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Adjuvant radiotherapy for extremity and trunk wall atypical lipomatous tumor/well-differentiated LPS (ALT/WD-LPS): a French Sarcoma Group (GSF-GETO) study

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Background: The role of adjuvant radiotherapy (RT) in the management of atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WD-LPS) remains controversial.

Methods: Two hundred eighty-three patients with operable ALT/WD-LPS, no history of previous cancer, chemotherapy (CT) or RT, treated between 1984 and 2011 registered in the Conticabase database were included and described. Overall (OS), progression-free survival (PFS) and time to local relapse (TTLR) were evaluated from the time of first treatment.

Results: Three of 20 centers enrolled 58% of the patients. Median age at diagnosis was 61 (range 25–94) years, 147 patients (52%) were males, 222 (78%) patients had their primary tumor located in an extremity while 36 (13%) and 25 (9%) had tumors involving the girdle and the trunk wall, respectively. The median size of primary tumors was 17 cm (range 2–48 cm). Adjuvant RT was given to 132 patients (47%). Patients who received adjuvant RT had larger tumors ($P = 0.005$), involving more often the distal limbs ($P < 0.001$). Use of adjuvant RT varied across centers and along the study period. Other characteristics were balanced between the two groups. Median follow-up was 61.7 months. None of the patients developed metastasis during follow-up. The 5-year local relapse-free survival rates were 98.3% versus 80.3% with and without adjuvant RT, respectively ($P < 0.001$). Once stratified on time period (before/after 2003), adjuvant RT, tumor site and margin status (R0 versus other) were independently associated with TTLR. No OS difference was observed ($P = 0.105$).

Conclusion: In this study, adjuvant RT following resection of ALT/WD-LPS was associated with a reduction of LR risk.

Key words: well-differentiated liposarcoma, atypical lipomatous tumor, surgery, radiotherapy

introduction

Liposarcoma account for ~25% of soft tissue sarcomas and can be subdivided into three histological and molecular subtypes: atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WD-LPS) and dedifferentiated liposarcoma (DD-LPS), myxoid/round cell liposarcoma and pleomorphic liposarcoma. ALT/WD-LPS and DD-LPS are by far the most frequent subtypes, represent different stages of differentiation of the same disease and are characterized by supernumerary rings and/or giant rod chromosomes that contain amplified sequences of MDM2, HMGA2 and CDK4. Tumor location is of paramount importance in determining the prognosis of these tumors [1]. Indeed, although WD-LPS are low-grade malignancies, retroperitoneal tumors, for example, have a higher risk of local relapse, likely due to several tumor-related factors as well as anatomical constraints. Furthermore, retroperitoneal WD-LPS recur more often in a dedifferentiated form. WD-LPS of the extremities and trunk wall, on the other hand, have no metastatic

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potential, unless they are dedifferentiated [2–4] and are accordingly called ALT [5]. The risk of local recurrence is low after adequate resection, although the definition of adequate resection in this disease entity remains controversial: some authors considering marginal resection (shelling out) adequate while other recommend wide excision [6]. The role of radiation therapy (RT) in the management of these tumors is even more controversial: some physicians considering the risk of recurrence not worth the toxicity of RT [7]. Some authors also argue that ALT may not respond to RT because of their low-grade nature. In this study, we tried to address these questions on a large dataset of patients extracted from the Conticabase (https://conticabase.sarcomabcb.org/).

patients and methods

patients

The Conticabase database was searched on 20 May 2012 for all cases of primary ALT/WD-LPS (item: liposarcoma—well differentiated) affecting an extremity or the trunk wall. Intra-abdominal, retroperitoneal, intrathoracic and head and neck tumors were excluded. This search yielded 309 patients. Among them, 18 had a previous history of other cancer and/or a history of previous RT and were excluded from further analysis. Five patients who received neoadjuvant RT and two patients who received neoadjuvant chemotherapy (CT) were excluded, as well as one elderly patient who refused any kind of therapy, thus leaving 283 patients for the analysis reported here (Figure 1). All cases were reviewed by a pathologist from the French Sarcoma Group (FSG). By definition, all patients had grade 1 tumors. Ethics approval for this study was obtained from the Comité de Protection des Personnes Lyon Est IV.

