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Research Article

Risk Factors of Survival in Dedifferentiated Liposarcoma

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ABSTRACT

Background: Liposarcoma is the most common malignant soft tissue sarcoma for which surgical resection is the most utilized therapeutic option. In this study, we aimed to explore the associations of surgical margins among other risk factors on survival in patients with dedifferentiated liposarcoma.

Patients and Methods: The National Cancer Database (NCDB) was used to select patients with dedifferentiated liposarcoma to determine if surgical margins were associated with worse overall survival after controlling for age, gender, race, Charlson-Deyo score, anatomic site, treatment approach, tumor size, tumor grade, and presence of metastases through multivariable analysis.

Results: Multivariable analyses showed that mortality risk increased for dedifferentiated liposarcoma patients with the following: older age, male, metastasis, high tumor grade, macroscopic residual tumor compared to no residual tumor.

Conclusion: Older age, male sex, presence of metastasis, retroperitoneal/abdomen primary site, high grade tumors, and macroscopic residual tumor present after surgery led to an increased risk of mortality.

Introduction

Soft tissue sarcomas comprise a heterogeneous collection of neoplasms that arise in mesenchymal tissue with an estimated annual incidence of 11,930 patients within the United States, where 10-15% of cases occur within the retroperitoneum [1-3]. Among the types of soft tissue sarcomas, liposarcoma is the most common malignant soft tissue neoplasm group, which includes the well-differentiated liposarcoma (WDLPS) subtype that is characterized by locally aggressive malignancy [3, 4]. WDLPS is capable of undergoing dedifferentiation and transitioning into another subtype of liposarcoma called dedifferentiated liposarcoma (DDLPS), the focus of this study [5]. DDLPS has similar local effects as WDLPS with locally aggressive malignancy, but DDLPS has a relatively low metastatic rate (10-15%) [6]. At the time of presentation, DDLPS is often characterized by high-grade dedifferentiation, similar to malignant fibrous histiocytoma or high-grade fibrosarcoma [7]. DDLPS and WDLPS both arise from abnormal genetic amplification of the 12q13-15 chromosomal region, which includes the CDK4 and MDM2 cell cycle oncogenes [8]. DDLPS, specifically, is associated with additional amplification in the 6q23 and 1q32 chromosomal regions [8]. DDLPS presents as a primary tumor in 90% of cases, and in 10% of cases, it arises from the transition of recurrent WDLPS [9]. Prognosis of DDLPS includes local recurrences (40-60%), especially within the retroperitoneum [5, 7]. The five-year mortality rate ranges between 30-40% [5]. Considering therapeutic options, surgical resection with curative intent is most used to treat retroperitoneal sarcomas. Successful, complete resection has been shown to be an influential predictive factor of local recurrence and overall survival of retroperitoneal sarcoma cases [6]. However, high degrees of adipocyte differentiation in the retroperitoneal space renders detection of liposarcomas difficult, often resulting in late detection of retroperitoneal liposarcomas; therefore, tumors present with a relatively large size (>10 cm) at the time of diagnosis [2, 6]. Additionally, the presence of DDLPS in the retroperitoneum elicits complications for complete resection due to the proximity of vital organs and are subject to higher rates of recurrence as opposed to DDLPS located in the limbs.

Local control of the tumor has also been shown to be a determinant of survivability, which brings into consideration more locally focused modalities such as radiation therapy [1, 10]. Neoadjuvant radiotherapy

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has been shown to increase the rate of relapse-free survival of patients with retroperitoneal sarcomas in general [1, 11]. However, chemotherapy as a therapeutic option for DDLPS remains controversial. One study involving 208 cases of unresectable and/or metastatic WDLPS or DDLPS compared the efficacy of combination chemotherapy (41%) and single-agent chemotherapy (59%). It was shown that patients treated with combination chemotherapy had a significantly higher objective response rate and clinical benefit rate which was defined as the rate of complete, partial response, or stable disease of at least 6 months duration. However, progression-free survival and overall survival remained unaffected [12]. Two other retrospective studies involving patients with retroperitoneal soft tissue sarcomas of varying histologies who underwent surgical resection showed that the use of adjuvant radiation therapy and chemotherapy as separate treatments did not have any significant impact on survival [13, 14]. Considering the outcomes of the therapies described above, we hope to provide a better understanding of therapeutic outcomes, particularly with regards to dedifferentiated liposarcoma, since most existing studies either solely focus on site-specific soft tissue sarcomas or histology-specific tumors. In this study, we aimed to explore the implications of varying degrees of surgical margins and other prognostic factors on dedifferentiated liposarcoma.

