Milan reported similar observations in 203 patients. A more recent analysis from the MDACC in 2007 was unable to reproduce the results from 1999, and margin positivity could no longer be substantiated as a significant prognostic factor (17). Thereafter, the MSKCC published its actualized data analyzing 495 patients, revealing no statistical association between surgical margin status and RFS (11); however, in the specific subgroup analysis of tumors measuring <5 cm, R1 margins were found to have an increased risk of local recurrence compared with R0. In 2011, a European multicenter-based study including 426 patients was unable to determine any significant differences in RFS when comparing patients with R0 and R1 margins (1).

The aforementioned findings have subsequently subverted the role of surgical resection as an initial treatment step, and have prompted the present review of our institutional experience. The aim of the current study was to identify the prognostic indicators of RFS in patients with primary aggressive fibromatosis who underwent surgical resection. The analysis focused particularly on the effect of surgical margins on disease outcome.

Patients and methods

Patients. Between June 2000 and July 2014, 114 patients with aggressive fibromatosis were treated surgically at BG-University Hospital Bergmannsheil (Bochum, Germany). Of the 114 patients, 82 presented with primary disease in our institution, while 32 patients were subsequently referred to our center following incomplete resection or the diagnosis of recurrence ≥3 months after definitive surgery on the primary tumor performed at other institutions. From this group of 114 patients, 17 patients were excluded due to the unavailability of data regarding the surgical margins of the initial surgical procedure. Furthermore, 7 patients were lost to follow-up. Thus, the current analyses were restricted to 90 participants with full information available on the surgical margins at the initial procedure. The clinicopathological characteristics of the patients are summarized in Tables I and II. Patient follow-up information was obtained from our database and from patient correspondence. The study was approved by the local ethics committee and all patients provided their written informed consent.

Treatment. The goal of surgical treatment for all patients was function-preserving and limb-sparing resection of the primary tumor with clear margins. The indication for adjuvant treatment was determined at the discretion of the interdisciplinary tumor board of our institution or the referring institutions.

A total of 27 patients received adjuvant radiotherapy following resection of the primary tumor, with a median overall dose of 59.7 Gy (range, 50.0-66.0 Gy), and a further 19 patients underwent first adjuvant radiotherapy subsequent to an initial recurrence, with a median overall dose of 53.7 Gy (range 50.0-64.0 Gy). Adjuvant non-steroidal anti-inflammatory drugs (NSAIDs) were administered following primary tumor resection in 19 patients, and a further 7 patients received NSAIDs following the initial recurrence (ibuprofen, 1,200-1,800 mg/day; or indomethacin, 150 mg/day. NSAIDs were given for a minimum of three months (range, 3-14 months). Two patients received tamoxifen following primary resection. Additionally, 4 patients were treated with imatinib and 1 patient with epirubicin.

Histopathological classification. All pathology slides were analyzed or reviewed for consensus diagnosis by experienced soft tissue pathologists.

Statistical analysis. All patients were retrospectively analyzed with regard to potential prognostic factors affecting RFS (Table I). RFS was defined as the period of time from the date of surgery for primary disease to the date of first recurrence. Survival rates were estimated according to the Kaplan-Meier method with respective 95% confidence intervals (CIs), and were compared using the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model. Variables that were associated with $P<0.10$ in the univariate analysis were included in the multivariate regression to assess independent prognostic factors for RFS. $P<0.05$ was considered to indicate a statistically significant result. All analyses were performed using Stata software (Version 11.2; StataCorp, College Station, TX, USA).

Analysis of surgical margins. In order to determine the impact of surgical resection margins on RFS, the three following variables were analyzed. In 'margin status after primary resection' (Table II), RFS was assessed with regard to the resection status that was achieved following the resection of the primary tumor in our or the referring institution. In those patients with negative margins (R0 group) after primary resection, the effect of the clear surgical margin width was assessed as 'distance of closest negative surgical margin at resection of the primary tumor (R0 group)' (Table II). The variable 'margin status after last resection in patients with ≥1 recurrence' (Table II) concerned the prognostic influence of the surgical margin status that was attained at the final resection of the recurring tumor in patients who developed ≥1 recurrence following the resection of the primary tumor.

