RESEARCH ARTICLE

Is there a role for chemotherapy and radiation in the treatment of patients with low-grade myofibroblastic sarcoma?

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Abstract

Purpose Low-grade myofibroblastic sarcoma (LGMS) is a rare entity with a predilection for the head and neck. There are still no optimal treatment strategies for patients with LGMS. We retrospectively investigated the efficacies of chemotherapy and radiation treatment for patients with LGMS.

Methods/patients We obtained data from the Surveillance, Epidemiology, and End Result (SEER) database for 96 patients diagnosed with LGMS between 2001 and 2015. We used Kaplan–Meier curves and log-rank tests to estimate overall survival (OS) and Cox proportional hazard regression to identify prognostic factors.

Results The median age of the patients was 55.0 years. Twenty-two of the patients had LGMS in the head and neck region. Of the 96 patients, 86 (89.6%) received surgical treatment, 28 (29.2%) received radiation treatment, and 20 (10.4%) received chemotherapy. The mean OS was 125.2 [95% confidence interval (CI) 106.3–144.2] months. The 1, 3, 5, and 10-year OS rates were 88%, 77%, 70%, and 59%, respectively. Age greater than 60 years, positive nodal status, and no surgical treatment were independent prognostic factors for patients with LGMS, whereas chemotherapy and radiation treatment were not.

Conclusions Surgical resection is the most effective therapy for LGMS. Chemotherapy and radiation had limited effects on survival improvement for patients with LGMS. Therefore, chemotherapy and/or radiation therapy should not be routinely performed in LGMS, especially for those with negative margins after surgery.

Keywords Low-grade myofibroblastic sarcoma · Chemotherapy · Radiation · SEER program · Prognostic factors

Background

Low-grade myofibroblastic sarcoma (LGMS), first reported by Mentzel in 1998 [1], is an extremely rare entity originated from the mesenchyme with a predilection for the head and neck [2]. LGMS is characterized by myofibroblastic proliferation with fibromatosis-like features [3]. Recent literature describes LGMS at various sites including the skin [4], larynx [5], tongue [6], orbit [7], breast [3], femur [2], and posterior chest wall [8]. Local recurrence of LGMS is

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much more common than distant metastases [9]. When distant metastasis occurs in LGMS, the heart or lungs may be involved [10].

Owing to the rarity of LGMS, the optimal treatment is still unclear. Like other soft-tissue sarcomas, LGMS is primarily treated with surgical excision [11]. For patients without clear tumor margins, radiotherapy is an option [6]. A previous population-based cohort study that included 49 patients with LGMS from the Surveillance, Epidemiology, and End Results (SEER) database described the demographic and clinical characteristics of LGMS and investigated prognostic factors [12]. That study was hardly able to investigate the efficacies of adjuvant treatments, because information on chemotherapy was not available, and none of the patients had radiation as a single treatment modality. In two other cohort studies that included 18 and 15 patients with LGMS, only 4 and 3 patients, respectively, received chemotherapy or radiation [1, 13]. Therefore, the roles of radiation and chemotherapy in LGMS are still controversial. The purpose of the present study was to investigate the roles of chemotherapy and radiotherapy in the treatment of patients with LGMS using updated data from the SEER database.

Methods

Data source and patient population

We included patients with LGMS from the SEER database release of April 2019, named as Incidence—SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying), which included information about radiotherapy and chemotherapy. The patients were selected according to the third-edition ICD-O (ICD-O-3) histological code 8825/3: Myofibroblastoma, malignant, which represents LGMS. Patients diagnosed from 2001 to 2015 were included. Patients who were diagnosed at autopsy or via death certificate were excluded from our study.

The following data were retrieved for each patient: age at diagnosis (< 60 years or ≥ 60 years), gender (male or female), marital status (married, unmarried, or unknown), race (white or nonwhite), insurance status (insured, uninsured, or unknown), tumor grade (grade I–II, grade III–IV, or unknown), tumor size (< 4 cm, ≥ 4 cm, or unknown), nodal status (negative, positive, or unknown), SEER historic stage (localized, regional, distant, or unknown), surgical treatment (surgery or no surgery), and treatment with radiation and chemotherapy (yes, no, or unknown for each). The primary tumor site was classified as "head and neck" or "non-head and neck" according to Site Recode ICD-O-3/WHO 2008.