data collection

The following parameters were collected for analysis:

- Patients demographic: care center, gender, age at diagnosis, date of first treatment.
- Tumor characteristics: status at referral, site, size, depth and multifocality. For status at referral, patients were classified as 'untreated primary tumors' if the tumor was managed at the FSG from the first presentation (including the biopsy), as 'previously treated primary' if the primary tumor was treated outside and patients were referred for follow-up or recurrence and as 'primary tumors' if the biopsy (percutaneous or surgical) was done before referral. For further analysis, tumor sites were grouped as follows: trunk = abdominal wall, chest wall and trunk wall; girdles = axilla, shoulder girdle, buttock and groin; extremities = ankle, elbow, toe, knee, leg, thigh, upper arm and forearm. This classification was based on anticipated difficulties for surgical excision, girdles being considered as more difficult locations due to the presence of large vascular and neural structures.
- Molecular analyses carried out to confirm diagnosis (immunohistochemistry, FISH or PCR).
- Treatment characteristics: primary surgery in a FSG center or outside; type of procedure before referral: open biopsy, unplanned resection (termed 'whoops'), marginal resection (shelling out) where the tumor is dissected with no tumor-free tissue and wide resection where the tumor is resected with a tumor-free margin; whether or not a re-excision was done at the FSG center; type of surgery for the primary tumor; margin status defined as R0 if microscopically complete, R1 if macroscopically complete with presence of tumor tissue at the rim of the surgical specimen and R2 if resection was macroscopically incomplete, and uncertain (RU) if data on margin status were missing; tumor spillage during the surgical procedure.
- Administration of RT, as well as the dose of radiation given, was recorded.

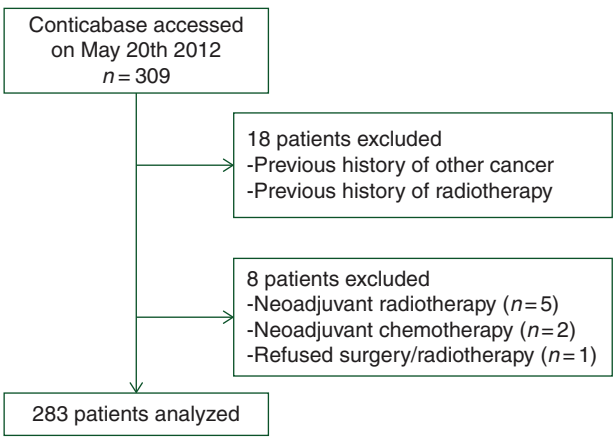

Figure 1. Flow chart of patients' selection for this study.

statistical analysis

Study population was described and data compared between patients with and without RT using Student's or nonparametrical Wilcoxon's test for continuous data and Pearson's χ^2 test or Fisher's exact test for categorical data.

Survival durations were defined as follows: overall survival (OS) was defined as the time from initial treatment (date of surgery) to the date of death (all causes) or censored at date of last follow-up. Progression-free survival (PFS) was defined as the time from surgery to the date of recurrence (local or distant) or death (all causes) or censored at the date of last follow-up. Time to local recurrence (TTLR) was defined as the time from surgery to local relapse; patients who died without local recurrence were, in this instance, censored at the time of death. Survival distributions were estimated by the Kaplan–Meier method [8] and compared with the log-rank test [9] between patients with and without RT.

To assess the prognostic significance of adjuvant RT and other covariates, univariate Cox proportional hazard models [10] were built. All variables significant at 10% level in univariate analysis were included in the initial multivariate models, as well as interactions significant at 5% level. The final Cox multivariate models were constructed using a backward step-by-step manual selection procedure, by retaining only variables which were significant at the 5% level. Furthermore, multivariate models were always stratified on treatment period (before/after 2003) to take into account changes in RT practices over time leading to shorter follow-up for patients without RT.