Patients and Methods

I Data Source

We utilized data from the American Cancer Society and American College of Surgeons' National Cancer Database (NCDB), a repository for de-identified information for approximately 70% of cancer cases from all 50 states. Available information was requested for soft tissue sarcoma cases, which was obtained *via* a participant user file (PUF).

II Case Definition

We first identified dedifferentiated liposarcoma patients (morphology =8858) who underwent a surgical procedure of one of the following ICD-O-3 topographical sites:

i. Head or Neck: C07.9, C13.9, C15.3, C32.8, or C49.0;
ii. Extremities: C47.2, C49.1, or C49.2;
iii. Pelvis: C47.5, C49.5, C51.9, C54.2, C55.9, C56.9, C57.9, C61.9, C62.X, C63.X;
iv. Thorax and Trunk: C34.1, C38.0, C38.1, C38.2, C38.3, C38.8, C44.5, C44.7, C47.6, C49.3, C49.6, C50.4, C50.8, or C50.9;
v. Retroperitoneum, Peritoneum, or Abdomen: C16.0, C16.5, C16.6, C16.9, C17.0, C17.9, C18.X, C19.9, C22.0, C23.9, C24.1, C25.0, C25.2, C25.9, C47.4, C48.X, C49.4, C64.9, C65.9, C74.0, or C74.9.

Exclusion criteria consisted of patients with missing or unknown information concerning age, biological sex, vital status and associated time, insurance status, Charlson-Deyo score, Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade, tumor size via collaborative stage site-specific factoring, status of metastases at diagnosis via collaborative stage data collection system, chemotherapy or radiation administered as the first course of therapy, treatment sequence, or surgical margins. Three mutually exclusive groups were created and represented patients who received i) no chemotherapy or radiation, ii) neoadjuvant chemotherapy or radiation, and iii) adjuvant chemotherapy or radiation.

III Statistical Analyses

Unadjusted differences associated with categorical variables cross-classified by the group were examined with the chi-square or Fisher's exact test when appropriate. The Mann-Whitney test was used to examine continuous variables and associated unadjusted group differences. Survival was examined with the Kaplan-Meier method, and a multivariable Cox regression model was employed after checking that the proportional hazards assumption was met for each pertinent variable. The functional form of continuous variables was examined with loess curves to determine if higher-order terms were potentially appropriate. SAS version 9.4 was used for all analyses, and $p<0.05$ was considered significant.

Results

Of the 1,004 identified patients, 64.4% were male, 87.0% were white, and the median age was 63 years (Table 1). It was found that within this cohort of patients, 78.1% had a Charlson-Deyo score of zero (Table 2). In regard to the primary anatomic site, the majority of patients had liposarcoma of the retroperitoneum, peritoneum, or abdomen, and 95.4% had no metastases at the time of diagnosis (Table 2). High-grade liposarcoma was recorded in 91.5% (Table 3). For the status of surgical margins, 50.8% had no residual tumors (histologically negative), 26.1% had microscopic residual tumors, 4.3% had macroscopic residual tumors, 14.9% had residual tumors that were not otherwise specified (NOS) as to the method of identification of residual tumor, and finally, 3.9% had margins that were not evaluable (Table 3). It was found that 33.5% of these patients died.

Table 1: Epidemiology variables for 1,004 patients diagnosed with dedifferentiated liposarcoma.

Variable	N=1,004	% of total
Sex		
Male	647	64.4
Female	357	35.6
Age (years)		
0-10	0.0	0.0
11-20	1	0.1
21-30	13	1.3
31-40	45	4.5
41-50	123	12.2
51-60	256	25.5
61-70	281	28.0
71-80	198	19.7
81-90	87	8.70
Race		
White	873	86.9
African American	79	7.9
Other	52	5.2

Table 2: Primary site, metastasis status, tumor grade, and Charlson-Deyo score demographics for 1,004 patients diagnosed with dedifferentiated liposarcoma.

