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Natural history of well-differentiated liposarcoma of the extremity compared to patients treated with surgery

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ABSTRACT

Background: Patients with well-differentiated liposarcoma (WDLPS) of the extremity are mostly treated surgically, thereby possibly inducing severe morbidities. Despite the excellent prognosis, the natural history is barely studied. The aim of this study was to evaluate the natural history of extremity WDLPS by evaluating the outcome of patients treated with active surveillance (AS), who thereby exhibited the natural history of extremity WDLPS, and of patients treated surgically.

Methods: A large retrospective database of patients with extremity WDLPS was assessed to evaluate treatment, dedifferentiation and disease-specific survival. Lastly, our experience with patients treated with AS was explored.

Results: Distant metastases (5/191 patients, 2.6%) were mainly seen after a dedifferentiated local recurrence. Death of disease occurred in 4/191 patients (2.1%); two patients died from metastatic disease (although not pathologically proven), two patients died of treatment-related complications. In our center, 24 patients are treated with AS. Time of AS varied from 0.1 to 8.9 years (median 1.8). Four patients eventually underwent surgery after a period of AS (range 14–52 months) because of symptoms and/or tumor growth. No areas of dedifferentiation were found in these resection specimens. The other patients are still under active surveillance.

Conclusion: Since surgical treatment might induce morbidity and even mortality, there might be overtreatment of these patients. Evaluation of the natural history of extremity WDLPS showed that AS could be a reasonable option for selected patients. Prospective studies in patients with extremity WDLPS are needed to assess the safety of AS as a treatment option.

1. Introduction

Well-differentiated liposarcoma (WDLPS) is the most common subtype of liposarcoma, accounting for approximately half of all liposarcoma patients. Most WDLPS patients present with a deep-seated, slowly growing and painless mass, most frequently located in one of the extremities. WDLPS are low-grade tumors and have very little to no metastatic potential. However, they can dedifferentiate into a more aggressive subtype, thereby gaining the ability to metastasize [1]. Patients with extremity WDLPS have a good prognosis with very low dedifferentiation rates and excellent survival rates of 90–100% after 10 years of follow-up [1]. Because of this indolent disease course, extremity WDLPS is considered borderline malignant, and is therefore also called an atypical lipomatous tumor [1–3].

Despite of these disease characteristics, almost all patients undergo (extensive) surgery, optionally preceded or followed by radiotherapy. Although consensus has shifted from radical amputation to wide excision – and even marginal excision now is considered appropriate and adequate more often in case of localization in one of the extremities – patients still have to deal with the morbidities and complications induced by surgery, such as loss of limb function and wound infections [4–6].

To date, the natural history of extremity WDLPS has rarely been described in these patients. While this is much more studied in other borderline malignant tumors, such as desmoid-type fibromatosis [7–11], no study has ever been published yet in extremity WDLPS evaluating its natural history. Therefore, the aim of this study was to describe the natural history of patients with extremity WDLPS and to

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Table 1
Patient characteristics.