Statistical analysis

Quantitative data were described as the mean ± standard deviation (SD). Categorical data were presented as the number and percentage (N, %). Overall survival (OS) was defined as the time from LGMS diagnosis to death due to any cause or last known follow-up. Disease-specific survival (DSS) was defined as the time from LGMS diagnosis to cancer-related death or last known event (death or last follow-up). The variable of 'SEER cause-specific death classification' in the SEER database was used to identify cases died due to LGMS. Survival curves were generated using the Kaplan–Meier method. Log-rank test was used to determine the significance of differences between survival curves. To investigate the effect of treatments on survival, surgery, chemotherapy, radiotherapy, and other factors with $P < 0.05$ in the log-rank test were further analyzed in a multivariate Cox proportional hazard regression model. All statistical analyses were performed using SPSS 22.0 (IBM Corporation, Armonk, NY). All survival charts were prepared using MedCalc 18.11.3. Two-sided $P < 0.05$ was considered statistically significant.

Ethics statement

The SEER database is an open database. Data released from the SEER database do not require informed patient consent, because cancer is a reportable disease in every state of the United States. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Characteristics of the patients

A total of 96 patients were included in the analysis. The patient characteristics are shown in Table 1. Overall, there was a slight preponderance of females in the study sample (53.1% vs. 46.9%). The median age was 55.0 (interquartile range: 36.5–66.8) years. The majority of the patients were married (52.1%), white (79.2%), and medically insured (71.9%). Seventy-four patients had primary tumors located in regions other than the head and neck, including the extremities, abdomen, pelvis, and thoracic region. The other 22 patients had primary tumors in the head and neck region. The tumor grade was I–II and III–IV in 52.1% and 22.9% of the patients, respectively. Most of the tumors were larger than 4 cm (52.1%) and with negative nodal status (84.4%) at the time of first diagnosis. According to the SEER stage, 49 (51.0%) of the tumors were localized, 24 (25.0%) were

Table 1 Characteristics of the low-grade myofibroblastic sarcoma patients in the SEER database and the results of log-rank test for the Kaplan–Meier method in subject characteristics

Characteristics	No. (%)	OS		DSS	
		Mean survival (mon)	P (Log-rank)	Mean survival (mon)	P (Log-rank)
Age					
< 60	57 (59.4)	147.2	0.002	167.1	0.025
≥ 60	39 (40.6)	74.9		92.5	
Gender					
Male	45 (46.9)	106.8	0.616	124.4	0.523
Female	51 (53.1)	119.3		147.7	
Marital status					
Married	50 (52.1)	116.0	0.577	136.6	0.143
Unmarried	41 (42.7)	120.0		157.0	
Unknown	5 (5.2)	90.2		90.2	
Race					
White	76 (79.2)	130.0	0.548	152.4	0.878
Nonwhite	20 (20.8)	97.1		119.9	
Insurance					
Insured	69 (71.9)	79.3	0.440	89.6	0.660
Uninsured	2 (2.1)	–		–	
Unknown	25 (26.0)	133.7		156.4	
Primary site					
Head and neck	22 (22.9)	116.6	0.134	121.6	0.421
Non–head and neck	74 (77.1)	117.5		149.2	
Laterality					
Unilateral	54 (56.3)	119.1	0.151	135.0	0.423
Not a paired site	42 (43.8)	114.7		146.9	
Grade					
Grade I-II	50 (52.1)	130.2	0.028	150.7	0.016
Grade III-IV	22 (22.9)	87.6		115.5	
Unknown	24 (25.0)	115.5		133.3	
Tumor size					
< 4 cm	20 (20.8)	132.9	0.088	–	0.014
≥ 4 cm	50 (52.1)	86.7		98.3	
Unknown	26 (27.1)	128.7		142.9	
Nodal status					
Negative	81 (84.4)	109.8	0.036	122.9	0.012
Positive	3 (3.1)	15.3		15.3	
Unknown	12 (12.5)	104.3		155.9	
SEER stage					
Localized	49 (51)	132.6	0.004	156.5	0.017
Regional	24 (25)	123.5		128.8	
Distant	8 (8.3)	58.3		90.2	
Unknown	15 (15.6)	68.3		79.6	
Surgery					
Yes	86 (89.6)	131.2	0.011	153.3	0.450
No	10 (10.4)	71.1		119.1	
Radiation					
Yes	28 (29.2)	105.9	0.326	121.9	0.163
No/unknown	68 (70.8)	129.8		159.6	
Chemotherapy					
Yes	10 (10.4)	80.7	0.021	112.6	0.016
No/unknown	86 (89.6)	119.5		140.8	