All analyses were carried out using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

results

patients, tumor and treatment characteristics

The medical charts of 283 patients operated between May 1984 and July 2011 at 20 FSG centers were analyzed. One hundred thirty-two patients (47%) received adjuvant RT (RT group) while 151 patients were observed (surveillance group). The main patients demographic and tumor characteristics are depicted in Table 1. Briefly, the median age was 61 (range 25–94) years, 147 patients were male. Three centers [Institut Bergonié (IB), Institut Gustave Roussy (IGR) and Université Claude Bernard Lyon 1 (UCBL) which comprises the Centre Léon Bérard and the University Hospital of Lyon] contributed to ~58% of the patients in this study.

Table 1. Patients, tumors and treatment characteristics

	Adjuvant radiotherapy for primary tumor		All	Test
	No	Yes		
	N = 151	*N* = 132	*N* = 283	
Demographics				
Center				
IB	23 (15.2%)	47 (35.6%)	70 (24.7%)	χ^2
IGR	29 (19.2%)	29 (22.0%)	58 (20.5%)	$P \leq 0.001$
UCBL	23 (15.2%)	14 (10.6%)	37 (13.1%)	
Others	76 (50.3%)	42 (31.8%)	118 (41.7%)	
Gender				
Female	71 (47.0%)	65 (49.2%)	136 (48.1%)	χ^2
Male	80 (53.0%)	67 (50.8%)	147 (51.9%)	$P = 0.709$
Age at diagnosis				
N	151	132	283	*t*-Test
Missing	0	0	0	$P = 0.889$
Mean (standard)	62.03 (14.55)	61.80 (12.03)	61.92 (13.41)	
Median (min–max)	60.90 (24.90–94.00)	61.55 (28.30–84.40)	61.10 (24.90–94.00)	
Q1–Q3	50.90–73.20	52.30–72.75	51.80–72.90	
Date of first treatment				
≤2003	41 (27.2%)	61 (46.2%)	102 (36.0%)	χ^2
>2003	110 (72.8%)	71 (53.8%)	181 (64.0%)	$P \leq 0.001$
Tumor characteristics				
Status at referral				
Previously treated primary	34 (22.5%)	26 (19.7%)	60 (21.2%)	χ^2
Primary tumor	19 (12.6%)	31 (23.5%)	50 (17.7%)	$P = 0.056$
Untreated primary	98 (64.9%)	75 (56.8%)	173 (61.1%)	
Site of primary tumor				
Girdles	21 (13.9%)	15 (11.4%)	36 (12.7%)	Fisher's exact
Extremities	107 (70.9%)	115 (87.1%)	222 (78.4%)	$P \leq 0.001$
Trunk	23 (15.2%)	2 (1.5%)	25 (8.8%)	
Trunk				
No	128 (84.8%)	130 (98.5%)	258 (91.2%)	Fisher's exact
Yes	23 (15.2%)	2 (1.5%)	25 (8.8%)	$P \leq 0.001$
Girdles				
No	130 (86.1%)	117 (88.6%)	247 (87.3%)	χ^2
Yes	21 (13.9%)	15 (11.4%)	36 (12.7%)	$P = 0.522$
Extremity				
No	44 (29.1%)	17 (12.9%)	61 (21.6%)	χ^2
Yes	107 (70.9%)	115 (87.1%)	222 (78.4%)	$P \leq 0.001$
Tumor characteristics				
Size of primary tumor (mm)				
N	148	131	279	*t*-Test
Missing	3	1	4	$P = 0.005$
Mean (standard)	158.82 (75.00)	184.31 (76.83)	170.79 (76.79)	
Median (min–max)	150.00 (20.00–400.00)	180.00 (40.00–480.00)	170.00 (20.00–480.00)	
Q1–Q3	100.00–200.00	130.00–230.00	120.00–220.00	
Depth of primary tumor				
Missing data	0	1	1	Fisher's exact
Deep	142 (94.0%)	128 (97.7%)	270 (95.7%)	$P = 0.150$
Superficial	9 (6.0%)	3 (2.3%)	12 (4.3%)	
Multifocal tumor				
No	144 (95.4%)	115 (87.1%)	259 (91.5%)	χ^2
Yes	7 (4.6%)	17 (12.9%)	24 (8.5%)	$P = 0.013$
Treatment characteristics				
Surgery outside FSG center				
No	110 (72.8%)	103 (78.0%)	213 (75.3%)	χ^2
Yes	41 (27.2%)	29 (22.0%)	70 (24.7%)	$P = 0.313$