		Total (N = 191)		Rotterdam (N = 113)		Warsaw (N = 79)		p-value[$]
		N	%	N	%	N	%	
Sex	Female	103	53.9	61	54.5	42	53.2	0.859
	Male	88	46.1	51	45.5	37	46.8	
Age at diagnosis (years)[a]		59 (49–67)		60 (50–68.5)		58 (48–64.5)		0.104
Site	Lower extremity	163	85.3	97	86.6	66	83.5	0.556
	Upper extremity	28	14.7	15	13.4	13	16.5	
Size (cm)[a]		17 (12–23)		18.5 (13–23)		16 (10.5–20.3)		0.106
Resection margins	R0	83	43.7	19	17.1	64	81.0	< 0.001
	R1/R2	78	41.1	63	56.8	15	19.0	
	Unknown	29	15.3	29	26.1	0	0.0	
Neoadjuvant treatment	None	143	74.9	107	95.5	36	45.6	< 0.001[‡]
	Radiotherapy	44	23.0	1	0.9	43	54.4	
	ILP	2	1.0	2	1.8	0	0.0	
	Unknown	2	1.0	2	1.8	0	0.0	
Adjuvant treatment	None	175	91.6	98	87.5	77	97.5	0.042[‡]
	Radiotherapy	14	7.3	12	10.7	2	2.5	
	Unknown	2	1.0	2	1.8	0	0.0	
Local recurrence	None	154	80.6	79	70.5	75	94.9	< 0.001
	Yes	37	19.4	33	29.5	4	5.1	
	Time to local recurrence (months)[a]	41 (15–57)		41 (15–57)		43 (21.5–64)		0.869
Dedifferentiation	None	186	97.4	109	97.3	77	97.5	0.448[‡]
	Yes	4	2.1	3	2.7	1	1.3	
	Unknown	1	0.5	0	0.0	1	1.3	
Distant metastasis	None	186	97.4	109	97.3	77	97.5	1.000[‡]
	Yes	5	2.6	3	2.7	2	2.5	
	Time to metastasis (months)[a]	24 (18–26)		24 (21–25)		68.5 (17–120)		1.000
Survival	Alive	174	91.1	98	87.5	76	96.2	0.110[‡]
	Death of disease	4	2.1	3	2.7	1	1.3	
	Death of other/unknown cause	13	6.8	11	9.8	2	2.5	
Follow-up (months)[a]		49 (24–75.5)		49.5 (19–82.5)		48 (27–74)		0.949

[a] Presented as median (interquartile range). [$]Calculated by χ^2-tests (categorical data) or Mann-Whitney U tests (continuous data). [‡]Fisher's Exact test.

initiate and open a discussion on the treatment of patients with extremity WDLPS by discussing active surveillance as a treatment option for these patients. With this purpose we looked in detail into the disease course of both treated and untreated patients with extremity WDLPS.

2. Methods

2.1. Data collection

Data of surgically treated patients with primary WDLPS located in one of the extremities were extracted from the database previously described by Vos et al. [12] This database was revolved around patients diagnosed with primary liposarcoma in the extremity in the Erasmus MC Cancer Institute in Rotterdam, the Netherlands, and the Maria Skłodowska-Curie Institute-Oncology Center in Warsaw, Poland, between 1986 and 2015. Both centers are designated as tertiary referral and expertise centers for soft tissue sarcoma. One patient in this cohort eventually did not undergo surgery because of minimal complaints, although at start there was the intent to operate, and was excluded. Imaging, in particular an MRI scan, was part of the standard diagnostic work-up in both expertise centers. In some patients the diagnosis was confirmed by fluorescent in situ hybridization (FISH) for *MDM2* amplification, but in most of the patients the diagnosis was based on histological, morphological and/or immunohistochemical criteria. Patients who presented with a local recurrence or metastatic disease were excluded in this dataset. Although these patients underwent surgery, the results from this cohort gave rise to the current study and the discussion on treatment of these patients.

In the Erasmus MC Cancer Institute, Rotterdam, the Netherlands, already a few selected patients are being treated with active surveillance, thereby exhibiting the natural history of extremity WDLPS. These patients were identified during weekly multidisciplinary tumor board meetings, by the treating physicians and through the institutional database on liposarcomas. This group also includes patients who initially started with active surveillance but eventually underwent surgery after a period of active surveillance because of anxiety, occurrence of/increase in symptoms and/or tumor growth. Frequency of follow-up and imaging during active surveillance was in accordance with the national soft tissue sarcoma guidelines [13] and was similar to the follow-up schedule of low-grade sarcomas, or more often if indicated: first two years every 4 months, year three to five every 6 months and after five years once a year, with an X-ray of the thorax yearly and a MRI scan if indicated. Of these patients, data on characteristics such as primary or recurrent tumor, age at start of active surveillance, symptoms, time of active surveillance and vital status (death/alive) were obtained. If patients opted to undergo surgery after a period of active surveillance, the resection specimen was examined for (areas of) dedifferentiation. Time of active surveillance was defined as time between start of active surveillance and last follow-up or date of surgery.