SEER Surveillance, Epidemiology, and End Result; *OS* overall survival, *DSS* disease-specific survival
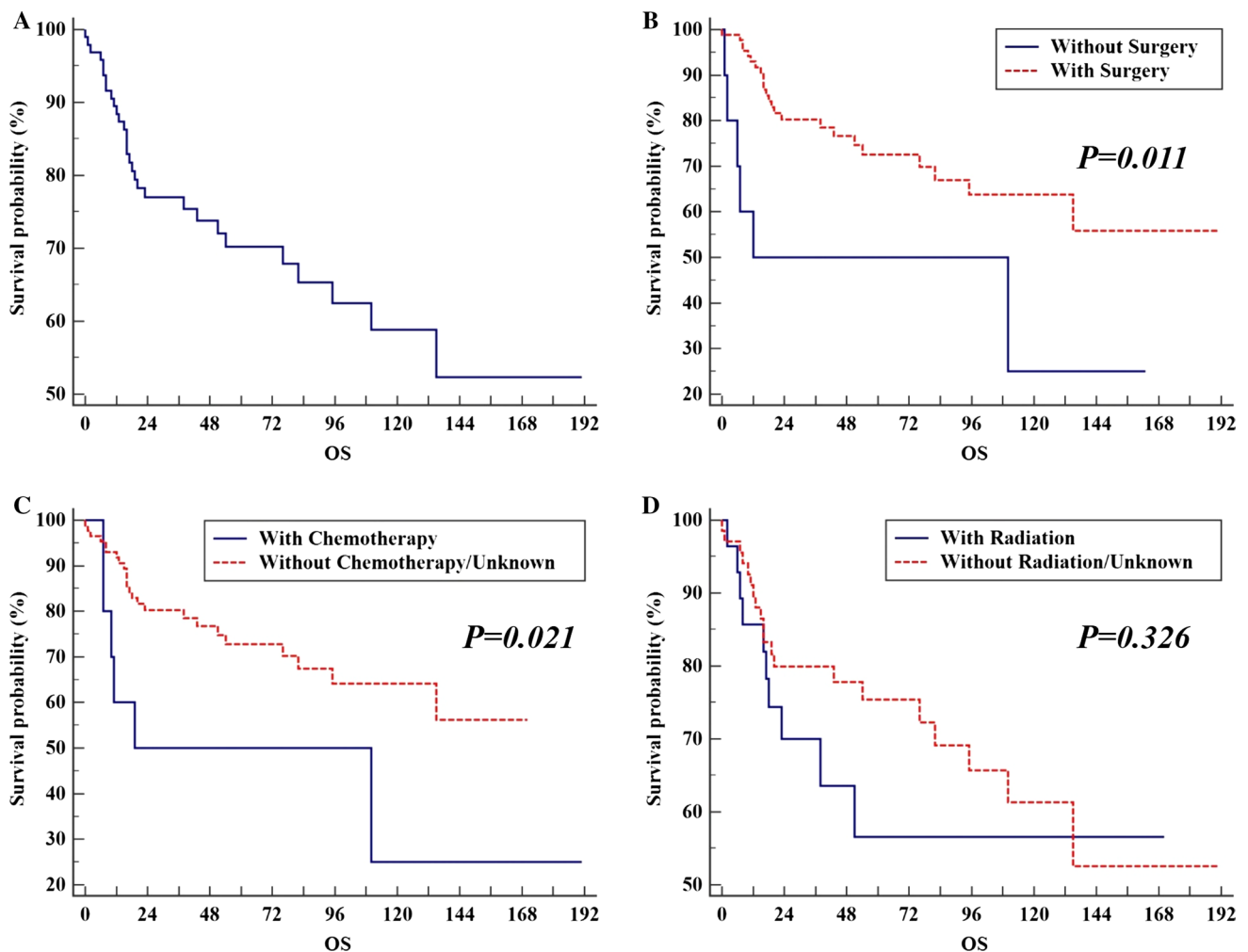
Fig. 1 Overall survival for the total cohort (**a**) and survival curves for patients with and without surgery (**b**), chemotherapy (**c**) and radiation (**d**)

regional, and only 8 (8.3%) were distant. Eighty-six (89.6%) of the patients received surgical treatment, 28 (29.2%) received radiation treatment, and 20 (10.4%) received chemotherapy.