Variable	N=1,004	% of Total
Primary Site		
Head or Neck	11	1.10
Retroperitoneum or Abdomen	612	61.0
Thorax or Trunk	72	7.2
Extremities	184	18.3
Pelvis	125	12.4
Metastases at Diagnosis		
No distant metastasis	958	95.4
Distant lymph node(s)	1	0.1
Distant metastasis except distant lymph node(s), Carcinomatosis	25	2.5
Distant metastasis plus distant lymph nodes	1	0.1
Distant metastasis, NOS	19	1.9
Metastasis Status		
Metastasis	46	4.6
No Metastasis	958	95.4
Charlson-Deyo Score		
0	784	78.1
1	169	16.8
2	37	3.7
3+	14	1.4

Table 3: Tumor grade, treatment modality, and surgical margin status demographics for 1,004 patients diagnosed with dedifferentiated liposarcoma.

Variable	N=1,004	% of Total
Tumor Grade		
High	919	91.5
Low	85	8.5
Treatment Modality		
No Chemotherapy or Radiation	498	49.6
Neoadjuvant Chemotherapy	13	1.3
Neoadjuvant Radiation	95	9.5
All Else	398	39.6
Surgical Margin Status		
Negative Margins	510	50.8
Microscopic Residual Tumor	262	26.1
Macroscopic Residual Tumor	43	4.3
Residual Tumor, NOS	150	14.9
Indeterminate	39	3.9

Overall, 1- and 5-year survival probabilities for the 1,004 patients with DDLPS were 86.8% and 55.5%, respectively, shown in (Table 4) and in the Kaplan-Meier curve for overall survival in (Figure 1). As age increased, the 5-year survival probability decreased shown (Table 4). Males showed 1- and 5-year survival probabilities of 85.7% and 55.3%, while females showed 88.8% and 56.1% (Table 4). Median survival was shown to be higher in those of white race (73.3 $\pm$ 5.2 months) as opposed to African American race (63.5 months) (Table 4). Median survival data was higher in those without metastasis (73.4 $\pm$ 3.6) as compared to those with metastatic disease (16.3 $\pm$ 6.6), as shown in (Table 4 & Figure 2). Pelvis primary site had the highest 5-year survival probability at 72.4% compared to the other sites, while the worst 1- and 5-year survival probabilities were both seen in the retroperitoneal or abdomen primary site at 84.2% and 46.8%, respectively, shown in (Table 4) and the Kaplan Meier curve of overall survival by primary site in (Figure 3). High tumor grade had a lower 1- and 5-year survivability (85.9% and 54.0%) compared to low tumor grade (95.2% and 71.7%) shown in (Table 4 & Figure 4). Therapy groups without additional chemotherapy or radiation treatment showed the lowest median survival at 63.5 months compared to the neoadjuvant chemotherapy or radiation group at 75.6 $\pm$ 13.1 months and adjuvant chemotherapy or radiation group at 73.3 $\pm$ 3.8 months (Table 4). Surgical margins status where there was no residual tumor had the highest 1- and 5-year survival probability at 90.2% and 61.0%, where the macroscopic residual tumor had the lowest probabilities that showed 69.8% and 44.0% (Table 4 & Figure 5).

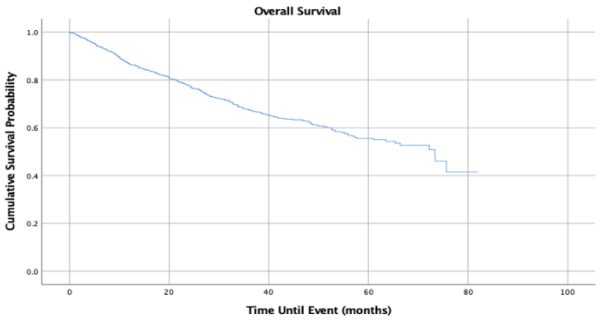

Figure 1: Overall survival for 1,004 patients diagnosed with dedifferentiated liposarcoma.