Continued

Table 1. *Continued*

	Adjuvant radiotherapy for primary tumor		All	Test
	No	Yes		
	$N = 151$	$N = 132$	$N = 283$	
Type of surgery before referral				
Enucleation or woops	16 (10.6%)	9 (6.8%)	25 (8.8%)	
No	110 (72.8%)	103 (78.0%)	213 (75.3%)	
Open biopsy	8 (5.3%)	11 (8.3%)	19 (6.7%)	
Resection	17 (11.3%)	7 (5.3%)	24 (8.5%)	
Procedure unknown	0 (0.0%)	2 (1.5%)	2 (0.7%)	
For patients with outside surgery ($n = 70$)				
Re-excision in center				
Missing data	5	13	18	
No	21 (58.3%)	4 (25.0%)	25 (48.1%)	
Yes	15 (41.7%)	12 (75.0%)	27 (51.9%)	
For operated patients ($n = 283$)				
Type of surgery for the primary tumor				
Missing data	2	2	4	Fisher's exact
Amputation	3 (2.0%)	0 (0.0%)	3 (1.1%)	$P = 0.005$
Excision	75 (50.3%)	46 (35.4%)	121 (43.4%)	
Wide resection	71 (47.7%)	84 (64.6%)	155 (55.6%)	
Margin status				
RU[a]	18	20	38	Fisher's exact
R0	57 (42.9%)	48 (42.9%)	105 (42.9%)	$P = 0.512$
R1	70 (52.6%)	62 (55.4%)	132 (53.9%)	
R2	6 (4.5%)	2 (1.8%)	8 (3.3%)	
Tumor spillage				
Missing data	36	59	95	
No	102 (88.7%)	68 (93.2%)	170 (90.4%)	
Yes	13 (11.3%)	5 (6.8%)	18 (9.6%)	

[a]RU, margin status unknown.
IB, Institut Bergonié; IGR, Institut Gustave Roussy; UCBL, University Claude Bernard Lyon.

As could be expected given the controversial role of RT, there were significant differences in the proportion of patients receiving adjuvant RT among centers ($P < 0.001$). There were also variations in the pattern of use of adjuvant RT with time: patients were more frequently given adjuvant RT before 2003 than after ($P < 0.001$).

Overall, most patients ($n = 222$, 78.4%) had ATL originating from the distal extremities, while 12.7% and 8.8% had tumors originating from the girdles or trunk wall, respectively. The median tumor size was 170 mm (range 20–480 mm), the vast majority of tumors ($n = 270$, 95.7%) were deep seated. One hundred thirty-two patients (47%) had their status for MDM2 or CDK4 available and among them only nine patients were found negative for both markers.

There was a significant association between the use of adjuvant RT and several tumor-related parameters: patients who received adjuvant RT had larger tumors [180 mm in median (range 40–480) versus 150 mm (range 20–400), $P = 0.005$], and were more likely to have distal tumors (87% versus 71%, $P < 0.001$).

Seventy five percent of patients ($n = 213$) were referred at a FSG center before any treatment, while almost 10% of patients ($n = 27$) were referred after initial shelling out or 'woops' procedure (Table 1). Twenty-seven patients benefited from an immediate re-excision of their primary tumor at an FSG center, 18 of which after shelling out or 'woops' procedure. In the other hand, 25 patients were not reoperated after outside first procedure and 21 of them (84%) were in the group that did not received RT either. The final surgical procedure was an amputation in 3 patients (none of which received adjuvant RT), a wide resection in 155 (55.6%) and a shelling out in 121 (43.4%). Margin status was R0 in 105 patients (37.1%), R1 in 132 (46.6%), R2 in 8 (2.8%) and unknown (RU) in 38 (13.4%). There was a significant correlation between the type of surgical procedure and the use of RT: more patients had wide resection in the RT group ($P = 0.005$). Despite this, no significant correlation was found between the margin status and adjuvant RT (Table 1, $P = 0.512$). Finally, the dose of RT was recorded for 121 patients (92% of the RT group): the median dose of RT was 52 Gy (range 42.5–70 Gy).