Results

Patient characteristics and surgical margins. The median age at the time of initial recurrence was 38.7 years (range, 16.1-74.2 years). The patient group included in the analysis consisted of 37 males (41.1%) and 53 females (58.9%). Tumors were located in the lower extremities in 30 patients (33.3%), in the upper extremities in 21 patients (23.3%), in the intra-abdominal cavity in 14 patients (15.6%), in the head and neck area in 7 patients (7.8%), and in the superficial trunk in 18 patients (20.0%). During follow-up, 45 patients (50%) developed ≥1 recurrence, whereas 23 patients (25.6%) had ≥2 local recurrences (range, 2-5 recurrences). Time-to-recurrence ranged from 3 months to 14 years (median, 17 months). No patient exhibited multifocal disease. Mortality occurred in 1 (female) patient with 5 recurrences and macroscopic residual disease subsequent to the last resection, following infiltration of the internal carotid artery at 6.1 years after the primary diagnosis. Only 2 patients had Gardner syndrome.

Table I. Results of univariate analyses to determine factors predictive of recurrence-free survival in 90 patients with aggressive fibromatosis.

Variable	Total no. of patients	No. of patients with recurrences	Estimated RFS rate, % (95% CI)			P-value (log-rank)[a]
			1-year	2-year	5-year	
Patient age, years						0.794
<50	61	31	78.5 (65.9-86.9)	70.2 (56.9-80.1)	54.5 (40.4-66.6)	
≥50	29	14	86.2 (67.3-94.6)	57.7 (37.6-73.4)	46.6 (27.6-63.6)	
Gender						0.315
Male	37	22	83.5 (67.0-92.2)	72.2 (54.4-84.0)	59.2 (40.7-73.7)	
Female	53	23	79.2 (65.7-87.9)	62.3 (47.8-73.8)	47.8 (33.6-60.7)	
Tumor site						0.387
Extremity	51	21	78.4 (64.4-87.4)	58.5 (43.7-70.6)	40.0 (25.9-53.8)	0.074[b]
Abdominal cavity	14	10	85.7 (53.9-96.2)	78.6 (47.2-92.5)	78.6 (47.2-92.5)	0.147[c]
Head/neck	7	3	57.1 (17.2-83.7)	57.1 (17.2-83.7)	57.1 (17.2-83.7)	0.530[d]
Truncal wall	18	11	94.1 (65.0-99.1)	82.4 (54.7-93.9)	63.5 (35.9-81.8)	0.241[e]
Tumor size, cm						0.799
<5	26	15	84.3 (63.3-93.8)	63.5 (41.5-79.1)	59.0 (37.1-75.6)	
≥5	64	30	79.7 (67.6-87.7)	67.2 (54.2-77.2)	50.3 (37.2-62.0)	
Previous history of trauma at disease site						0.296
Yes	15	5	80.0 (50.0-93.1)	53.3 (26.3-74.4)	45.7 (20.1-68.3)	
No	75	40	81.2 (70.3-88.4)	68.9 (57.0-78.1)	53.3 (40.8-64.3)	

[a]Log-rank test for equality of survivor functions; [b]Extremity vs. non-extremity tumors; [c]Abdominal cavity vs. non-abdominal cavity tumors; [d]Head/neck vs. non-head/neck tumors; [e]Truncal wall vs. Non-truncal wall tumors. RFS, recurrence-free survival; CI, confidence interval.

Plastic surgical tissue transfer was necessary in 21 patients following the resection of the primary tumor; specifically, 19 patients with soft tissue defects received local flaps, while 2 patients with mere skin defects were transplanted with split-thickness skin grafts. The R0 rates were 52.2% (36/69) for patients with primary closures and 66.7% (14/21) for patients who underwent plastic surgical tissue transfer.

Follow-up and survival. As of August 2014 (cut-off date), the reverse Kaplan-Meier estimate of median follow-up time following primary resection was 7.7 years (95% CI, 5.6-8.1 years) (18). The Kaplan-Meier-estimated rates of RFS for the entire group were 52.2% (95% CI, 40.9-62.3) at 5 years and 42.7% (95% CI, 28.8-55.9) at 10 years.

Univariate analysis of survival. In the entire series, patient age and gender were not found to be significant predictors of RFS (Table I). Similar to findings in previous studies (1,17), tumors arising in the extremities appeared to have a poorer prognosis compared with lesions at other sites [5-year RFS rates, 40.0% (95% CI, 25.9-53.8%) vs. 68.0% (95% CI, 50.4-80.4%), respectively]; however, this survival distribution failed to reach statistical significance in the univariate analysis (P=0.074). In contrast to the results of previous studies, tumor size did not exhibit any effect on RFS in the present series.

