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Review Article

Epidemiology and Survivorship of Myxoid Leiomyosarcoma: A National Cancer Database (Ncdb) Review

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Abstract

Background: Myxoid Leiomyosarcoma (LMS) is a rare and aggressive subtype of soft tissue sarcoma. Currently the true incidence and prognosis of myxoid leiomyosarcoma is unknown. This study examines several epidemiologic factors associated with patients diagnosed with myxoid LMS utilizing the National Cancer Database (NCDB).

Methods: There were 485 patients diagnosed with myxoid LMS in the NCDB from 2004-2014. Kaplan-Meier analyses were used to estimate 5-year survival, and log-rank tests were used to compare survival amongst stage.

Results: Median age at diagnosis for Myxoid LMS was 54 years. 82.5% of patients were female and 17.5% were male. 76.1% of cases were in Caucasian patients and 56.1% were located in female reproductive tract. The most common pathologic stage was Stage I (16.3%) and 13.9% of patients had metastases present at the time of diagnosis. Treatment involved surgery in 89.5%, 37% received chemotherapy and 26.8% received radiation. Overall median survival was 74.5 months. Average 5-year survival rates for Stages I and II based on NCDB Analytic Stage were 68% and 62%, respectively, while the 5-year survival rate for Stage IV was 18.6%.

Conclusion: This study found myxoid leiomyosarcoma was most common in Caucasian females with a median age at diagnosis of 54 and occurring most commonly in the uterus. 5-year survival was much worse at Stage IV compared to stages I and II.

Introduction

Soft tissue sarcomas are a heterogeneous group of mesenchymal-derived tumors that comprise approximately 0.7% of all malignancies. Approximately 5-10% of soft tissue sarcomas are leiomyosarcomas [1]. Myxoid leiomyosarcoma is a rare and aggressive variant of leiomyosarcoma. Of all cases of soft tissue sarcoma reported to the NCDB between 2004 and 2014, only 0.2% were myxoid leiomyosarcomas. Little over 100 cases of this cancer have been reported in the literature, most frequently as a uterine tumor [2]. This cancer was first described in 1982, and since that time few epidemiologic studies have been published. First described in 1982 by King, this tumor was characterized by its gelatinous appearance grossly and large amount of myxoid stroma on microscopic examination [3]. While most commonly reported in the literature as a uterine malignancy, myxoid leiomyosarcoma has been found in multiple locations, including the liver, heart, lung and extremities [4-7]. The true incidence and prognosis of myxoid leiomyosarcoma is unknown, as these are rare tumors and only 100 cases have been published in the literature [8]. In King's initial description of this tumor, 2 of the 6 developed recurrences and 4 of the 6 affected patients died of the disease [2]. In a study of 30 cases of myxoid leiomyosarcoma by Parra-Herran et al, follow-up data for 18 of the subjects showed an overall 5-year survival rate of 11.1% [2]. Conversely, authors of a prognostic study of 18 cases of uterine myxoid leiomyosarcoma in Norway found this cancer had a slightly better 5-year survival rate with a 51% 5-year survival when diagnosed at stage I [9].

We sought to determine the clinical, demographic and survivorship characteristics of patients diagnosed with myxoid leiomyosarcoma in order to provide a more comprehensive cohort of patients. This study examines several clinicopathological factors as well as survival data associated with 485 patients diagnosed with myxoid leiomyosarcoma from 2004-2014.

Material and Methods

The National Cancer Database (NCDB) is a nationwide oncology outcomes database established by the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society in 1989. The database contains approximately 70% of all newly diagnosed cases of cancer in the U.S., which are reported by CoC accredited cancer programs [10]. Access to this Health

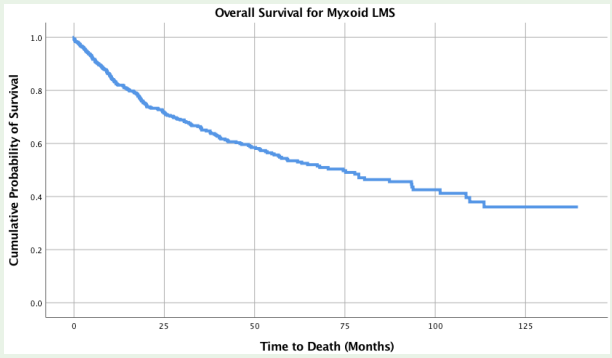

Figure 1: Overall survival for patients with Myxoid Leiomyosarcoma, n= 485.