This study was approved by the local ethics committee and performed in accordance with local ethics committee guidelines and national legislation.

2.2. Statistical analyses

All statistical analyses were performed by using SPSS (IBM SPSS Statistics for Windows, Version 24.0, IBM Corporation, Armonk, NY, USA). Categorical variables are shown as numbers with percentages in parentheses and continuous variables as medians with the interquartile ranges (IQRs) in parentheses. χ^2-tests, Fisher's Exact tests and Mann-Whitney U tests were used to test for differences in clinicopathological variables between groups when appropriate. Two-sided p-values < 0.05 were considered statistically significant.

3. Results

3.1. Course of disease of the surgically treated patients – distant metastasis

In total, 191 patients with primary WDLPS located in the extremity who were treated surgically were identified: 112 in the Rotterdam-cohort and 79 in the Warsaw-cohort. As described and discussed before [12], there was a difference in the number of radical resections, use of neoadjuvant and adjuvant radiotherapy and percentage of patients experiencing a local recurrence between the two centers (Table 1). In brief this study showed that an aggressive approach with radical surgery and neoadjuvant/adjuvant radiotherapy led to excellent local control, while a more conservative approach with enucleation of the tumor (i.e. R1-resection) and without radiotherapy led to higher local recurrence rates, but also that these differences in treatment did not lead to a difference in disease-specific survival for patients with extremity WDLPS [12]. Distant metastases were scarcely observed, neither were dedifferentiation and death of disease, with a median follow-up time of 49 months (IQR 24–75.5, Table 1). In total, five patients out of 191 patients developed metastatic disease (Table 2). Three of these five patients first developed a dedifferentiated local recurrence before developing metastatic disease, the fourth patient developed a local recurrence and a distant metastasis simultaneously. The local recurrent tumor was confirmed by biopsy, showing WDLPS without any signs of dedifferentiation, but no material from the metastatic site was obtained for pathological examination. The patient is still alive, after 'palliative' radiotherapy with a total of 24Gy, with a follow-up period of 60 months (42 months after diagnosis of metastatic disease). The last patient developed massive distant metastases in lungs and liver as a first manifestation of recurrent disease, within four months since the prior follow-up visit with a 'clean' chest X-ray, and died one month later. No data on confirmation of the LPS diagnosis and dedifferentiation in the metastases were available, although the aggressive course of disease suggests either dedifferentiation or that these lesions were metastases from another unknown primary tumor. So, it is questionable whether the last two patients with 'metastases', without a dedifferentiated local recurrence, really had metastatic WDLPS.

3.2. Course of disease of the surgically treated patients - survival

Death of disease was also rarely observed in this group of patients (4 out of 191 patients), with a 5-year disease-specific survival of 98.3% [12]. Two of the deceased patients were two of the patients with metastatic disease described above; the other two deaths were both one month after diagnosis of the primary tumor and turned out to be treatment-related, instead of disease-related. One patient died a few days after neoadjuvant treatment with isolated limb perfusion, and the second patient a few days after surgical resection of the primary tumor due to acute myocardial infarction.

3.3. Natural history of extremity WDLPS in untreated patients

These observations raised questions on the treatment of patients with extremity WDLPS. Since patients only die of the disease after dedifferentiation, dedifferentiation rates are low, dedifferentiation only occurred in local recurrences after surgical removal of the primary tumor, and surgery might induce morbidity and even mortality, we could be overtreating these patients. This might especially apply for patients with inconveniently localized or deep-seated and large tumors (i.e. surgeries where chances of inducing morbidity are substantial) without any debilitating symptoms, elderly patients and/or patients with significant comorbidities.