Survival estimates and prognostic factors

The mean OS stratified by each variable is listed in Table 1. For the total cohort, the mean OS was 125.2 (95% CI 106.3–144.2) months. The 1, 3, 5, and 10-year OS rates were 88%, 77%, 70%, and 59%, respectively (Fig. 1a). OS curves for patients that received surgery, chemotherapy, and radiotherapy are shown in Fig. 1b–d. In the log-rank test, age, tumor grade, nodal status, SEER stage, surgery, and chemotherapy had significant effects on survival; however, radiotherapy did not. In the multivariate Cox regression analysis, age greater than 60 years [hazard ratio (HR) = 4.34; 95% CI 1.67–11.31], positive nodal status (HR = 16.31; 95% CI 2.15–123.76), and no

surgical treatment (HR = 4.84; 95% CI 1.15–20.33) were independent prognostic factors for patients with LGMS. Treatment with chemotherapy or radiation had no independent effects on OS in the multivariate analysis. The results of multivariate Cox regression analysis are shown in Table 2.

Overall, the mean DSS was 152.4 (95% CI 135.9–169.0) months. The 1, 3, 5, and 10-year DSS rates were 93%, 85%, 79% and 76%, respectively (Fig. 2a). The mean DSS stratified by each variable is listed in Table 1. The log-rank test showed that age, tumor grade, tumor size, nodal status, SEER stage, and chemotherapy had significant effects on DSS. DSS curves for patients that received surgery, chemotherapy, and radiation are shown in Fig.2b–d, respectively. Except for unknown SEER stage, positive nodal status was the only independent prognostic factor for DSS (HR = 24.90; 95% CI 2.24–276.87). Neither surgery, nor chemotherapy, nor radiation was an independent prognostic factor for DSS.

Table 2 Multivariable Cox regression for analyzing the prognosis factors for low-grade myofibroblastic sarcoma patients in the SEER database

Subject characteristics	OS		DSS	
	P value	HR (95% CI)	*P* value	HR (95% CI)
Age				
< 60	1.0	1	1.0	1
≥ 60	0.003	4.34 (1.67–11.31)	0.089	2.98 (0.85–10.52)
Grade				
Grade I-II	1.0	1	1.0	1
Grade III-IV	0.083	2.30 (0.90–5.89)	0.070	3.86 (0.90–16.60)
Unknown	0.484	0.66 (0.20–2.13)	0.852	1.16 (0.25–5.42)
Tumor size				
< 4 cm	1.0	1	1.0	1
≥ 4 cm	–	–	0.932	NA
Unknown	–	–	0.936	NA
Nodal status				
Negative	1.0	1	1.0	1
Positive	0.007	16.31 (2.15–123.76)	0.009	24.90 (2.24–276.87)
Unknown	0.596	1.38 (0.42–4.52)	0.961	1.06 (0.11–9.89)
SEER stage				
Localized	1.0	1	1.0	1
Regional	0.362	1.62 (0.58–4.56)	0.094	3.44 (0.81–14.61)
Distant	0.136	2.95 (0.71–12.24)	0.989	0.98 (0.07–13.93)
Unknown	0.086	2.66 (0.87–8.12)	0.020	7.70 (1.38–42.96)
Surgery				
Yes	1.0	1	1.0	1
No	0.031	4.84 (1.15–20.33)	0.344	2.80 (0.33–23.55)
Radiation				
Yes	1.0	1	1.0	1
No/unknown	0.053	0.39 (0.15–1.01)	0.140	0.34 (0.08–1.43)
Chemotherapy				
Yes	1.0	1	1.0	1
No/unknown	0.805	0.85 (0.22–3.21)	0.832	0.83 (0.14–4.92)

SEER Surveillance, Epidemiology, and End Result, *OS* overall survival, *DSS* disease-specific survival

The results of the multivariate Cox regression analysis for DSS are shown in Table 2.

The role of chemotherapy and radiation in patients treated with surgery

Of the ten patients that did not receive surgery, three received radiotherapy, and two underwent chemotherapy. Of the other 86 patients, 54 received surgical treatment alone. The mean OS among those patients was 114.8 (95% CI 99.2–130.4) months. Seven patients received both surgery and chemotherapy. The mean OS among those patients was 88.6 (95% CI 22.8–154.3) months. Four of the patients that received surgery and chemotherapy were deceased by the time of last follow-up, three because of tumor-related causes. Twenty-four patients received both surgery and radiotherapy. The mean OS among those patients was 115.9 (95% CI 82.9–148.9) months. One patient received surgery,

chemotherapy, and radiotherapy and was still alive at the last follow-up with 39 months of survival. The distribution of patient survival outcomes is shown according to the different treatment strategies in Fig. 3. Survival curves for patients that received the different treatments are shown in Fig. 4.

