• Clinical Research •

Adjuvant therapy for orbital non-rhabdomyosarcoma soft tissue sarcoma: comparison of long-term outcome between radiotherapy and chemotherapy

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Abstract

● **AIM:** To illustrate clinicopathological features of orbital non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and to compare the treatment outcome between postoperative radiotherapy (RT) and chemotherapy in a retrospective analysis nearly 20y.

● **METHODS:** A retrospective cohort study of 56 patients with orbital NRSTS were reviewed, 34 of whom received postoperative RT, and 22 received postoperative chemotherapy. The clinicopathological features, local recurrence, metastases, and survival data were recorded. Survival analysis was performed using the Kaplan-Meier method.

● **RESULTS:** During follow-up (111.8mo, ranged 8-233mo) for 56 patients, 19 patients of them developed local recurrence, and 7 patients developed distant metastases. Fifteen patients died during follow-up period. Overall survival rates considering the whole study group was 78.57% at 5y, and 72.16% at 10y after the initial diagnosis. Compared with chemotherapy, RT was associated with lower risk of local recurrence [hazard ratio for RT *vs* chemotherapy, 0.263, 95% confidence interval (CI), 0.095-0.728, *P*=0.0015]; with lower risk of distant metastasis (hazard ratio for RT *vs* chemotherapy, 0.073, 95%CI, 0.015-0.364, *P*=0.0014); and with lower risk of death from disease (hazard ratio for RT *vs* chemotherapy, 0.066, 95%CI, 0.022-0.200, *P*<0.0001). The 5-year survival rate in RT group was 97.06% compared to 50% in chemotherapy group.

● **CONCLUSION:** In patients with orbital NRSTS, postoperative RT provides better control of local recurrence, distant metastasis, and death from disease than chemotherapy. RT is the more preferrable adjuvant therapy compared to chemotherapy possibly.

● **KEYWORDS:** orbital tumor; non-rhabdomyosarcoma soft tissue sarcoma; oncological outcome; adjuvant radiotherapy; adjuvant chemotherapy

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INTRODUCTION

Soft tissue sarcomas (STSs) are rare malignant entities arising from mesenchymal tissues, while non-rhabdomyosarcoma soft tissue sarcomas (NRSTSs) are even rare. A heterogeneous group of nearly 50 histopathological subtypes can be assigned into NRSTSs[1]. Orbital STSs account for 3% to 5% of orbital tumors in adults and 4% to 7% in children[2-3], however, little studies focus on orbital NRSTS.

Surgical resection is the standard treatment for all localized NRSTS, but recurrence and metastases occur in approximately half of the patients with localized NRSTS. Little studies focus on the treatment for orbital sarcoma, except for pediatric rhabdomyosarcoma, which is the most common pediatric orbital malignant tumor[4]. Previous studies convinced rhabdomyosarcoma including orbital lesions was relatively sensitive to chemotherapy and irradiation[5-7].

For most types of NRSTSs, surgery with wide margins remains the cornerstone of curative intent treatment, however, wide margins in the orbit are often difficult to achieve due to the proximity of vital structures or the destruction of appearance. Therefore, surgery combined with adjuvant therapy has been

utilized to improve the outcome of localized NRSTS. There is variability in the chemosensitivity and radiosensitivity of sarcoma subtypes. However, there were little literatures revealing the efficiency difference between radiotherapy (RT) and chemotherapy for orbital NRSTS. We herein report our observations in a series of orbital NRSTSs treated at our center, including our observations regarding the efficacy of RT and chemotherapy.

SUBJECTS AND METHODS

Ethical Approval This project was approved by the Research Ethics Committee of Fudan Eye and ENT Hospital [approval number: [2021](2021082)], and was in accordance with the tenets of the Declaration of Helsinki. The requirement for patient informed consent was waived given the retrospective nature, for the study will not affect patient treatment and will not lead privacy leakage. In addition, bias might be introduced into the study if we only include those patients for whom consent was obtained. This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Patient Recruitment Patients with orbital tumors who referred to Fudan Eye and ENT Hospital from 2002 to 2014 were reviewed. The inclusion criteria were as follows: 1) patients who had a clear pathology diagnosis of sarcoma; 2) patients who had the orbital region listed as the primary disease lesion. We identified 91 patients with a diagnosis of orbital sarcoma received surgery in our institution during the study period. The exclusive criteria were as follows: 1) patients who were diagnosed as rhabdomyosarcoma (n=26); 2) patients who couldn't be followed by any type of communication (n=2); 3) patients who were treated by surgery alone (n=4); 4) patients who received chemotherapy plus irradiation (n=3). Finally, 56 patients were included in the study.

Clinicopathologic Information The clinical data encompassing age, gender, laterality, main symptom, duration of symptoms, clinicoradiological information needed for the American Joint Committee on Cancer (AJCC) TNM category (location, tumor size, invasion of orbital structures and/or adjacent periorbital structures, and presence of lymph node metastasis, distant metastasis at presentation), resection margin, World Health Organization (WHO) histologic categorization, the French Federation of Cancer Centers Sarcoma Group (FNCLCC) staging (G1, G2, G3), and adjuvant treatment (RT, chemotherapy) were comprehensively reviewed. The computed tomography (CT) and magnetic resonance imaging (MRI) scans, when available, were reviewed by an experienced ophthalmologist.

