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Well-Differentiated Extremity and Retroperitoneal Liposarcoma: A Population based Outcomes Study

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[1]Idea, Data collection, Data analysis, Statistics, review of manuscript

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Abstract

Introduction: Lipomatous neoplasms account for approximately 50% of soft tissue tumors with well-differentiated liposarcoma (WDL) being the most common histological subtype. WDL are low-grade neoplasms with low propensity for local recurrence and metastasis. Surgery is the primary treatment and the role of radiation therapy is highly debated for this subtype. This study compares demographic, clinical characters, and the impact of radiation therapy on the long-term survival of extremity (EX) versus retroperitoneal (RP) WDL.

Materials and Methods: 1,358 patients with EX and RP WDL were identified in the Surveillance Epidemiology and End Results (SEER) database (1973-2008) and analyzed for age, gender, race, stage, surgical treatment, radiation therapy, and long-term survival. *Chi*square test was used to compare categorical data and the Student's *t* test was used for continuous data. Kaplan Meier survival analysis was performed to examine the impact of surgery and radiation therapy on long-term actuarial survival.Mantel-Cox log rank test was used to establish statistical significance. Data analysis was performed using SPSS version 20.0 (SPSS, Inc.).

Results: The mean age at WDL diagnosis was 61.4 ± 14.5 years for both groups. There was no Male: Female difference overall or between primary sites (p = 0.6). EX WDL were more common in non-whites compared to RP WDL (p< 0.001). The majority of patients in both primary sites had localized disease however, regional spread and distant metastasis was more common in RP WDL (p= 0.001). Surgery was performed in 95% of all WDL patients though slightly more commonly for EX WDL (p= 0.001).Radiation therapy was used in 19.1% of all patients, and substantially higher percentage of EX WDL (p = 0.02). Mean survival was higher and mortality rates were lower in EX WDL compared to RP WDL (p = 0.01). 5-year survival rates were 34% for both RP and EX WDL, while the10-year mortality rate was 8% for RP and 6% for EX WDL. Multivariate analysis identified age at diagnosis (Odds Ratio [OR] = 2.9), no surgery (OR = 5.4), and RP WDL (OR = 2.4) as associated with increased mortality.

Conclusion: RP WDL occurs more commonly in younger patients and whites, have a higher rate of metastasis, and are associated with a worse overall survival compared to EX WDL. Increased age at presentation, RP location, and failure to perform surgery are associated with increased mortality among all WDL patients. The addition of radiation therapy did not improve median survival in either the EX or RP WDL patient subgroups.

Keywords: Well-differentiated liposarcoma; Radiation therapy; Outcomes

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Introduction

Soft tissue sarcoma (STS) is a rare heterogeneous group of mesenchymal tumors that account for less than 1% of all cancers with a global incidence of 1.8 to 5 per 100,000 population per year

Table 1: Demographic and clinical characteristics of 1,358 Patients with Well-differentiated Liposarcoma (WDL) from the SEER Database (1973-2008).

Variables	Overall	Retroperitoneal (RP) WDL	Extremity (EX) WDL	p value
N (%)	1358	468 (34.5)	890 (65.5)	
Age, (Mean ± SD)	61.4 ± 14.5	60.4 ± 14.2	62.0 ± 14.7	0.047
Gender, N (%)				0.064
Male	700 (51.5)	225 (48.1)	475 (53.4)	
Female	658 (48.5)	243 (51.9)	415 (46.6)	
Race, N (%)				0.06
White	1117 (82.3)	399 (85.3)	718 (80.7)	
Black	109 (8.0)	25 (5.3)	84 (9.4)	
Asian or Pacific Islander	112 (8.2)	37 (7.9)	75 (8.4)	
Others	20 (1.5)	7 (1.5)	13 (1.5)	
Stage, N (%)				0.001
Localized	939 (69.1)	262 (56.0)	677 (76.1)	
Regional	313 (23.0)	139 (29.7)	174 (19.6)	
Distant	45 (3.3)	41 (8.8)	4 (0.4)	
Un-staged	61 (4.5)	26 (5.6)	35 (3.9)	

Table 2: Treatment and Outcome of 1,358 Patients with Well-differentiated Liposarcoma (WDL) from the SEER Database (1973-2008).