time to local relapse, progression-free and overall survival

The median follow-up was 61.7 months [95% confidence interval (CI) 56.4–71.2] for the entire study population ($n = 283$),

but, due to changes in practice over time, the median follow-up was longer for patients in the RT group [median of 75.8 months (95% CI 68.2–94.3) versus median 54.7 months (95% CI 45.9–60.9)]. There were 26 local recurrences: 5 in the RT group and 21 in the surveillance group, but none of the patients in this series developed distant metastasis. Five patients in the surveillance group (3%) and 4 patients in the RT group (3%) were diagnosed with another cancer during follow-up. There were 16 deaths, only one of which was attributed to liposarcoma. Five patients died of another cancer, four in the surveillance group and one in the RT group, six patients died of other causes and the cause of death was unknown for four patients. TTLR and PFS both significantly favored the RT group [5-year local relapse-free survival rate: 98.3% (95% CI 93.4–99.6) versus 80.3% (95% CI 70.4–87.2) ($P < 0.0001$) (Figure 2) and 5-year PFS rate: 95.7% (95% CI 89.9–98.2) versus 74.2% (95% CI 63.9–82.0) ($P < 0.0001$)] while OS was not significantly different ($P = 0.1047$) (supplementary Figure S1, available at *Annals of Oncology* online).

univariate and multivariate analyses

Univariate and multivariate analyses of TTLR and PFS were conducted. Adjuvant RT, primary tumor site and margin status met the prespecified threshold of 10% in univariate analysis and were incorporated in the multivariate model for TTLR (supplementary Table S1, available at *Annals of Oncology* online). In multivariate analysis, once stratified on the treatment period (before or after 2003); adjuvant RT, tumors of the extremity and R0 resection were associated with a significant reduction in the risk of local relapse (Table 2).

Adjuvant RT, primary tumor site and margin status also met the prespecified threshold of 10% in PFS univariate analysis (supplementary Table S1, available at *Annals of Oncology* online) and were incorporated in the multivariate model for PFS where only adjuvant therapy and R0 resection were associated with improved PFS when stratified on treatment period (Table 3). A trend for an interaction between adjuvant RT and margin status was found when modeling TTLR ($P = 0.0715$) and needed to be explored.

subgroup analysis

In an effort to further clarify the role of RT in ALT, we analyzed the impact of RT on local relapse in the following subsets of patients.

We first focused on patients with primary surgery at a high-volume center (IB, IGR and UCBL) for an untreated primary tumor ($n = 95$). In this subgroup, adjuvant RT significantly reduced the risk of local recurrence (TTLR analysis) ($P = 0.0154$), in line with the results seen in the whole study population.

Then, patients with R0 resection ($n = 105$) were analyzed separately; the overall risk of relapse was very low and the effect of