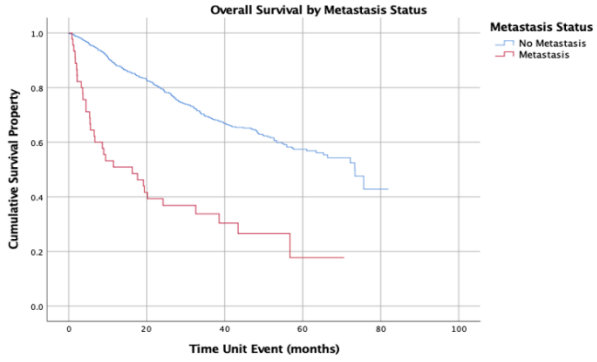

Figure 2: Overall survival by metastasis status for 1,004 patients diagnosed with dedifferentiated liposarcoma, p<0.0005.

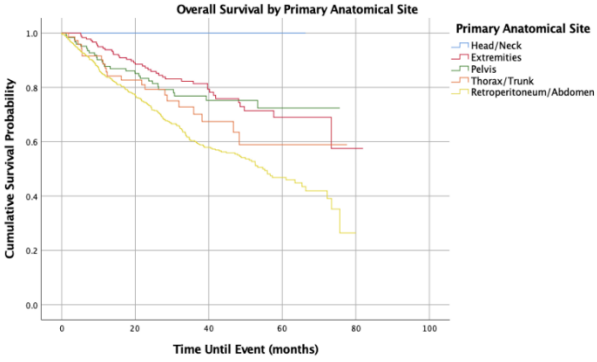

Figure 3: Overall survival by primary anatomical site for 1,004 patients diagnosed with dedifferentiated liposarcoma, p<0.0005.

Table 4: Median and 1- and 5-year survival probabilities for 1,004 patients diagnosed with dedifferentiated liposarcoma by age, sex, race, stage, primary site, treatment group, Charlson-Deyo score, and surgical margins.

Variable	Probability of 1-Year Survival (%)	Probability of 5-Year Survival (%)	Median Survival (months)
Overall Survival	86.8	55.5	73.3±3.9
Age Group (years)			
0-20	100	*	*
21-40	94.4	77.3	*
41-60	89.0	57.9	*
61-80	83.6	43.9	*
>80	83.7	23.1	*
Sex			
Male	85.7	55.3	73.3±11.6
Female	88.8	56.1	75.6.5±11.2
Race			
White	87.1	55.9	73.3±5.2
African American	84.6	55.7	63.5[a]
Other	84.2	50.6	*
Metastasis Status			
Metastasis	50.8	17.7	16.3±6.6
No Metastasis	88.5	57.4	73.4±3.6
Primary Site			
Head or Neck	*	*	*
(Retro)Peritoneum/Abdomen	84.2	46.8	*
Thorax/Trunk	87.2	58.9	*
Extremities	93.8	69.0	*
Pelvis	87.8	72.4	*
Tumor Grade			
High	85.9	54.0	72.2±5.0
Low	95.2	71.7	*
Therapy Group			
No Chemotherapy or Radiation	83.9	46.5	63.5[a]
Neoadjuvant Chemotherapy or Radiation	88.4	56.9	75.6±13.1
Adjuvant Chemotherapy or Radiation	88.5	48.1	73.3±3.8
Charlson-Deyo Score			
0	88.1	57.1	73.4±3.5
1	80.8	48.2	51.7±12.0
2	83.4	52.9	*
3+	92.9	63.7	*
Surgical Margins Status			
No Residual Tumor	90.2	61.0	73.4[a]
Microscopic Residual Tumor	87.5	54.9	73.3±14.3
Macroscopic Residual Tumor	69.8	44.0	31.3±7.5
Residual Tumor, NOS	79.6	44.9	55.2±8.6
Indeterminate	84.6	42.5	50.0±3.9

*: Median or percent survival data not available.

a: Error data not available due to sample size limitations.