	Overall	Retroperitoneal WDL	Extremity WDL	*p* value
Intervention, N (%)				0.001
No therapy	61 (4.5)	36 (7.7)	25 (2.8)	
Surgery Only	1,037	359 (76.7)	678 (76.2)	
Surgery + Radiation	260 (19.1)	73 (15.6)	187 (21.0)	
Overall survival, (months ± SD)	78.4 ± 72.7	67.5 ± 60.9	84.2 ± 77.6	0.001
Mortality, N (%)	394 (29.0)	188 (40.2)	206 (23.1)	0.001

Abbreviations: N; number of patients, SD; standard deviation

[1]. Liposarcoma (LPS) is the most common soft tissue sarcoma, accounting for 24% of extremity and 45% of retroperitoneal STSs [2]. Enzinger and Weiss described four histological subtypes of liposarcoma including well-differentiated, myxoid, round cell, and pleomorphic [3]. Well-differentiated liposarcoma (WDL), also known as atypical lipomatous tumor (ALT), account for most cases of LPS (40% to 45%) [4]. There is much debate as whether to name these tumors WDL or ALT. Atypical lipomatous tumor is suggestive of a benign lesion with no metastatic potential. Those in favor of naming it a well-differentiated liposarcoma point to the high rate of recurrence and potential to dedifferentiate into a tumor with metastatic potential [9]. WDL is a slow-growing, well-circumscribed lesion characterized by proliferation of mature-appearing adipocytes with variable numbers of atypical hyperchromatic nuclei scattered between adipocytes or within fibrous septa and multivacuolated lipoblasts [5]. The histological hallmark of multivacuolated lipoblasts is often rare and equivocal, therefore cytogenetic analysis is commonly utilized for diagnosis of WDL [5]. Cytogenetic analysis reveals the presence of giant ring and marker chromosomes composed of the q12-15 region of chromosome 12 [5]. Surgical resection with negative margins (R0 resection) offers highest survival [6]. WDL has indolent behavior with very low risk of distant metastasis but higher chance of local recurrence, necessitating adjuvant therapy [6]. The role and effectiveness of adjuvant radiation therapy for increased local control and improved quality of life in patients with WDL has been highly debated. Currently there are no consensus guidelines with regards to the use of radiation therapy in WDL patients, except for recurrent disease [2,6]. This report aims to compare demographics, clinical characteristics, and the impact of radiation therapy on long-term survival between extremity (EX) and retroperitoneal (RP) WDL.

Methods

Data for the current study was extracted from the Surveillance, Epidemiology, and End Result database provided by the National Cancer Institute between1973-2008. SEER Stat software version 8.0.4 was utilized to extract data from 18 SEER registries (Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah). All available data variables were extracted with selection criteria including International Classification of Disease for Oncology (ICD-O-3) codes "8851/3" to identify patients with well differentiated liposarcoma (WDL). 1,358 (12.2%) cases of WDL were identified and divided into two main groups based on primary tumor location: Retroperitoneum (RP, SEER primary site code C48.0) and Extremity (EX, SEER primary site code C49.1 and C49.2). Demographic and clinical data including age, gender, race, primary tumor site, SEER historic stage, clinical management (no therapy, surgery only, surgery and radiation), mean survival, overall survival and mortality were compared between RP WDL and EX WDL. The two survival end-points examined were 5-year and 10-year survival. Categorical variables were compared using the *Chi*square test, and continuous variables were compared using Students *t*-test and analysis of variance

Table 3: Overall survival of 1,358 Patients with Well-differentiated Liposarcoma (WDL) from the SEER Database (1973-2008).

Primary Site	Type of treatment	Overall	Alive	Dead	*p* value
Retroperitoneum WDL, N (%)	Surgery Only	359 (83.1)	222 (61.8)	137 (38.2)	0.12
	Surgery + Radiation	73 (16.9)	51 (69.9)	22 (30.1)	
Extremity WDL, N (%)	Surgery Only	678 (78.4)	534 (78.8)	144 (21.2)	0.18
	Surgery + Radiation	187 (21.6)	141 (75.4)	46 (24.6)	

Abbreviations: N; number of patients

Table 4: Mean survival of 1,358 Patients with Well-differentiated Liposarcoma (WDL) from the SEER Database (1973-2008).

	Overall		Retroperitoneal WDL		Extremity WDL	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
No Therapy	61	3.7 ± 5.2	36	2.1 ± 3.8	25	6.1 ± 6.2
Surgery Only	1037	6.1 ± 6.0	359	5.5 ± 5.1	678	6.4 ± 6.4
Surgery + Radiation	260	6.7 ± 6.2	73	5.1 ± 4.9	187	7.3 ± 6.5

Abbreviations: N; number of patients, SD; standard deviation

Table 5: Review of selected single institution studies on Well-differentiated Liposarcoma published after 1990.