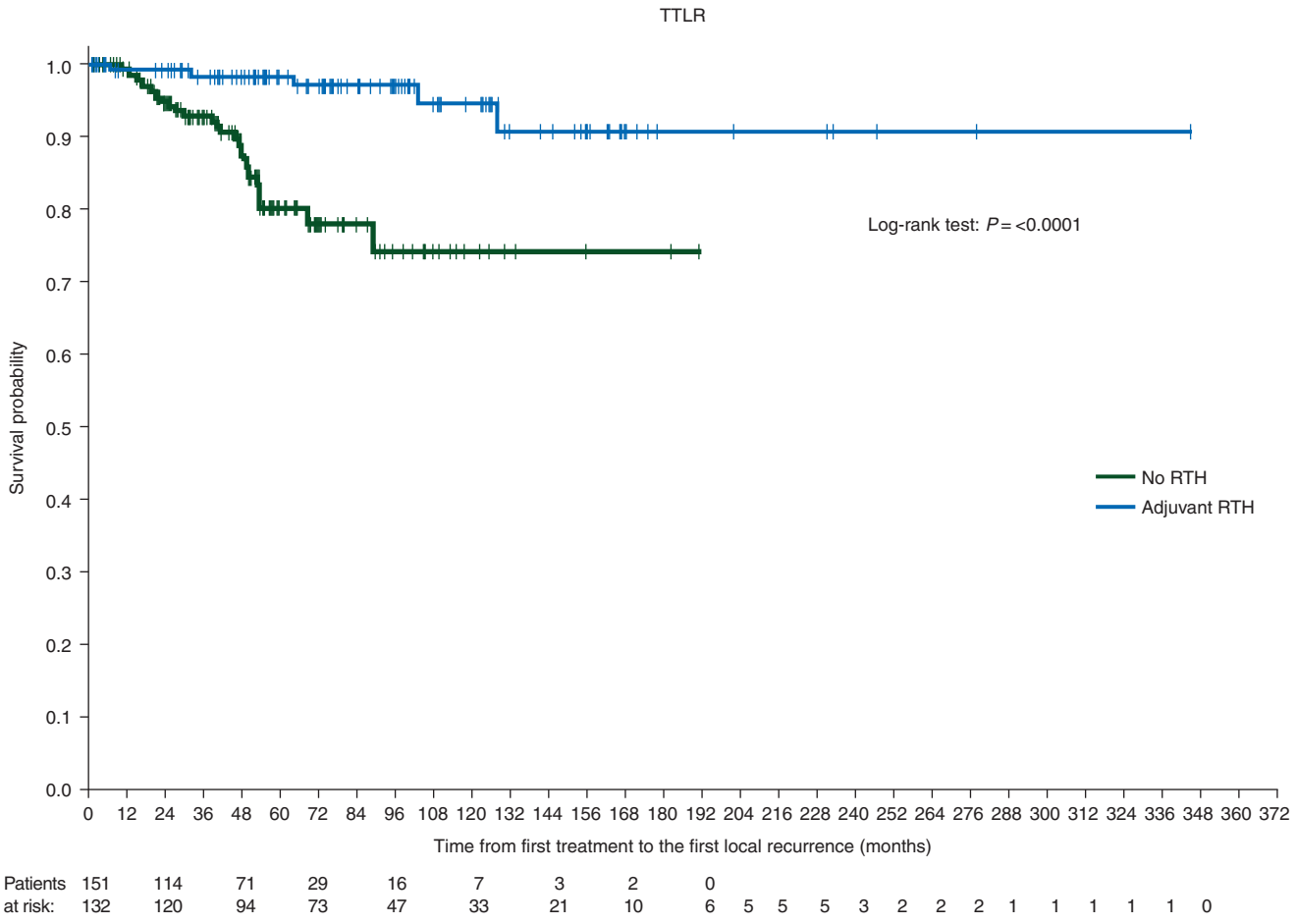

Figure 2. Time to local recurrence according to adjuvant therapy (log rank, $P < 0.0001$).

Table 2. Multivariate model for time to local recurrence (TTLR)

Variables	*N*	HR	95% CI	*P*
Adjuvant radiotherapy for primary tumor	245			
No		1	–	0.0166
Yes		0.26	0.08–0.78	
Site of primary tumor				
Trunk or girdles		1	–	0.0137
Extremities		0.32	0.13–0.79	
Margin status				
R0		1	–	0.0030
R1 or R2		6.49	1.89–22.25	

Table 3. Multivariate model for progression-free survival

Variables	*N*	HR	95% CI	*P*
Adjuvant radiotherapy for primary tumor	245			
No		1	–	0.0003
Yes		0.23	0.10–0.51	
Margin status				
R0		1	–	0.0146
R1 or R2		2.54	1.20–5.36	

adjuvant RT on TTLR in this subgroup was not statistically significant ($P = 0.7195$) (supplementary Figure S2, available at *Annals of Oncology* online).

In univariate analyses of TTLR, patients with R1 or R2 resection ($n = 140$) were at higher risk of local relapse, as were patients with tumors of the trunk wall ($n = 25$). In patients with R1 and R2 resection, adjuvant RT significantly reduced the risk of local relapse ($P = 0.0004$) (supplementary Figure S2, available at *Annals of Oncology* online). In patients with tumors for the trunk wall, the effect of adjuvant RT did not reach statistical significance, and no conclusion could be drawn as a result of the small number of patients in this subgroup.