Therefore, in the Erasmus MC Cancer Institute Rotterdam, the Netherlands, already a few patients with extremity WDLPS have been treated with active surveillance, in whom the natural history of extremity WDLPS can be studied. In all these patients, a conscious decision for active surveillance was taken. Most of these patients have local recurrent WDLPS without any (debilitating) symptoms (19 out of 24 patients treated with AS), in a smaller number of patients the primary tumor is treated with AS (5 out of 24 patients). Reasons for choosing active surveillance included one, or a combination, of the following motives: the absence of any debilitating symptoms, no/minimal tumor growth, an inconvenient localization (i.e. minimal chance of radical resection), and/or a high risk of inducing severe morbidity during surgery. Follow-up of the patients treated with active surveillance ranges from a few months to almost 9 years (median 22 months, IQR 10–51 months, total range 1–107 months) and the median age at time of start of active surveillance was 70 years (IQR 62–74.5) (Table 4). Of these 24 patients, four patients opted to undergo surgery after a period of active surveillance, because of symptoms and/or tumor growth. Time of active surveillance in these four patients was 14, 16, 24 and 52 months. After surgery, no areas of dedifferentiation were found in any of the tumor specimens. The tumors of the remaining 20 patients are still in situ (with a median follow up of 26 months, IQR 5–51 months). These patients are monitored according to the follow-up schedule of low-grade sarcomas as stated in the national soft tissue sarcoma guidelines, including imaging on indication, except for two patients (one patient died to a cause unrelated to WDLPS, one patient is lost to follow-up). Although some of the patients only have been treated with active surveillance for a few months so far, there is no/minimal growth of these tumors and they do not have any signs of dedifferentiation up to date, even not in the patient treated with active surveillance for almost nine years.

4. Discussion

The cases described above in a large dataset of 191 surgically treated patients with extremity WDLPS outline that patients do not or seldom die because of extremity WDLPS, unless the recurrent tumor has dedifferentiated, while two deaths were induced by its treatment. These observations raised questions about the possible overtreatment of this patient group, and led to a discussion on whether a more conservative treatment or even no treatment at all (active surveillance) is more appropriate and justified in selected cases.

In line with the results of our study, other studies of extremity WDLPS have reported low rates of dedifferentiation [1,6,14,15], metastatic disease [4,16] and mortality [17–19]. Despite these excellent outcomes, treatment of these patients remains almost similar to that of patients with more aggressive subtypes, such as dedifferentiated, myxoid or pleiomorphic liposarcoma. The extent of treatment of extremity WDLPS is already under debate, with ongoing discussions regarding the harms and benefits of wide excision versus marginal excision, [4,6,20] and the use of neoadjuvant/adjuvant radiotherapy [21,22]. To this debate, we can now add the question whether excision – or treatment in general – is indicated at all. The morbidity and risks of marginal resections (i.e. R1 resections) are generally quite low, but they are still present and should be taken into account. The results of this study, together with those of other studies reporting excellent survival rates, indicate that not all cases of extremity WDLPS may require surgical removal. In selected cases, especially in elderly patients, patients with comorbidities and/or patients with inconveniently localized, large and deep-seated tumors without any symptoms in whom surgical resection most probably will lead to substantial morbidity, it may be appropriate and adequate to pursue conservative treatment in the form of active surveillance. The appropriateness of active surveillance was further underscored by the observation that it has been safe so far to apply this approach in selected patients with extremity WDLPS who do not experience any debilitating symptoms and who have inconveniently localized tumors at the Erasmus MC Cancer Institute, although follow-up is still short. In these patients, the natural history of extremity WDLPS showed no/minimal growth of the tumors. In the few patients (4/24) who did experience growth/symptoms after a period of active

Table 2
Patients with metastatic disease.