Study Year	N	Terminology	Site	Mean follow-up (Years)	Age (Range)	Gender M:F	Size ± SD (Range, cm)	R0 N (%)	R1/R2 N %)	Radiation N (%)	Recurrence N (%)	Recurrence in positive margin N (%)	Average time for recurrence Years (Range)
Lucas et al., [14] 1993	58	WDL	Extremities Retroperitonium Scrotum Abdominal wall Cheek	9.3 (0.5-35)	58 (31-84)	24:34:00	22.6 (4-71)	54 (93)	4 (7)	14 (24)	31 (53)	NM	5.2 (0.5-19)
Weiss et al, [19] 1997	91	WDL	Retroperitonium Extremities Groin ††Miscellaneous	10 (1-35)	(30-80)	53:39:00	NM	NM	NM	Nil	55 (60)	NM	8 (1-13)
Rozental et al., [17] 2002	31	Atypical Lipomatous Masses	Extremity	7 (1-28.8)	57 (32-87)	16:15	14.4 ± 8.9	9 (29)	22 (71)	Nil	16 (52)	15 (93.8)	4.7 (2.3-10)
†Kooby et al., [18] 2003	91	Atypical Lipomatous Tumor/WDL	Extremity Trunk	4 (1-18.5)	56.5 (44-70)	56:35:00	16 ± 9	53 (58)	38 (42)	17 (19)	5 (5.5)	NM	5 (5-10)
Bassett et al., [12] 2004	51	Atypical Lipomatous Tumor	Extremity Chest wall	5.1*	57* (34-85)	22:29	18* (1.1-18.5)	NM	NM	Nil	14 (27)	NM	4 (1.1-12.4)*
Sommerville et al., [20] 2005	61	Atypical lipoma	Extremity	4.1 (2-9.5)	57 (11-83)	28:33:00	18 (4-30)	NM	NM	Nil	5 (8)	NM	3.1 (0.5-5.5)
Serpell et al., [10] 2007	13	Deep Atypical Lipoma Well-differentiated Lipoma like Liposarcoma WDL	Extremity Trunk Neck	1.5 (1-10.5)	NM	NM	NM	NM	NM	4 (31)	3 (23)	NM	14.3 (3-25)
†Billing et al., [13] 2008	50	Atypical Lipoma	Extremity	9.5 (1-23)	NM	34:16:00	15.3 (5-28)	NM	NM	Nil	5 (10)	NM	7.8 (1-16)*

Abbreviations: N: number of patients, M: male, F; female, SD: standard deviation, cm: centimeters, R0: surgical resection with negative margins, R1: surgical resection with microscopic margins, R2: surgical resection with macroscopic positive margins, WDL: well differentiated liposarcoma, NM: not mentioned

† Some of the values were calculated from the information in the manuscript

†† Head and Neck, Trunk and Mediastinum

*Median value

(ANOVA). Multivariate analysis using the "backward wald" method was performed to determine independent factors affecting survival. Missing/unknown data was excluded from multivariate analysis. Kaplan-Meier analysis was used to compare long-term actuarial survival between groups.

Results

A total of 1,358 cases of WDL (RP = 34.5% and EX = 65.5%) were identified from SEER database (1973-2008). Both RP and EX WDL liposarcoma occurred most frequently in the 6th decade of life, with no significant difference in male to female ratio. Overall both RP and EX WDL were more common in Caucasians compared to other ethnic groups. The EX WDL (9.4%) was nearly twice as common in AA compared to RP WDL (5.3%). Majority ofEX WDL patients had localized disease (76.1%) compared to RP WDL (56%).Further distant metastasis was more common in RP WDL (8%) compared to EX WDL (0.4%), p= 0.001 (Table 1).

Over two-thirds of patients with RP or EX WDL underwent surgery alone (76.4%) as a primary treatment compared to surgery with radiation (19.1%) or no treatment (4.5%), p = 0.001. Patients with EX WDL (21%) received radiation more frequently compared to RP WDL (15.6%). Substantially, more RP WDL patients (7.7%) did not receive any intervention compared to EX WDL (2.8%), p= 0.001. Overall survival was significantly longer for EX WDL (84.2 months) compared to RP WDL (67.5 months), p = 0.001. Mortality rate for RP WDL (40.2%) was nearly twofold higher than EX WDL (23.1%), p = 0.001 (Table 2).