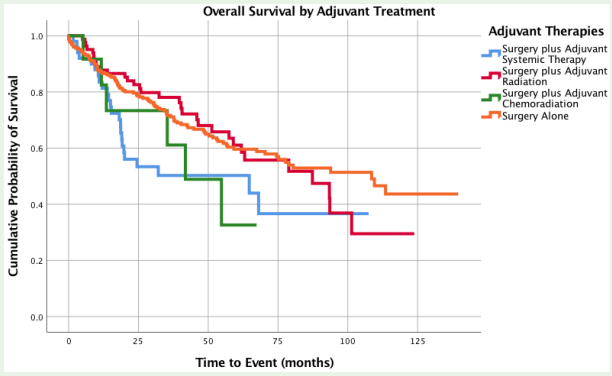

Figure 3: Overall Survival by Adjuvant Therapy, n = 422 and p value=0.048.

Insurance Portability and Accountability (HIPAA)-compliant data was provided to the authors as part of the NCDB's Participant Use File (PUF) program [11].

This was a retrospective study of myxoid leiomyosarcoma in patients diagnosed from 2004-2014. Patients were extracted based on ICD-O-3 histology code 8896. Only patients that had isolated malignant myxoid leiomyosarcoma were analyzed and patients with myxoid leiomyosarcoma and other tumors were excluded from this analysis. This was accomplished by excluding primary sequence codes other than 00. Data analyzed in this study include age, race, sex, year of diagnosis, anatomic site of primary tumor, tumor grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated and cell type not determined), American Joint Commission on Cancer (AJCC) 7th edition pathologic and clinical stages, NCDB analytic stage group and adjuvant therapies. Anatomic site was coded based on the ICD-O-3 topography codes.

Overall survival rates were calculated for all patients, for each of the four NCDB analytic stages (Figures 1& 2, Table 4) and by adjuvant therapies (Figure 3, Table 7). The NCDB analytic stage groups were the AJCC 7th edition pathological staging groups if available. If pathological staging was not available, AJCC clinical staging was utilized. Adjuvant therapy reported was radiation, chemoradiation, or systemic therapy administered after surgery to decrease the chance of cancer recurrence. These three adjuvant therapy groups, along with surgery only therapy, were compared for survival outcomes. Overall survival was calculated from the date of diagnosis to the last known date of contact or date of death. Patients coded with incomplete data (Code 99) or not applicable (Code 88) were excluded from the descriptive and survival analysis. This study was deemed not to require Institutional Review Board (IRB) review by the Creighton University IRB as the data does not involve human subject under 45 CFR 46.102(f). Descriptive statistics and Kaplan-Meier survival curves were generated from the NCDB for all measures using SPSS version 25. Kaplan-Meier analyses were used to estimate 5-year overall survival, and log-rank tests were used to compare survival amongst stage and adjuvant therapy.

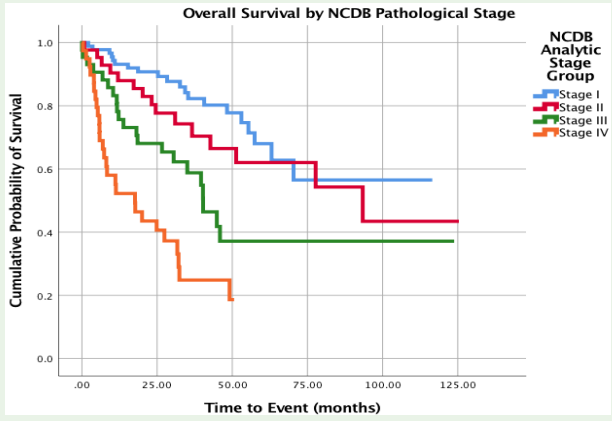

Figure 2: Overall Survival by NCDB Pathological Stage, n = 193 and p value<0.0005.

Results

Epidemiological variables, including age, year of diagnosis, sex and race, are displayed in Table 1. Median age at diagnosis was

Table 1: Epidemiologic Variables of 485 Patients with Myxoid Leiomyosarcoma.

Variable	N = 485	% of total
Age		
10-19	1	0.2
20-29	17	3.5
30-39	39	8.0
40-49	115	23.7
50-59	138	28.5
60-69	80	16.5
70-79	49	10.1
80-89	41	8.5
≥90	5	1
Year of Diagnosis		
2004-2009	258	53.2
2010-2014	227	46.8
Sex		
Male	85	17.5
Female	400	82.5
Race		
Caucasian	369	76.1
African American	93	19.2
Asian	5	1
American Indian, Aleutian or Eskimo	2	0.4
Asian Indian, or Pakistani	1	0.2

Table 2: Tumor Characteristics of 485 Patients with Myxoid Leiomyosarcoma.