A TTLR analysis in the group of patients who did not receive RT ($n = 151$) was carried out with the aim to identify patient at low risk of relapse with surgery alone: the only variable associated with time to local relapse at the 10% level was the margin status ($P = 0.0107$). Relapses were seen in all subgroups of patients, but were rarer in patients with R0 resection (1 of 57) and wide resection (5 of 71).

discussion

In this study, we analyzed a large cohort of patients with primary localized ALT/WD-LPS of the extremities and trunk wall with the aim to better define the role of RT in the management of these tumors. Unlike older series, we specifically addressed the question of adjuvant RT in ATL/WD-LPS as opposed to liposarcoma in general. The clinical behavior of these tumors is strikingly distinct from that of other sarcomas, including other forms of liposarcoma. The lack of metastatic dissemination in our study, which confirms finding by others [3, 4, 7, 11], illustrates these differences.

The lack of metastatic potential leads to the reclassification of ALT/WD-LPS as tumors without metastatic potential in the new WHO classification of soft tissue and bone tumors [5]. Local tumor control is therefore the main aim of therapy for patients presenting with ALT/WD-LPS, bearing in mind the relatively indolent and benign evolution of this tumor. There were 21 local recurrences among patients who did not receive adjuvant RT for a 5-year local relapse-free rate of 80.3% (95% CI 70.4–87.2) which is consistent with findings from other studies of ALT [12]. Conversely, only five relapses were seen in patients who received RT. After adjustment on covariates, the addition of RT to surgery led to a reduction of 74% in the risk of local relapse (HR = 0.26), suggesting that WD-LPSs are sensitive to RT. Another interesting finding is that, even for these low-grade tumors, the margin status has a significant impact on time to local recurrence, with more than 20% of patients with R1/R2 resection experiencing local recurrence if not given adjuvant RT.

The questions are therefore: (i) should all patients be treated with adjuvant RT and (ii) if not, which patients (if any) are candidate for this intervention? In multivariate analysis, the other parameters independently associated with a reduced risk of local relapse were R0 resection and tumors originating from the extremities in comparison with the trunk wall or the girdles. Furthermore, in a subgroup analysis focusing on patients with R0 resection, the relapse rate between patients who received adjuvant RT and those who did not was not significant, suggesting that the benefit, if any in this subgroup, is limited. In line with the low rate of relapse and the lack of metastatic potential, and after ~5 years of follow-up, only 16 of 283 patients (6%) died, among which only one death could be attributed to progression of WD-LPS/ALT. As expected, the addition of RT did not affect OS.

In light of these findings, patients with tumors of the limbs which have been resected R0 should be spared adjuvant RT because of the low risk of local relapse. However, because the risk of distant relapse is nil, a wait-and-see policy could also be adopted for patients with R1 or R2 resection, provided that reoperation is feasible. Finally, for tumors located at sites where reoperation may be more complicated due to the presence of vital or functionally important structures, such as large nerves or blood vessels, RT may be given systematically to prevent relapse. The girdles may be considered such anatomical locations.

Safety and toxicity and, therefore, the benefit-risk ratio are criteria which may guide the use of adjuvant RT following surgical resection. Unfortunately, safety data are not recorded in the Conticabase and were not available for analysis in this study; therefore, no conclusion can be drawn on this subject. The main toxicities that could be expected from the addition of RT to surgery in limb and trunk wall sarcomas are wound healing complications and consequences on limb function [13]. The incidence of second cancers during follow-up was comparable in the RT and the surveillance groups, although the current follow-up is not sufficient (~6 years in the RT group) to draw definitive conclusions. A separate safety and quality analysis covering the three main institutions in this series (IB, IGR and UCBL) is currently underway and will be the subject of a different report.

In conclusion, in this large series (the largest series of ALT/ WDLPS), adjuvant RT reduces the risk of local relapse.

This procedure can be spared in patients with ALT/WDLPS, such as those with R0 resection and a very limited risk of life-threatening relapse or relapse requiring mutilating surgery. As previously noted for other sarcomas, the management of patients with liposarcomas, which involves complex multidisciplinary decisions, should be done at centers with significant experience.

disclosure

The authors have declared no conflicts of interest.

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