Univariate analysis identified only the surgical margin status attained at the resection of the primary tumor as a significant predictor of outcome. Patients who underwent complete R0 resection of their primary tumor had a significantly improved outcome (5-year RFS rate, 68.8%; 95% CI, 53.5-79.9%) when compared with patients in whom incomplete R1 or R2 resection was achieved (5-year RFS rate, 34.1%; 95% CI, 19.9-48.9%; P=0.001 vs. R0) (Table II; Fig. 1A). Furthermore, R0 status was associated with a more favorable RFS rate when compared only with R1 status (5-year RFS rate, 28.6%; 95% CI, 13.5-45.6%; P<0.001 vs. R0) (Fig. 1B). R1 and R2 status had comparably diminished RFS rates (P=0.341). Notably, surgical margin width did not influence the RFS rates in patients who underwent an R0 resection of their primary tumor (≤1 vs. >1 mm, P=0.301; and ≤5 vs. >5 mm, P=0.245)] (Table II; Fig. 1C).

However, surgical margins exhibited prognostic significance at the resection of the primary tumor only; patients who developed ≥1 recurrence did not gain a survival benefit from an R0 resection of the recurring tumor (5-year RFS rate, 77.9%; 95% CI, 54.5-90.2%) compared with an R1/2 resection of the recurring tumor (5-year RFS rate, 50.2%; 95% CI, 24.0-71.6%; P=0.269 vs. R0) (Table II; Fig. 1D).

Regarding adjuvant treatment modalities, radiation treatment did not result in an improved outcome compared with no radiation treatment [5-year RFS rates, 48.4% (95% CI, 27.8-66.3%) vs.

Table II. Univariate analyses of recurrence-free survival with respect to treatment characteristics.

Variable	Total no. of patients	No. of patients with recurrences	Estimated RFS rate, % (95% CI)			P-value (log-rank)[a]
			1-year	2-year	5-year	
Margin status after primary resection						
R0	50	34	87.9 (75.0-94.4)	75.5 (60.8-85.3)	68.8 (53.5-79.9)	
R1/2	40	11	72.5 (55.9-83.7)	55.0 (38.5-68.8)	34.1 (19.9-48.9)	0.001[b]
R1	28	7	71.4 (50.9-84.6)	46.4 (27.6-63.3)	28.6 (13.5-45.6)	<0.001[c]
R2	12	4	75.0 (40.8-91.2)	75.0 (40.8-91.2)	47.6 (18.2-72.4)	0.341[d]
Distance of closest negative surgical margin at resection of the primary tumor (R0 group), mm						
≤1	26	16	84.4 (63.7-93.9)	76.2 (54.4-88.6)	62.9 (40.5-78.8)	0.301[e]
>1	24	18	91.7 (70.6-97.8)	75.0 (52.6-87.9)	75.0 (52.6-87.9)	
≤5	44	31	88.5 (74.6-95.1)	79.1 (63.6-88.5)	71.5 (55.2-82.7)	0.245[f]
>5	6	3	83.3 (27.3-97.5)	50.0 (11.1-80.4)	50.0 (11.1-80.4)	
Wound closure after primary resection						0.069
Primary closure	69	31	78.1 (66.4-86.2)	60.2 (47.6-70.7)	47.0 (34.4-58.6)	
Non-primary closure (plastic surgical tissue transfer)	21	14	90.5 (67.0-97.5)	85.7 (62.0-95.2)	69.3 (43.6-85.1)	
Adjuvant radiotherapy						0.861
Yes	27	13	81.5 (61.1-91.8)	73.9 (52.9-86.6)	48.4 (27.8-66.3)	
No	63	32	80.8 (68.7-88.6)	63.0 (49.8-73.7)	54.4 (41.1-65.9)	
Adjuvant NSAID treatment						0.080
Yes	19	7	73.7 (47.9-88.1)	47.4 (24.4-67.3)	36.8 (16.5-57.5)	
No	71	38	83.0 (72.1-90.0)	71.5 (59.4-80.6)	56.9 (44.0-67.8)	
Margin status after last resection in patients with ≥1 recurrence						0.269
R0	25	11	87.6 (66.3-95.8)	77.9 (54.5-90.2)	77.9 (54.5-90.2)	
R1/R2	20	12	89.2 (63.1-97.2)	77.6 (50.7-91.0)	50.2 (24.0-71.6)	