Variable	N = 485	% of Total
Primary Site of Cancer*		
Head, face, or neck	7	1.4
Upper limb or shoulder	25	5.2
Lower limb or hip	56	11.6
Heart	2	0.4
Thorax	11	2.3
Abdomen	53	10.9
Pelvis	45	9.3
Female Reproductive Organs**	272	56.1
Trunk, NOS	6	1.2
Overlapping lesion	1	0.2
Other soft tissues, NOS	7	1.4
Tumor size		
< 10 cm	184	37.9
≥ 10 cm	211	43.5
Unknown	90	18.5
Tumor grade		
Well-differentiated	48	9.9
Moderately-differentiated	60	12.4
Poorly-differentiated	98	20.2
Undifferentiated, an plastic	51	10.5
Cell type not determined	228	47.0
AJCC Pathologic Stage		
Stage I	79	16.3
Stage II	43	8.9
Stage III	38	7.84
Stage IV	33	6.80
Not Applicable or Unknown	292	60.2

*All include connective, subcutaneous and other soft tissue of: **A breakdown of female reproductive organs listed in table 3.

54 years. Four hundred (400) of the patients were female (82%) and 85 (18%) were male.Seventy-six (76%) percent of cases were in Caucasian patients and 19.2% occurred in African Americans. Table 2 shows descriptive statistics about the primary sites of cancer, tumor size, tumor grade and AJCC pathological stage. The majority of primary tumors were located in the female reproductive tract (56.1%). Specifically, the uterus (56.6%) was the most common site of myxoid LMS in the female reproductive system. A breakdown of the different female reproductive organs affected by myxoid LMS is shown in Table 3. Most of the tumors were at least 10 cm in size and the mediantumor size was 12.0. Excluding missing data, the most common pathologic stage was Stage I (16.3%). Approximately 13.9% of patients had metastases present at the time of diagnosis. Metastasis data, including metastases present at diagnosis and the location of these metastases, is shown in Table 4.

As shown in Table 4, approximately 90% of patients received surgery as the primary treatment, while 26.8% received radiation, and 37% received chemotherapy. Table 5 shows adjuvant therapy choices based on which stage the patient was in. Median overall survival was 74.5 months. The overall estimated 5-year survival was approximately 53.5% and shown in Figure 1. There was a statistically

Table 3: Female Reproductive Organ Primary Sites of Cancer.

Variable	N= 272	% of Total
Female Reproductive Organ		
Uterus	154	56.6
Myometrium	67	24.6
Endometrium	33	12.1
Vagina and Vulva	12	4.4
Ovary	5	1.8
Breast	1	0.4

significant difference in probability of survival between all stages as the log-rank test reported a p value of <0.0005. 5-year survival probability and median survival descriptive statistics on staging were shown in table 6. As shown in Figure 2, average 5-year survival rates for Stages I and II based on NCDB analytic stage were 68% and 62%, respectively. The 5-year survival rate for Stage III was 37% and Stage IV was approximately 19%.

Table 6 and Figure 3 shows probability of 5-year survival and median survival for adjuvant therapies in addition to surgery. A log-rank comparison between the therapy groups resulted in a significance of 0.048. The surgery only therapy had the highest median survival of 108.5 months, while surgery with adjuvant radiation resulted in a median survival of 87.3 months. The highest 5-year survival was seen in surgery with adjuvant radiation at 61.1%. The second highest 5-year survival was surgery alone with 59.6%. The worst 5-year survival and median survival was surgery with adjuvant chemoradiation with 32.6% and 41.8 months, respectively.

Table 4: Metastases Present at Diagnosis and Treatment Modality.

Variable	N= 485	% of Total
Metastases Present at Diagnosis		
No distant metastasis	392	80.8
Distant lymph node(s)	3	0.6
Distant metastasis except distant lymph node(s), Carcinomatosis	62	12.8
Distant metastasis plus distant lymph nodes	10	0.5
Unknown	18	3.7
Location of Metastases		
Bone	3	0.6
Lung	18	3.7
Liver	9	1.9
Brain	1	0.2
Lymphatic or Vascular invasion	35	7.2
Primary Treatment Modality	**N=485**	**% of Total**
Surgery	434	89.5
Radiation	130	26.8
Chemotherapy	179	37
Adjuvant Therapy	**N=434**	**% of Total**
Surgery Only	268	61.8
Surgery with Radiation	90	20.7
Surgery with Systemic Therapy	61	14.1
Surgery with Chemoradiation	15	3.5

Table 5: Adjuvant Therapy Choice by Stage.

NCDB Stage	Surgery Only	Surgery with Systemic Therapy	Surgery with Radiation	Surgery with Chemoradiation
I	65	12	17	2
II	27	8	17	2
III	23	8	14	0
IV	13	4	7	2

Table 6: Survival by Stage, n = 193p value<0.0005.