			Primary tumor		Local Recurrence				Distant Metastases			Follow-up			Remarks
No.	Age[a]	R/W	Margins	RTx	LR	TLR	Dediff.	Treatment	TSD	Metastatic sites	Treatment	Survival	Total FU[‡]	FU since DM[◊]	
1	48	R	R1	No RTx	Yes	5	Yes	Surgery + RTx	26	Lungs, later multiple	CTx + RTx	DOD	75	49	
2	42	R	Unknown	No RTx	Yes	19	Yes	Surgery + RTx	24	Multiple sites (subcutaneous)	Surgery + CTx (CR)	Alive	198	174	
3	47	W	R0	Neoadj. RTX	Yes	45	Yes	Surgery	120	Lungs	Surgery, CTx, RTx	Alive	145	25	Second local recurrence in 2009, treated with surgery + RTx
4	80	R	Unknown	No RTx	Yes	18	No	None	18	Paravertebral	RTx (24Gy)	Alive	60	42	No biopsy of metastatic site
5	64	W	R0	Neoadj. RTX	No	NA	NA	NA	17	Lungs and liver	None	DOD	18	1	No biopsy of metastatic site. Aggressive course suggests dedifferentiated disease

TSD: time to systemic disease (in months), dediff.: dedifferentiation, RTx: radiotherapy, LR: local recurrence, TLR: time to local recurrence (in months), FU: follow-up time (in months), DOD: death of disease.
[a] Age at time of diagnosis (of primary tumor). R/W: Rotterdam-cohort (R) or Warsaw-cohort (W). [‡]Follow-up in months from date of diagnosis to date of death or last date of follow-up. [◊]Follow-up in months from date of diagnosis of distant metastases to date of death of last follow-up.

Table 3
Patients with disease-related death.

	Age[a]	R/W	Primary tumor		Local Recurrence				Distant metastasis			Follow-up			Remarks
			Margins	(Neo)adj. treatment	LR	TLR	Dediff.	Treatment	DM	TSD	Treatment	Survival	FU since DM[◊]	Total FU[‡]	
1	64	W	R0	Neoadj. RTx	No	–	–	–	Yes	17	None	DOD	1	18	Unfit for CTx
2	48	R	R1	None	Yes	5	Yes	Surgery + RTx	Yes	26	CTx + RTx	DOD	49	75	
3	91	R	–	(Neoadj.) ILP	–	–	–	–	–	–	–	TRD	–	1	Died few days after (neoadj.) ILP
4	59	R	R1	None	–	–	–	–	–	–	–	TRD	–	1	Died few days after surgery

R/W: Rotterdam-cohort (R) or Warsaw-cohort (W), ILP: isolated limb perfusion, RTx: radiotherapy, LR: local recurrence, TLR: time to local recurrence (in months), NA: not applicable, dediff.: dedifferentiation, DM: distant metastasis, TSD: time to systemic disease (in months), CTx: chemotherapy, DOD: death of disease, TRD: treatment-related death, FU: follow-up time (in months).
[a] Age at time of diagnosis (of primary tumor). [‡]Follow-up in months from date of diagnosis to date of death or last date of follow-up. [◊]Follow-up in months from date of diagnosis of distant metastases to date of death of last follow-up.

Table 4
Patients characteristics, presented as N (%) unless otherwise stated, of the 24 patients treated with active surveillance.

Sex	Female	9 (37.5)
	Male	15 (62.5)
Age at time of start AS (years)[a]		70 (62–74.5)
Site	Upper extremity	1 (4.2)
	Lower extremity	23 (95.8)
Presentation	Primary tumor	5 (20.8)
	Local recurrence	19 (79.2)
Surgery	No, tumor still in situ	20 (83.3)
	Yes	4 (16.7)
Follow-up/duration of AS (months)[a]		21.7 (9.5–51.1)

[a] Presented as median (interquartile range). AS: active surveillance.

surveillance and therefore opted to undergo surgery, no dedifferentiation was found in the specimens. However, it remains unknown whether it is preferable to remove these large and inconveniently localized WDLPS quickly after diagnosis, or to observe them for a period of time for possible tumor growth and/or dedifferentiation.