[a]Log-rank test for equality of survivor functions; [b]R0 vs. R1/2; [c]R0 vs. R1; [d]R1 vs. R2; [e]≤1 vs. >1 mm; [f]≤5 vs. >5 mm. RFS, recurrence-free survival; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

54.4% (95% CI, 41.1-65.9%), respectively; P=0.861). Adjuvant treatment with NSAIDs was associated with a marginally diminished RFS rate when compared with untreated patients [5-year RFS rates, 36.8% (95% CI, 16.5-57.5%) vs. 56.9% (95% CI, 44.0-67.8%), respectively; P=0.080] (Table II).

Multivariate analysis of survival. The only significant prognostic factor for RFS according to the Cox model was the margin status attained at the primary resection (Table III); the hazard ratio for recurrence was 2.73 (95% CI, 1.52-4.91; P=0.001) for patients with positive margins (R1/R2) vs. R0-resected patients. All other variables failed to reach statistical significance in the multivariate analysis.

Discussion

In the present study, the surgical margin status attained at the resection of the primary tumor was the only factor that exhibited prognostic significance in the analysis of RFS; patients with R0 margins after primary resection had a significantly improved RFS rate compared with patients who underwent R1 or R2 resections. Notably, narrow and wide negative margins had similar outcomes within the R0-resected subset, supporting a surgical approach aiming to achieve more conservative resections, rather than radical and wide excisions. In the entirety of the present series of patients, 6 out of 50 patients within the R0 subgroup underwent resections

Table III. Results of multivariate analysis on recurrence-free survival according to Cox proportional hazards model.

Category (reference)	Hazard ratio	95% CI	P-value
Margin status after primary resection: R1/R2 (vs. R0)	2.73	1.52-4.91	0.001
Tumor site: Extremity (vs. non-extremity)	1.66	0.83-3.32	0.153
Wound closure at primary resection: Primary (vs. non-primary)	1.38	0.64-2.96	0.411
Adjuvant NSAID treatment: Yes (vs. no)	1.93	0.88-4.23	0.101

CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug.

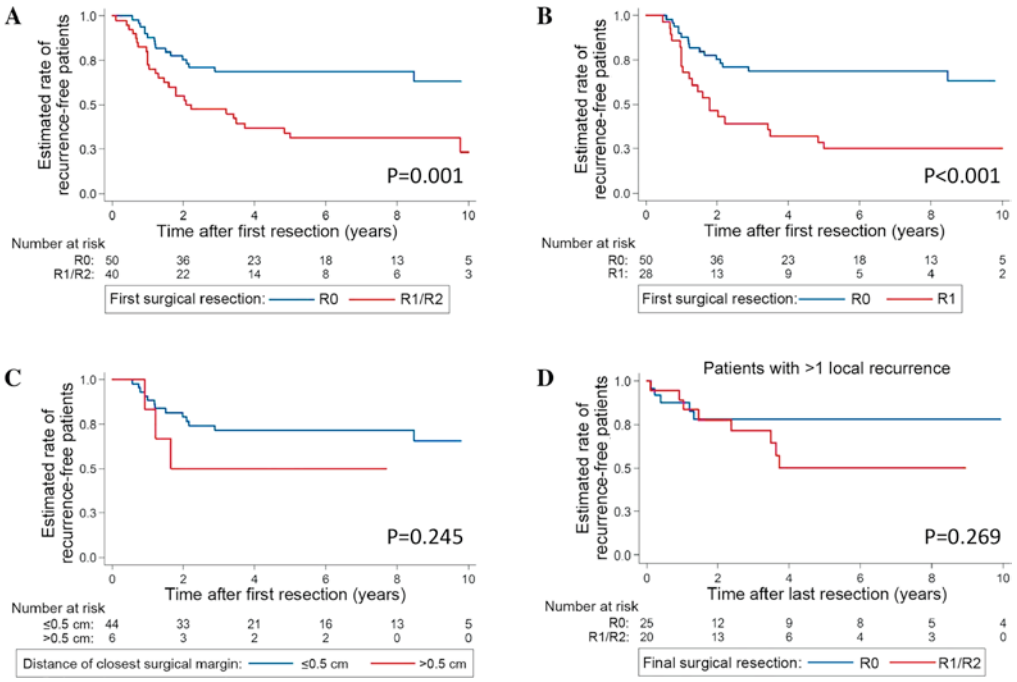

Figure 1. Effects of surgical margins on recurrence-free survival following resection in patients with aggressive fibromatosis. Kaplan-Meier curves show the comparison of (A) R0 vs. R1/2 status, (B) R0 vs. R1 status, and (C) close vs. wide surgical margins (≤5 vs. >5 cm) following the primary resection, as well as (D) R0 vs. R1/2 status following final resection in patients with ≥1 recurrence.