In the RP WDL group, the improved overall survival (OS) with combination of surgery and radiation (69.9%) compared to surgery alone (61.8%) was not statistically significant, p= 0.12. On the contrary, addition of radiation to surgery (75.4%) did not improve OS compared to surgery alone (78.8%) in the EX WDL group, p= 0.18 (Table 3).

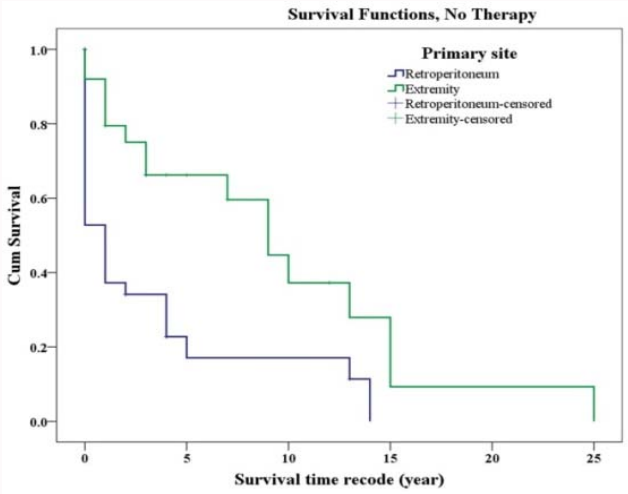
Overall surgery with radiation offered highest survival (6.7 ± 6.2 years) compared to surgery alone (6.1 ± 6.0 years) and no therapy (3.7 ± 5.2 years). When stratified specifically to the patients with RP WDL, mean survival was longest for surgery alone (5.5 ± 5.1 years) compared to surgery with radiation (5.1 ± 4.9 years) and those that did not receive any therapy (2.1 ± 3.8 years), p= 0.05. Conversely, mean survival for EX WDL was highest for patients who received surgery with radiation (7.3 ± 6.5 years), followed by patients who received surgery alone (6.4 ± 6.4 years) and no therapy (6.1 ± 6.2 years), p= 0.5 (Table 4).

On multi-variant analysis using stepwise Cox proportional hazards regression modeling, age >50 years (Odds Ratio = 2.9, Confidence Interval = 2.1 to 4.2), non-operative management (OR = 5.4, CI = 2.7 to 10.5), and RP WDL (OR = 2.4, CI = 1.6 to 2.7) served as prognostic indicators of increased risk of mortality in patients with WDL.

Discussion

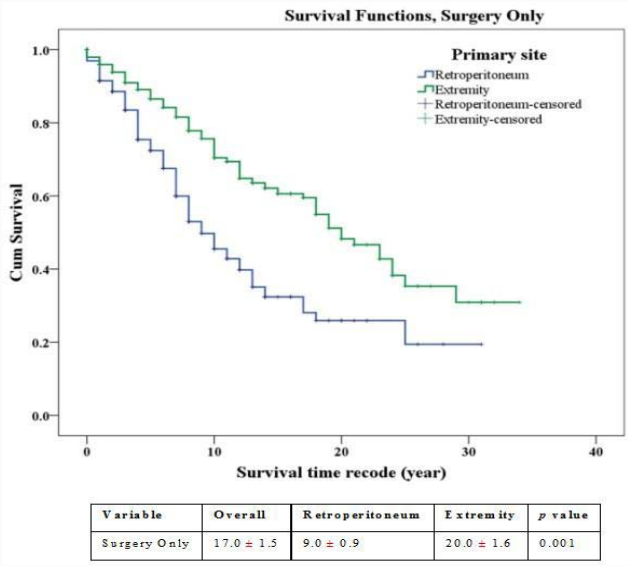
Well-differentiated liposarcoma is the most common variety of liposarcoma [2]. The clinical presentation of a WDL patient varies significantly depending on location. RP WDLs are often clinically silent until extensive growth leads to mass effect. Patients with RP WDLs frequently only present with non-specific abdominal discomfort [7]. The large area of the retroperitoneum allows for RP WDLs to grow quite large before becoming clinically evident. Conversely, EX WDL patients present with a painless slowly growing lump in the extremity [2]. In a study including 1,130 patients by Smith et al, intra abdominal and RP WDLs had amedian size of 18.0 cm compared to 14.0cm for EX WDLs [8].