Discussion

LGMS is classified as a distinct type of soft-tissue tumor by the World Health Organization [6]. The purpose of our study was to estimate the survival of patients with LGMS in the United States and to investigate the efficacies of chemotherapy and radiotherapy in the treatment of those patients. Our analysis revealed a series of prognostic factors. Nodal status was an independent prognostic factor for OS and DSS in the present study. Its clinical value should not be overestimated based on current statistical evidence, because only
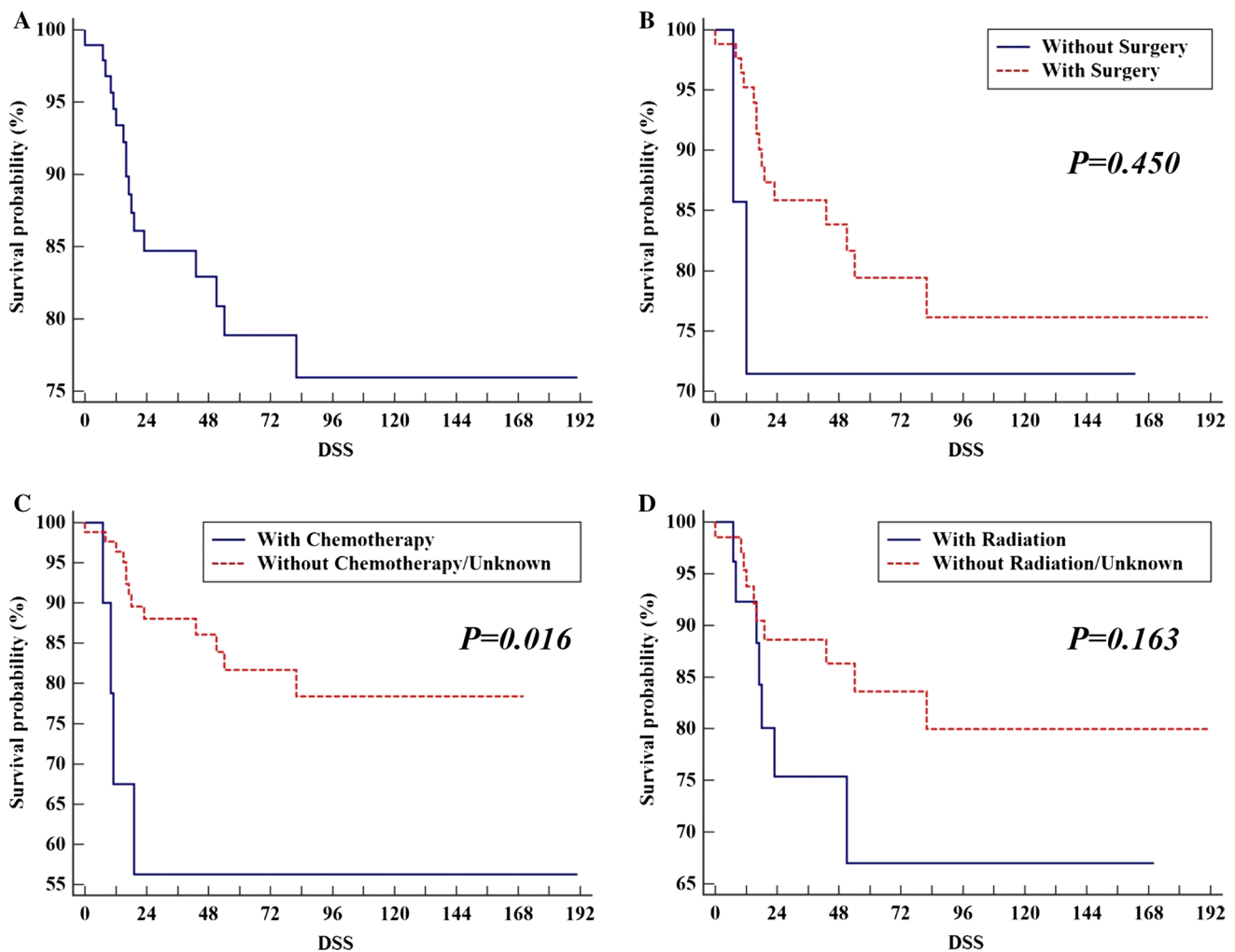
Fig. 2 Disease-specific survival for the total cohort (**a**) and survival curves for patients with and without surgery (**b**), chemotherapy (**c**) and radiation (**d**)