with margins of >5 mm of healthy tissue, reflecting a less radical treatment policy. In the cases with positive margins, tumors had infiltrated critical anatomical structures, such as large nerves of the extremities, or were too advanced and widespread for complete resection, which would have resulted in functional loss and increased morbidity. Taken together, these findings suggest that a less radical surgical approach with function-sparing resections should be employed when feasible, without leaving microscopic or macroscopic positive margins. However, surgical margins did not influence RFS in patients in whom tumors had recurred.

In contrast to the current findings, none of the large retrospective studies previously conducted by the MDACC, MSKCC, INT and the French Sarcoma Group were able to determine a predictive role of positive surgical margins (1,8,10,17). A mere descriptive comparison of the four studies mentioned with the present study does not allow a further explanation for these contrasting results. Notably, a significant difference regarding the RFS rates obtained between the different studies can be detected: The overall 5-year RFS rates for patients treated surgically in the MDACC (80%) and in the INT (76%) were markedly higher compared with that in the present study, which reported a 5-year RFS rate of only 52.2% (95% CI, 40.9-62.3%) for the entire series. As three out of the four centers pooled the RFS rates of R0 and R1 patients, only the MDACC data can be compared; the MDACC study reported a 5-year RFS rate of 75% for R1/R2-resected patients, which is markedly higher than that in the current series, which reported a rate of 34.1% (95% CI, 19.9-48.9%) for the corresponding patient group. This observation leads to the question of why patients with positive margins had such poorer outcomes in the current series compared with other studies.

A potential reason for this may be related to the adjuvant treatments administered to patients with positive margins. Nevertheless, adjuvant treatment modalities were not less intense in the current patient population: From the 45 patients with positive margins at our center, 23 (51.2%) received adjuvant treatment (15 radiation only, 2 NSAIDs only, 2 tamoxifen only, and 4 combined treatment). The frequency of adjuvant treatment was similar in the MDACC series, in which 36 (52.9%) out of 68 patients with positive margins received adjuvant therapy.

A final potential explanation for the low RFS rates in the present study may be found in the time point of recurrence detection. It must be noted that patients at our institution are intensely followed-up with contrast-enhanced magnetic resonance imaging assessments every 3 months in the first 2 years, and then every 6 months for ≥3 further years, enabling the detection of recurrences relatively rapidly and prior to the development of symptoms. However, we are unable to determine the true reason for these marked outcome differences between the studies.

In conclusion, the data from the present study suggest an improved outcome for patients with completely resected primary tumors. Tumor biology may dictate the outcome; however, given the diminished outcome of patients retaining positive margins, surgical efforts must aim for function-sparing resections with negative margins wherever feasible. In this context, close negative margins, even those <1 mm, appear to be adequate. However, it cannot be retrospectively concluded whether the R0 resection itself or the characteristic of 'R0 resectability' at the initial surgical procedure leads to the improved outcome; it is probable that tumors that cannot be completely resected have more aggressive biological features than completely resectable tumors, thus impairing the outcome more substantially. Subsequently, a positive margin status could be a result, rather than a cause, of biological aggressiveness, and it may not itself influence the outcome directly.

Finally, the time point of surgical resection must be addressed. As proposed by the European Organisation for Research and Treatment of Cancer (EORTC) in 2015, a wait-and-see strategy for ~1 or 2 years appears to be reasonable for patients with asymptomatic primary tumors at non-critical sites as a frontline approach, and can prevent unnecessary resections that may result in lifelong morbidity (19,20). Currently, a prospective observational study (NCT01801176) by the Institut Gustave Roussy is underway to assess the outcome of different treatment arms formulating the role of the wait-and-see policy in more detail. To date, the EORTC recommends a surgical resection in cases of progression if the expected postoperative functional impairment is limited. However, as this can be highly subjective, the postoperative consequences must be clearly discussed with each patient before decisions are made.

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