The workup for WDLs should include Computed Tomography (CT) scan for RP WDL and Magnetic Resonance Imaging (MRI) for EX WDL [2]. On imaging, WDL will have a similar signal intensity to fat [2]. Imaging that shows an enhancing centrally necrotic nodule in an appearing WDL may indicate the presence of dedifferentiation [8]. A CT scan of the chest is also commonly obtained to rule out metastasis [2]. Dedifferentiated liposarcoma most commonly metastasize to the lung [9]. Pre-operative histologic diagnosis may be obtained by core biopsy for EX WDL [2]. There is limited role of biopsy in RP WDL, unless the tumor is considered to be unrespectable on initial evaluation [2,6,10]. WDL is subcategorized into four subtypes including adipocytic, sclerosing, inflammatory, and spindle cell variants [11]. The four subtypes are defined by their



Variable	Overall	Retroperitoneum	Extremity	p value
No Therapy	3.0 ± 0.9	1.0 ± 0	9.0 ± 1.6	0.001

Figure 1: Kaplan Meier survival curve demonstrating actuarial survival in patient with Well-differentiated Liposarcoma who did not receive any kind of intervention.

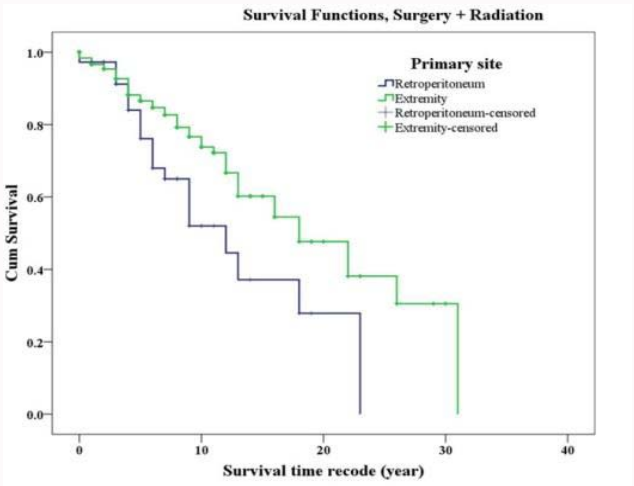


Variable	Overall	Retroperitoneum	Extremity	p value
Surgery Only	17.0 ± 1.5	9.0 ± 0.9	20.0 ± 1.6	0.001

Figure 2: Kaplan Meier survival curve demonstrating actuarial survival in patient with Well-differentiated Liposarcoma who received surgical resection alone.

histological characteristics. Cytogenetic studies are often necessary to differentiate WDL from benign lipoma, as nearly 10% to 26% of WDLs would be mistaken for a benign lipoma based on histological features alone [5,12,13].

Surgical resection with negative margins (R0) at the initial presentation offers highest survival rates for both RP and EX WDL [14].WDL is an encapsulated tumor which allows for marginal excision (shelling out), however the location of RP WDLs make this difficult and are more likely to be partially resected or resected with positive margins [15]. Ideally, wide excision is indicated when the lesion is not well-defined [14,16]. Limb salvage may be safely achieved in EX WDL at initial surgery, whereas amputation is reserved for recurrent tumors or tumors infiltrating motor nerves, where resection leads to non-functional limb [12,17]. Although WDL is an indolent



Variable	Overall	Retroperitoneum	Extremity	*p* value
Surgery + Radiation	18.0 ± 2.0	12.0 ± 2.5	18.0 ± 3.0	0.001

Figure 3: Kaplan Meier survival curve demonstrating actuarial survival in patient with Well-differentiated Liposarcoma who received surgical resection with radiation therapy.