three of the patients in the analysis had positive nodal status (3.1%). In a previous SEER cohort of patients with LGMS, there was only one case of lymph metastasis, so nodal status was not significantly associated with patient survival [12]; however, age greater than 60 years was associated with worse OS and DSS (OS: HR = 11.3, $P = 0.01$; DSS: HR = 15.5, $P = 0.02$) [12]. In accordance with those results, age at diagnosis was an independent prognostic factor for OS in our cohort. Because of the rarity of LGMS, more prognostic factors for patients with LGMS are likely to be found as more data become available.

Surgical resection with a negative margin is the primary means to prevent local recurrence in soft-tissue tumors [14]. Keller et al. emphasized the importance of surgery in the long-term survival of two children that were diagnosed with stage I myofibrosarcoma [11]. Due to low incidence of LGMS and the missing data, up to now, no large population-based studies investigated the correlation between surgical

margin and survival of LGMS [1, 12, 13]. Several case reports concluded that LGMS patients with negative margins were free of disease in follow-up [5, 15]. On the other hand, it was reported that three patients with positive margins dead of currencies despite of receiving radiation treatment after surgery [16]. In our cohort, patients that received surgical treatment had longer OS than those that did not receive surgical treatment. Absence of surgical treatment was a poor prognostic factor for OS, although it was not an independent prognostic factor for DSS. Surgical margins and operation methods were not available in the present database and their effect on survival should be investigated in further studies.

There is currently no guideline recommending chemotherapy for patients with LGMS, and the role of adjuvant chemotherapy remains unclear [12]. Previous reports have suggested a limited role for chemotherapy in the treatment of LGMS [11, 15]. There are some case reports of patients with LGMS that received chemotherapy [5, 8, 17]. The authors

Fig. 3 The distribution of patient's survival outcome according to different treatment strategies
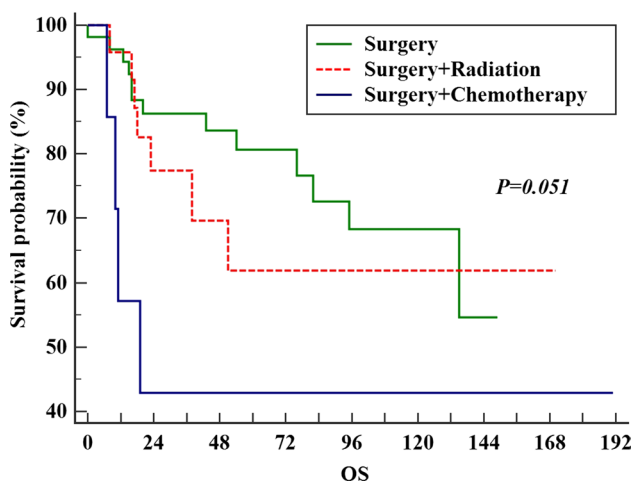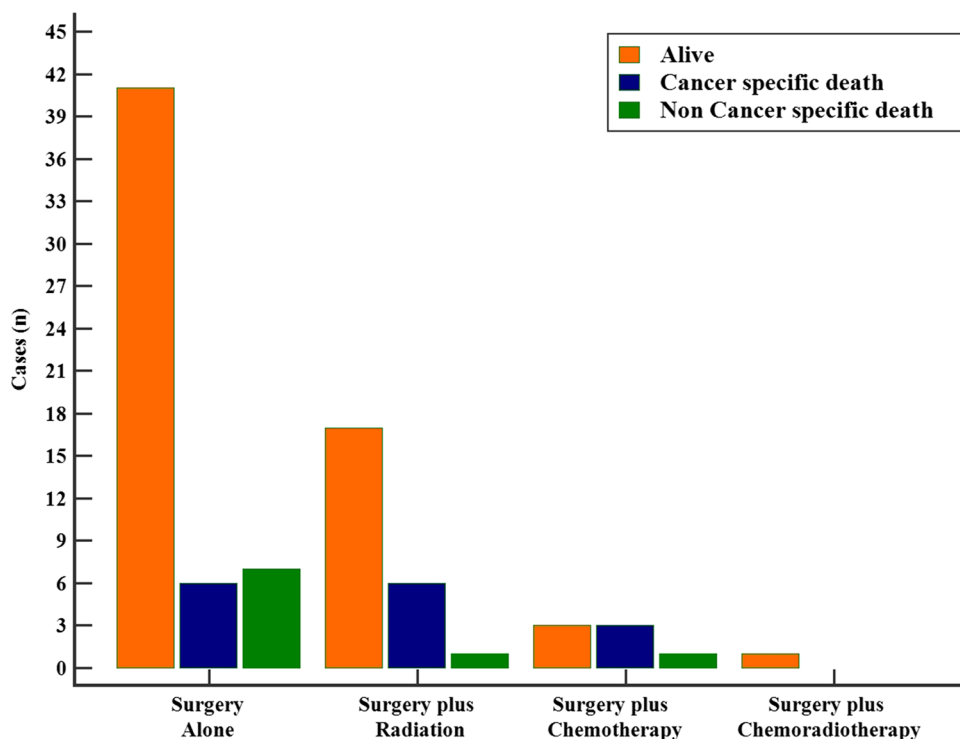