NCDB Stage	Number of Patients in Stage	Probability of 5-Year Survival (%)	Median Survival (months)
I	79	68	84.6*
II	43	62	93.4
III	38	37	40.3
IV	33	18.6	17.6

*Mean survival used when median survival was unavailable.

Table 7: Survival by Adjuvant Therapy to Surgery, Adjuvant Therapy.

Adjuvant Treatment	Probability of 5-Year Survival (%)	Median Survival(months)
Surgery Only	59.6	108.5
Surgery with Adjuvant Radiation	61.1	87.3
Surgery with Adjuvant Systemic Therapy	50.2	64.7
Surgery with Adjuvant Chemoradiation	32.6	41.8

n = 422, p value=0.048.

Discussion

This is the largest study evaluating myxoid leiomyosarcoma. In this NCDB analysis, the most common primary tumor site was the female reproductive tract (56.1%), more specifically the smooth muscle of the uterus. The second most common site was the lower limb or hip (11.6%). Seventy-six percent of patients who presented with this cancer were Caucasian and 19.2% were African American. The incidence among Caucasians (76.1 %) mirrored the racial statistics of the most recent United States census (Caucasian-76.9%, African American-13.3%; [12]), while African American myxoid LMS (19.2 %) was slightly higher than the corresponding African American US population. The median age at diagnosis was 54 years, which is very similar to the Abeler's reported median age of 56.26 years [9]. These tend to be large tumors at presentation and Parra-Herran reported a mean tumor size of 10.8 cm [2]. In this study, 43.5% of tumors were ≥ 10 cm at diagnosis with a median tumor size of 12 cm. Approximately 14% of patients had metastases at the time of diagnosis. The most common site of metastasis was the lung (3.7%), and the most common primary treatment modality was surgery (89.5%).

One previous study reported an overall 5-year survival rate as high as 73 percent, but 11 of the 18 patients (61%) were Stage I at diagnosis [9]. Another study reported an overall 5-year survival rate of 11% in 18 cases and surprisingly the majority of those patients (88%) also presented with Stage I disease [2]. Our study found an overall 5-year survival of approximately 53.5% for 485 cases, with 16.3% of patients presenting at Stage I. The median survival for Stage IV was 17.6 months, while the mean and median survival for Stages I and II was much better, at 84.6 and 93.4 months, respectively. It is worth noting that approximately 60.2% of the cohort didn't have a listed stage and these patients were excluded from survival analysis on staging.

This was the first study to evaluate the 5-year and median survivals of different adjuvant therapies. There were four groups studied: surgery alone, surgery with adjuvant radiation, surgery with systemic chemotherapy, and surgery with chemoradiation. The best median survival was surgery alone. This could be due to a slightly higher percentage of patients in stage I when compared to other treatment modalities. The best probability of 5-year survival was surgery with adjuvant radiation, while the worst outcome in both categories was surgery with adjuvant chemoradiation. Adjuvant chemoradiation was utilized evenly throughout the stages with 2 patients in stages I, II and IV electing for adjuvant chemoradiation.

This work has several limitations. The largest limitation is the nature of utilizing the national cancer registry in a rare sarcoma. Pathological interpretations may vary due to tissue slides read by multiple pathologists from various institutions. Not having access to the pathological samples prevented confirmation that the patients included in this study did indeed have myxoid leiomyosarcoma and not leiomyosarcomas or leiomyomas, which limits the conclusions that can be drawn from this study. Cancer registry studiescarry the disadvantage that data is reported and collected by multiple different registrars, with potential inter-observer error. In addition, data reported from CoC-approved hospitals are abstracted from patient medical records, which may be inaccurately, incompletely, or improperly reported [11]. Because of the differences in staging and therefore aggressiveness of the lesion, there is likely a selection bias for different treatment options. Another limitation is the histologic

diagnosis often made by core needle biopsy, which has been shown to be inaccurate for histology in approximately 25% of cases [13].

To further enhance the clinicopathological and survivorship data determined in this article, we hope to utilize Surveillance, Epidemiology and End Results (SEER) research data to further analyze myxoid leiomyosarcoma. SEER will allow us to determine epidemiology data over a longer time course (1973-2014) and will provide us with information related to disease-specific death. Multivariable analysis with a large cohort is required to determine the independent prognostic impact of adjuvant therapy.

In conclusion, this is the largest study to date on myxoid leiomyosarcoma and major findings include a median age at diagnosis of 54 years, a female predominance with the uterus being the most common primary anatomical site, survival probability of 54%, approximately 14% of patients had metastases at the time of diagnosis, and stage I expectedly demonstrated the best 5-year survival rates.

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