Table 5: Multivariable cox hazard model for the 1,004 patients diagnosed with dedifferentiated liposarcoma.

Variables	Hazard Ratio (Confidence Interval)	*p*-Value
Age (10 years)	1.37 (1.26-1.50)	0.045
Sex		
Males *vs.* Females	1.26 (1.01-1.58)	0.038
Race and Ethnicity		

African American *vs*. White	1.24 (0.82-1.87)	0.304
African American *vs*. Other	0.96 (0.51-1.79)	0.889
Other *vs*. White	1.30 (0.77-2.17)	0.326
Charlson-Deyo Score		
1 *vs*. 0	1.32 (0.99-1.75)	0.145
≥ 2 *vs*. 0	1.32 (0.84-2.07)	0.231
≥ 2 *vs*. 1	1.00 (0.59-1.69)	0.270
Primary Site		
Extremities *vs*. Head/Neck	>99.9 (>99.9 - >99.9)	<0.001
Extremities *vs*. Thorax/Trunk	0.60 (0.35-1.02)	0.060
Extremities *vs*. Pelvis	0.95 (0.57-1.56)	0.829
Thorax/Trunk *vs*. Head/Neck	>99.9 (>99.9 - >99.9)	<0.001
Pelvis *vs*. Head/Neck	>99.9 (>99.9 - >99.9)	<0.001
Pelvis *vs*. Thorax/Trunk	0.63 (0.36-1.10)	0.106
(Retro)Peritoneum/Abdomen *vs*. Head/Neck	>99.9 (>99.9 - >99.9)	<0.001
(Retro)Peritoneum/Abdomen *vs*. Extremities	2.34 (1.59-3.44)	<0.001
(Retro)Peritoneum/Abdomen *vs*. Thorax/Trunk	1.39 (0.86-2.24)	0.176
(Retro)Peritoneum/Abdomen *vs*. Pelvis	2.21 (1.46-3.35)	<0.001
Treatment Group		
No Chemotherapy or Radiation *vs*.Neoadjuvant Chemotherapy or Radiation	1.04 (0.68-1.60)	0.839
Adjuvant Chemotherapy or Radiation *vs*. Neoadjuvant Chemotherapy or Radiation	0.99 (0.64-1.53)	0.965
Adjuvant Chemotherapy or Radiation *vs*. No Chemotherapy or Radiation	0.95 (0.75-1.21)	0.662
Metastasis Status		
Metastasis *vs*. No Metastasis	4.26 (2.79-6.51)	<0.001
Tumor Grade		
High Grade *vs*. Low Grade	2.14 (1.35-3.41)	0.001
Surgical Margin Status		
Macroscopic Residual Tumor *vs*. Negative Margins	1.98 (1.25-3.15)	0.004
Microscopic Residual Tumor *vs* .Negative Margins	1.07 (0.82-1.40)	0.609
Microscopic Residual Tumor *vs*. Macroscopic Residual Tumor	0.55 (0.34-0.91)	0.020
Microscopic Residual Tumor *vs*. Indeterminate	0.74 (0.41-1.32)	0.312
Residual Tumor, NOS *vs*.Negative Margins	1.63 (1.20-2.20)	0.002
Residual Tumor, NOS *vs*. Macroscopic Residual Tumor	0.84 (0.51-1.38)	0.493
Residual Tumor, NOS *vs*. Microscopic Residual Tumor	1.52 (1.11-2.08)	0.009
Residual Tumor, NOS *vs*. Indeterminate	1.13 (0.63-2.01)	0.688
Indeterminate *vs*. Negative Margins	1.44 (0.82-2.52)	0.204
Indeterminate *vs*. Macroscopic Residual Tumor	0.75 (0.36-1.53)	0.426

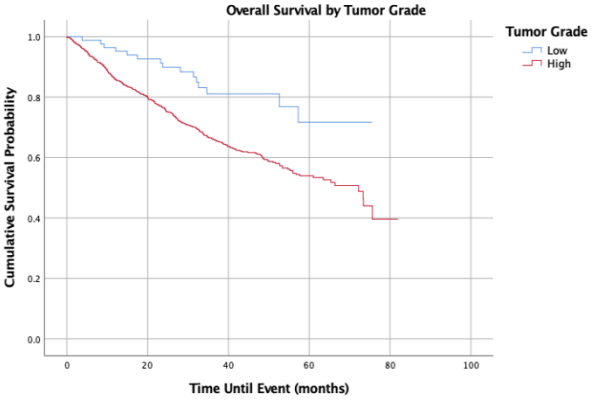

Figure 4: Overall survival by tumor grade for 1,004 patients diagnosed with dedifferentiated liposarcoma, p=0.001.