Fig. 4 Survival curves for different treatments in 86 patients treated with surgery

of those reports recommended adjuvant chemotherapy as a potential treatment strategy, particularly when complete excision of the tumor is difficult. Chemotherapy might also be considered if the tumor shows evidence of invasion into adjacent tissues or if there is evidence of lymphatic and/ or hematological metastasis [16]. One patient had substantial clinical improvement after chemotherapy [8]; however, because of the scarcity of clinical evidence on the efficacy and side effects, chemotherapy was not generally recommended [7]. An 8-year-old girl that was diagnosed with

LGMS presented a 0.5 cm increase in tumor diameter after receiving three courses of neoadjuvant chemotherapy. That patient subsequently underwent surgical treatment, and there was no imaging evidence of recurrence 6 years after surgery [11]. In our study, patients that did not receive chemotherapy or whose chemotherapy status was unknown had longer survival than patients that received chemotherapy. Chemotherapy was not an independent prognostic factor for patients with LGMS, however. The relatively longer survival of patients that did not receive chemotherapy might be explained by the small sample size of patients that received chemotherapy or by treatment bias on the part of the oncologists. Furthermore, as a type of rare sarcoma, LGMS may be pathological misdiagnosis, which leaded to overtreatment or undertreatment.

A previous case report suggested that radiation might be a curative treatment for intermediate-grade myofibroblastic sarcoma [6]; however, LGMS is generally thought to be poorly responsive to radiation therapy [18]. The role of radiation could not be assessed in a previous analysis of patients with LGMS in the SEER database, because none of the patients had radiation as a single-modality therapy [12]. In our cohort, 28 patients received radiation treatment, but only 2 of those had radiation as the single mode of treatment. Radiotherapy was not an independent prognostic factor for LGMS in our cohort.

This work had some limitations. First, some variables were not available in the SEER database, including the extent of surgical resection, lymph node dissection, and

margin status. Each of those variables has been associated with the survival of patients with soft-tissue sarcomas [19, 20]. Second, although previous studies reported that the oral cavity is the most common site of primary LGMS [7, 15], the oral cavity was the primary tumor site in only four patients in our cohort. That difference might be attributed to inaccurate coding within the SEER database [12]. Third, the specific regimen of the adjuvant chemotherapy was not available in the SEER database. Therefore, we could not analyze the effects of certain chemotherapy regimens on LGMS. Besides, there was more than 25% missing data for the factors of tumor grade and tumor size. During the analysis, we coded these cases with missing data as "unknown" and incorporated them into the multivariable regression model. Although the statistical power of the results was guaranteed, the results may be partly affected and the results should be explained with caution. Last but not least, detailed treatment performance information was not available in SEER database. Thus, the present study cannot give further analyses on different effects led by the order of treatment performance.