tumor with low metastatic potential, it carries high local recurrence rates. Distant metastasis is common in dedifferentiated liposarcoma [9,14]. Overall local recurrence rate for WDL is nearly 53%, with higher recurrence rates for RP WDL (91%) compared to EX WDL (43-52%) [18,19]. It is suggested that recurrence rates may be much higher if patients are followed for a longer period of time. Evans et al. reported a 100% recurrence rate in all the 19 patients who were followed for at least 10 years [14]. The median time to first recurrence is between 5 to 9 years, with shorter times to first recurrence in RP WDL [14,19]. Several factors influence recurrence in WDL including close or positive resection margin,[14,18] retroperitoneal location, [14] dedifferentiation (foci of high-grade non-lipogenic sarcoma), sclerosing subtype (lipoblasts with fibrosis >25% of low-powered field), prior recurrence and certain genetic alterations [18]. Increased recurrence in retroperitoneal tumors correlates with higher rates of R1 resections (surgical resection with microscopic margins) due to large tumor size, close proximity to vital structures, and high rates of dedifferentiation[12]. In contrast, Kooby et al. reported no increase in local recurrence in WDL patients with R1 resection (9/91), and further, all patients with recurrence (5/91) had sclerosing subtype of WDL and had positive resection margins. Finally, Kooby et al. concluded that their median follow-up was shorter than median time to the development of recurrence, indicating indolent nature of disease and possibility of late recurrence [18]. Several reports indicated increased recurrence in the dedifferentiated tumors with the exact cause for such a phenomenon largely unknown. Also, it is unclear whether dedifferentiation is time-dependent, related to a certain genetic alteration, or a de novo phenomenon [19].

The role of radiation therapy (RT) in the management of WDL is not clearly established. The current study did not show a significant benefit to RT. In the absence of randomized controlled trials, the proposed benefits of RT in these patients is largely anecdotal and limited to small study samples from single institutions with inadequate follow-up. There appears to be unclear benefit of RT in WDL, especially in patients with lipomatous variety, R0 resection and no evidence of dedifferentiation [18]. Additionally, increased risk of dedifferentiation following RT is concerning for the routine use of RT in all patients with WDL [20]. The use of RT for WDL in the published literature ranged from 19% to 31% for single institution studies [10,14,18]. In the current study, RT was used in 19.1% (RP WDL = 15.6%, EX WDL = 21.0%) of patients. In a randomized prospective study conducted at the National Cancer Institute, 50 patients with low-grade sarcoma of the extremities were randomized to surgical resection alone (N = 24) and surgical resection with radiation therapy (N = 26). There was significant reduction in the local recurrence among patients receiving adjuvant RT (4.5%) compared to surgical resection alone (31.6%), however there was no difference in the overall survival between the groups. It is difficult to generalize the findings of this study, as the study population was histologically diverse and included subtypes of low grade sarcoma beyond just WDL [21]. In another study, Kang et al. reported on 13 patients with WDL receiving RT for indications including subtotal resection (N = 2), local recurrence (N = 8), or progressive disease (N = 3). At a median follow-up of 65.1 months, all 13 patients treated with RT were alive without disease [22]. Most others have reported no significant improvement in local recurrence rates with the use of radiation therapy in patients with WDL [9]. Adjuvant RT is currently used for recurrent WDL, dedifferentiated liposarcoma with growth rate of >1cm/month, and dedifferentiated liposarcoma of the extremity >5cm in size with R0 or R1 resection margins [2,6]. RT may be indicated in patients with R1 resection and high risk histology such as sclerosing subtype and dedifferentiation [18].

In the current study, the average overall survival for WDL was 6.5 years. EX WDL had a longer overall survival at 7 years compared to RP WDL at 5.6 years, but this difference was not statistically significant. Studies have reported an overall 5-year and 10-year survival of 90-100% and 78-80%, respectively [14,18]. Overall disease-specific mortality for WDL is 10-11%, however it is much higher for RP WDL at 33-37.5% [15,17,19]. Conversely, numerous studies reported disease-specific mortality of 0% for EX WDL [15,17,19]. Several factors have been shown to affect overall survival, including certain histological variants of WDL, risk or presence of dedifferentiation, margin status, contiguous spread and retroperitoneal location [2,5,6,9-12,14,17-20,22,23].

The limitations of this study include those inherent to large administration databases, which consist of errors in coding and sampling, inability to confirm the specific site of distant metastasis, and individual tumor genetics. Furthermore, with the lack of data regarding the histological variants and disease-specific mortality in the SEER database, it is difficult to determine what factors influenced the course of treatment in these patients and therefore how this cohort influenced outcomes for each treatment modality is unknown.

In conclusion, WDL is a rare soft tissue tumor with indolent clinical behavior and increased propensity for local recurrence. Surgical resection offers highest survival benefit, while the role of radiation therapy in the management of these tumors is unclear. Our data suggests that RP WDL is best treated with surgery alone, while EX WDL is best treated with surgery and radiation therapy combined. The benefits versus risks of RT are still largely up for debate. Further randomized controlled trials are needed to demonstrate the benefits and establish well-defined indications for the use of radiation therapy in patients with WDL.

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