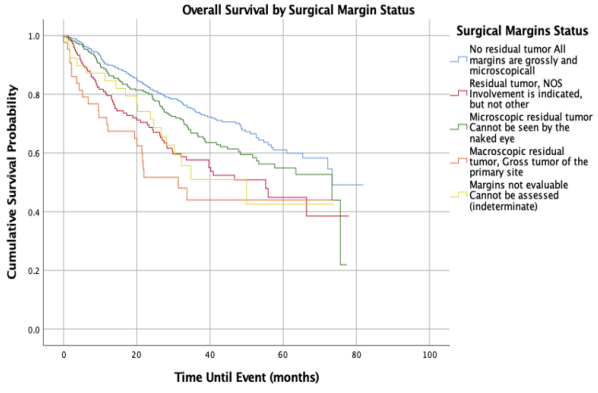

Figure 5: Overall survival by surgical margins for 1,004 patients diagnosed with dedifferentiated liposarcoma, p<0.0005.

Results from the multivariable Cox model are presented in (Table 5), which included the entire cohort of 1,004 patients. After adjusting for all else, it was found that for every ten-year increase in age, the risk of death increased by 37% (95% CI=26-50%; p=0.045). Due to a low number of head and neck cases, the associated hazard ratios were significant but most likely inflated. It was also found that patients with retroperitoneum, peritoneum, or abdominal primary sites in comparison to the extremities or pelvis had 134% (95% CI=59-244%; p<0.001) and 121% (95% CI=46-235%; p< 0.001) increased risk of death, respectively. Patients with metastatic disease had 326% increased risk of death in comparison to those without metastases (95% CI=179-551%; p<0.001), and for patients with high grade had 114% increased risk of death compared to those with low-grade tumors (95% CI=35-241%; p=0.001). Differences between adjuvant treatment modalities were found to be insignificant when compared to neoadjuvant treatment modalities or no additional chemotherapy or radiation.

Patients with macroscopic residual tumors had 98% increased risk of death compared to those with no residual tumors (95% CI=25-215%; p=0.004). Those with residual tumors that were not specified as to the method of identification of the residual tumor (NOS) in comparison to those with no residual tumors had 63% increased risk of death (95% CI=20-120%; p=0.002). Patients with microscopic vs. macroscopic residual tumors had 45% decreased risk of death (95% CI= -66 - -9%; p=0.020). Those with residual tumors that were not specified as to the method of identification of the residual tumor (NOS) as compared to those with microscopic residual tumors had 52% increased risk of death (95% CI=11-108%; p=0.009). Lastly, there was a lack of significance in the difference of risk of death in patients with microscopic vs. negative margins.

Discussion

We report the largest series involving dedifferentiated liposarcoma (DDLPS) and the effects of surgical margins as risk factors on survivability. This study focused on elucidating associations between various risk factors and survivability of DDLPS. Among recent literature, there is a lack of studies that separate out cohorts of patients with dedifferentiated liposarcoma from patients with other liposarcomas, such as well-differentiated liposarcoma [15]. There has yet been an adequate focus on the effects of anatomical site-specificity or histology specificity on survival of dedifferentiated liposarcoma, prompting us to investigate further [15].

The identified cohort was composed of almost two-thirds male patients with a median age of 63 years. This breakdown and the results of the study coincides with previous literature showing older males are more frequently affected than females, with the highest incidence occurring between the sixth and seventh decades of life [9]. It was also found that for every ten-year increase in age, the risk of death in association with DDLPS significantly increased by 37%, warranting that younger patients had increased survivability as opposed to older patients. It was also found that 87% of the cohort were white, which echoes the findings of a database study at the University of Maryland Medical Center that involved 28 patients with retroperitoneal liposarcoma (either DDLPS or WDLPS) where 86% of the afflicted patients were white among the diverse socioeconomic and ethnic population screened for the disease [14].