During treatment decision making numerous factors have to be taken into consideration, balancing the risks and benefits of the treatment for each patient. Radical local treatment leads to better local control, but comes at the costs of morbidity, impaired functional outcome and even mortality, but does not affect disease-specific survival [12]. Factors that influence this balance include patient-related factors, such as age, performance status, comorbidities and the patient's own wish, and tumor-related factors, such as symptoms, localization, tumor size and signs of dedifferentiation. A tumor localized in the extremity is particularly suitable for an active surveillance approach, since tumor growth can be monitored by physical examination – even by the patient him/herself – and does not completely rely on imaging alone [23,24]. For example, for the 91-year old patient in our study who died due to the treatment (Table 3), the risk of dying of an age-related disease (e.g. cardiovascular disease, stroke, dementia) was probably higher than the risk of developing dedifferentiated metastatic disease and dying as a result of extremity WDLPS. In retrospect, we feel that active surveillance with a natural course of disease might have been both feasible and adequate in this case. In patients who are younger and fitter or who have smaller and more favorable localized tumors (i.e. less complex surgery), this consideration is likely to be different and surgery might be the preferred option.

Active surveillance in WDLPS has been discussed and suggested before, but such discussions have mainly focused on specific situations, such as after resection of recurrent tumors, after surgical treatment of the primary tumor, or for large inoperable primary tumors [22,25–27]. There is a distinct lack of studies and data regarding patients with extremity WDLPS who actually have been treated with active surveillance. A further problem with previous studies is that overall or disease-specific survival alone might not be the most appropriate outcome measurements for this subgroup of patients, since survival rates approach 100% [1,17–19]. Other outcome measurements, such as quality of life, are becoming more and more relevant. To date, no studies on quality of life have been conducted in patients with extremity WDLPS. On the one hand, quality of life of patients with active surveillance might be better than those undergoing surgery, because they would avoid the necessity of surgery and its related complications and morbidities. On the other hand, their quality of life might be poorer than those undergoing surgery, because living with a tumor in situ might lead to tumor-related symptoms and cause anxiety.

A limitation of our study is that it was based on retrospective data – inherent when studying rare diseases – which relies on accurate recordkeeping and which has induced bias. We acknowledge that there is most probably a selection bias in the patients currently treated with active surveillance, although we believe that this type of treatment will always be subject to some extent of selection bias, since patients with symptoms most likely will refuse active surveillance and prefer surgical treatment. Notwithstanding these assumptions and bias, this study was set up to initiate a discussion regarding the (over)treatment of these patients and to generate hypotheses for further research to test the safety and feasibility of active surveillance in a larger prospective trial. A second limitation was that not all diagnoses were confirmed by FISH for *MDM2* amplification. Furthermore, data regarding imaging was missing, although imaging is part of the standard diagnostic work-up in both expertise centers.

Since the life expectancy is high and unaffected by local treatment, [12] we believe that active surveillance is feasible for selected cases, in particular for elderly patients with comorbidities and minimal symptoms and/or for patients with a large, deep-seated or otherwise inconveniently localized tumor without symptoms in whom surgical resection most probably will lead to substantial morbidity. However, further research is needed before active surveillance can be safely applied in daily clinical practice. Therefore, we propose a prospective observational study to investigate the differences between surgical treatment and active surveillance in patients with extremity WDLPS regarding disease-specific survival, dedifferentiation rates, tumor growth (using the RECIST criteria [28]) and quality of life, comparable to the prospective studies in patients with desmoid-type fibromatosis treated with active surveillance [10,29,30]. This future prospective trial should include regular MRI imaging, allowing for timely intervention in case of tumor growth and/or signs of dedifferentiation.

5. Conclusion

Although the numbers are small and the follow-up relatively short, the evaluation of the natural history of extremity WDLPS illustrated that active surveillance could be a reasonable option for selected patients. This highlights the observation that there might be an overtreatment of these patients, since surgical treatment might lead to morbidity and even mortality in patients with this borderline malignant tumor. The harms and benefits of surgical treatment and active surveillance should be carefully balanced, taking the extension and localization of the tumor (i.e. complexity of the surgery), comorbidities and the indolent disease course into account. This especially applies for elderly patients with comorbidities and/or patients with large, deep-seated or otherwise inconveniently localized tumors without symptoms. We propose to conduct a prospective observational study to assess the safety and outcomes of active surveillance in this patient group.

Conflicts of interest

None of the authors have any disclosures or conflicts of interest.

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