Conclusions

LGMS is an extremely rare sarcoma. The mean OS among 96 patients with LGMS was 125.2 months. Nodal status was an independent prognostic factor for OS and DSS. Age greater than 60 years and no surgical treatment were poor independent prognostic factors for OS. Surgical resection is the primary treatment modality for LGMS. Chemotherapy and radiotherapy showed limited effects on patient survival. Adjuvant application of chemotherapy and/or radiotherapy in patients with LGMS was not correlated with improved survival. Therefore, chemotherapy and/or radiotherapy should not be routinely performed to treat LGMS patients with negative margins. For patients with positive margins or recurrent disease, chemotherapy and/or radiation cloud be an alternative treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The SEER database is an open database. Data released from the SEER database do not require informed patient consent, because cancer is a reportable disease in every state of the United States. The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

References

1. Mentzel T, Dry S, Katenkamp D, Fletcher CD. Low-grade myofibroblastic sarcoma: analysis of 18 cases in the spectrum of myofibroblastic tumors. Am J Surg Pathol. 1998;22:1228–38.
2. Arora R, Gupta R, Sharma A, Dinda AK. A rare case of low-grade myofibroblastic sarcoma of the femur in a 38-year-old woman: a case report. J Med Case Rep. 2010;4:121.
3. Myong NH, Min JW. Low-grade myofibroblastic sarcoma arising in fibroadenoma of the breast-A case report. Diagn Pathol. 2016;11:33.
4. Diaz-Cascajo C, Borghi S, Weyers W, Metze D. Fibroblastic/myofibroblastic sarcoma of the skin: a report of five cases. J Cutan Pathol. 2003;30:128–34.
5. Covello R, Licci S, Pichi B, Spriano G, Vidiri A, Morelli L, et al. Low-grade myofibroblastic sarcoma of the larynx. Int J Surg Pathol. 2011;19:822–6.
6. Takacsi-Nagy Z, Murakozy G, Pogany P, Fodor J, Orosz Z. Myofibroblastic sarcoma of the base of tongue. Case report and review of the literature. Strahlenther Onkol. 2009;185:198–201.
7. Zhang S, Ma Y, Ma T, Wang Z. Low-grade myofibroblastic sarcoma of the orbit. Medicine. 2017;96:e9172.
8. Katalinic D Santek F. Giant low-grade primary myofibroblastic sarcoma of the posterior chest wall. World J Surg Oncol. 2017;5(1):96.
9. Agaimy A, Wunsch PH, Schroeder J, Gaumann A, Dietmaier W, Hartmann A, et al. Low-grade abdominopelvic sarcoma with myofibroblastic features (low-grade myofibroblastic sarcoma): clinicopathological, immunohistochemical, molecular genetic and ultrastructural study of two cases with literature review. J Clin Pathol. 2007;61:301–6.
10. Oylumlu M, Yildiz A, Ercan S, Oylumlu M, Davutoglu V. Cardiac metastasis of a low-grade myofibroblastic sarcoma. Echocardiography. 2014;31:E1–4.
11. Keller C, Gibbs CN, Kelly SM, Haller JR, White KS, Coffin CM, et al. Low-grade myofibrosarcoma of the head and neck: importance of surgical therapy. J Pediatr Hematol Oncol. 2004;26:119–20.
12. Chan JY, Gooi Z, Wong EW, Ng SK, Tong MC, Vlantis AC. Low-grade myofibroblastic sarcoma: a population-based study. Laryngoscope. 2017;127:116–21.
13. Montgomery E, Goldblum JR, Fisher C. Myofibrosarcoma: a clinicopathologic study. Am J Surg Pathol. 2001;25:219–28.
14. Eyden B, Banerjee SS, Shenjere P, Fisher C. The myofibroblast and its tumours. J Clin Pathol. 2009;62:236–49.

15. Tomohiro YTYN. Low-grade myofibroblastic sarcoma of the palate. Int J Oral Sci. 2012;4:170–3.

16. Meng GZ, Zhang HY, Bu H, Yang GH, Zhang XL, Yang G. Myofibroblastic sarcoma of the nasal cavity and paranasal sinus: a clinicopathologic study of 6 cases and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104:530–9.

17. Peng L, Tu Y, Li Y, Xiao W. Low-grade myofibroblastic sarcoma of the pancreas: a case report and literature review. J Cancer Res Ther. 2018;14:S796–S799799.

18. Smith DM, Mahmoud HH, Jenkins JR, Rao B, Hopkins KP, Parham DM. Myofibrosarcoma of the head and neck in children. Pediatr Pathol Lab Med. 1995;15:403–18.

19. Rosko AJ, Birkeland AC, Chinn SB, Shuman AG, Prince ME, Patel RM, et al. Survival and margin status in head and neck radiation-induced sarcomas and de novo sarcomas. Otolaryngol Head Neck Surg. 2017;157:252–9.

20. Johannesmeyer D, Smith V, Cole DJ, Esnaola NF, Camp ER. The impact of lymph node disease in extremity soft-tissue sarcomas: a population-based analysis. Am J Surg. 2013;206:289–95.