Primary anatomical sites of DDLPS were mostly located within the retroperitoneum or abdomen, which is consistent with previous literature findings that described these areas, specifically the retroperitoneum, as the most common sites for occurrence [16, 17]. The results of this study showed that the patients whose tumor was located in one of these primary anatomical locations had a more than 2-fold increased risk of death as compared to patients with primary anatomical sites in the extremities or in the pelvis. Occurrence in such a hidden location like the retroperitoneum, in addition to the initial painless growth of DDLPS, may contribute to afflicted patients remaining undiagnosed until a palpable abdominal mass, often accompanied by pain, is present [2]. When analysing the spread of the tumor, it was found that patients with initially identified metastatic disease had a 4.26-fold increased risk of death as opposed to patients with non-metastatic disease. In a retrospective study where 44 out of 148 patients with DDLPS had metastases, the results similarly showed that the median survival time was poorer for patients with metastases (28 months) as opposed to those without metastatic disease (38 months) [18]. DDLPS is commonly associated with high-grade tumors. It was found that patients who had high-grade tumors experienced a 2.14-fold increased risk of death in contrast to those presenting with low-grade tumors. This coincides with results from another study that found the median survival of patients with low-grade lesions was 80 months, and the five-year overall survival rate was 70%. In contrast, those with high-grade lesions were shown to have a median survival of 20 months and a five-year overall survival rate of 25% [2].

Adjuvant and neoadjuvant treatments were analysed and interestingly had a lack of significance in outcomes, which may point out unnecessary additional treatment when considering therapeutic plans. Surgical margins were analysed based on macroscopic and microscopic presence of the residual tumor, and the results showed that patients with a presence of macroscopic residual tumor after initial surgical resection had a 98% increased risk of death as opposed to patients that did not show residual tumor (histologically negative). It was also found that patients with the presence of microscopic residual tumor in comparison to those with macroscopic residual tumor had a 45% decreased risk of mortality. These results coincide with a study that included 119 patients with primary DDLPS located within the retroperitoneum who underwent surgical resection and similarly reported that having an R2 (macroscopically incomplete) resection was a significant independent predictor of worse distant-recurrence-free survival and overall survival based on multivariable analysis [15]. Interestingly, there was a lack of significance in the difference when comparing microscopic surgical margins and no residual tumor. These outcomes highlight the importance and benefits of negative or complete surgical margins as prognostic indicators for patients with DDLPS, especially considering that resection is the most commonly utilized therapeutic option.

Limitations

The NCDB covers approximately 70% of cancer incidents within the United States and reports all-cause mortality, therefore, a future study incorporating the surveillance, epidemiology, and end results (SEER) registry could enhance and possibly add to the results brought forth by this study. The SEER registry reports cancer-specific mortality but is associated with a lower volume of cases as compared to the NCDB. There exists an inherent risk from utilizing the NCDB database, which

is based on data entry into patient charts and is thus influenced by relevant inaccuracies in record-keeping or incomplete data. To reduce such error, this study excluded patients with missing data.

Conclusion

In conclusion, the results of multivariable analysis determined that patients with dedifferentiated liposarcoma had an increased risk of mortality if they presented any of the following characteristics: older age, male sex, retroperitoneal or abdominal primary tumor site, presence of metastasis, high-grade tumor, and macroscopic or any residual tumor present after surgical resection. These results regarding surgical margins stress the importance of obtaining negative surgical margins during surgical resection.

Conflicts of Interest

None.

Consent

For this type of study formal consent is not required.

Ethical Approval

The need for ethical approval was waived by the Creighton University Biomedical IRB (project number: 1351875-1).

Author Contributions

Kevin Nguyen: manuscript writing, manuscript edits, statistics; Jonathan Gootee: project design, manuscript edits; Sarah Aurit: statistics; Sara Albagoush: manuscript edits; Peter Silberstein: project design, manuscript edits.

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