The duration of symptoms was defined as the time interval between onset and surgery, presented as months. Tumor location was categorized into intraconal and extraconal according to the anatomical position of the point at the center of each lesion[8]. Tumor volume was counted by the largest diameter of the tumor on radiologic scans, or by the diameters recorded in the process of surgery. The surgery details were acquired from the surgical reports. All the tumors were resected with curative intent, and the tumor margins were assessed by surgery recording and pathology findings, which could be classified into: R0: negative/clean margins; R1: positive/involved margins; Rx: the presence of residual tumor cannot be assessed microscopically, for the tumors were resected piece by piece. TNM category was assessed based on the findings when the patient received surgery at our center according to the AJCC 8th edition criteria for orbital sarcoma[9].

Follow-up Data Follow-up data were acquired by electronic outpatient database or telephone interviews. All cases were followed up to January 2021, or the time of last follow-up. Time to recurrence, metastasis, and death were defined as the interval between the date of surgery and the date of corresponding event. Survival rates were calculated by survival analysis.

Statistical Analysis For continuous data, the differences between groups were analyzed using t-test when the data conformed to normal distribution, and using the non-parametric Mann-Whitney test when the data did not conform to normal distribution. The Two-tailed χ^2 test or Fisher's exact test for categorical variables was used to determine the differences. Survival analysis was performed using the Kaplan-Meier method. The statistical analyses mentioned above were conducted using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients' demographics and clinical characteristics are shown in Table 1. There are 33 (58.9%) male subjects. The mean age was 30.6±2.88y (range, 2-74y). The right eye was involved in 26 (46.4%) patients. Eleven (19.6%) cases were locally recurrent orbital tumors treated at another hospital before referred to our center, and none of secondary tumors originating from paranasal sinus to the orbit or of metastasis from tumors at distant sites. These tumors were extraconal in 57.1% of subjects (32 patients). The median tumor volume was 5.24 cm^3 (range, 0.21-26.82 cm^3). Tumor invasion of adjacent structures was seen in 9 (16.1%) patients, 2 of which affected cranial fossa, 4 of which affected nasal cavity and/or paranasal sinuses, and 3 of which affected temporal fossa. Notably, tumors with invasion of orbital bone were classified into tumors confined in the eye region. The detailed TNM categories are listed in Table 1.

Surgical resection was performed in all patients with curative intent. Forty-nine (87.5%) cases accepted eyeball preserved surgery. Seven (12.5%) patients received orbital exenteration surgery soon after biopsy, however, 1 of which still suffered

Table 1 Patient and tumor characteristics *n* (%)

Category	Total (*n*=56)	Adjuvant therapy		
		Radiotherapy (*n*=34)	Chemotherapy (*n*=22)	*P*
Age (y), mean±SD (range)	30.6±2.88 (2-74)	36.4±3.35 (2-74)	31.64±4.67 (3-68)	0.814
Gender				0.565
Male	33 (58.9)	19 (55.9)	14 (63.6)	
Female	23 (41.1)	15 (44.1)	8 (36.4)	
Laterality				0.013
Right	26 (46.4)	11 (32.4)	15 (68.2)	
Left	30 (53.6)	23 (67.6)	7 (31.8)	
Primary or recurrent at presentation				0.736
Primary	45 (80.4)	28 (82.4)	17 (77.3)	
Recurrent	11 (19.6)	6 (17.6)	5 (22.7)	
Tumor volume (cm^3), median (range)	5.24 (0.21-26.82)	5.53 (0.38-26.82)	5.04 (0.21-16.02)	0.609
TNM staging				
T category				0.694
T1	16 (28.6)	10 (29.4)	6 (27.3)	
T2	29 (51.8)	19 (55.9)	10 (45.5)	
T3	2 (3.6)	1 (2.9)	1 (4.6)	
T4	9 (16.1)	4 (11.8)	5 (22.7)	
N category				0.555
N0	53 (94.6)	33 (97.1)	20 (90.9)	
N1	3 (5.4)	1 (2.9)	2 (9.1)	
M category				NA
M0	56 (100)	34 (100)	22 (100)	
M1	0 (0)	0 (0)	0 (0)	
Tumor location				0.752
Extraconal	32 (57.1)	20 (58.8)	12 (54.5)	
Intraconal	24 (42.9)	14 (41.2)	10 (45.5)	
Invasion of adjacent periorbital structures				0.294
None	47 (83.9)	30 (88.2)	17 (77.3)	
Yes	9 (16.1)	4 (11.8)	5 (22.7)	
Surgical resection				0.692
Eyeball preserved	49 (87.5)	29 (85.3)	20 (90.9)	
Orbital exenteration	7 (12.5)	5 (14.7)	2 (9.1)	
WHO histologic categorization of tumor				0.450
Adipocytic	3 (5.4)	2 (5.9)	1 (4.5)	
Fibroblastic/myofibroblastic	17 (30.4)	11 (32.4)	6 (27.3)	
Vascular	9 (16.1)	5 (14.7)	4 (18.2)	
Undifferentiated	11 (19.6)	6 (17.6)	5 (22.7)	
Peripheral nerve	6 (10.7)	4 (11.8)	2 (9.1)	
Round cell	10 (17.9)	6 (17.6)	4 (18.2)	
FNCLCC grading				0.351
G1	14 (25)	10 (29.4)	4 (18.2)	
G2	36 (64.3)	22 (64.7)	14 (63.6)	
G3	6 (10.7)	2 (5.9)	4 (18.2)	
Resection margins				0.946
R0: negative	18 (32.1)	12 (35.3)	9 (40.9)	
R1: positive (microscopic)	19 (33.9)	12 (35.3)	7 (31.8)	
Rx	19 (33.9)	10 (29.4)	6 (27.3)	

SD: Standard deviation; NA: Not applicable; WHO: World Health Organization; FCNLCC: French Federation of Cancer Centers Sarcoma Group; Rx: The margins could not be assessed as the tumors were resected piece by piece.

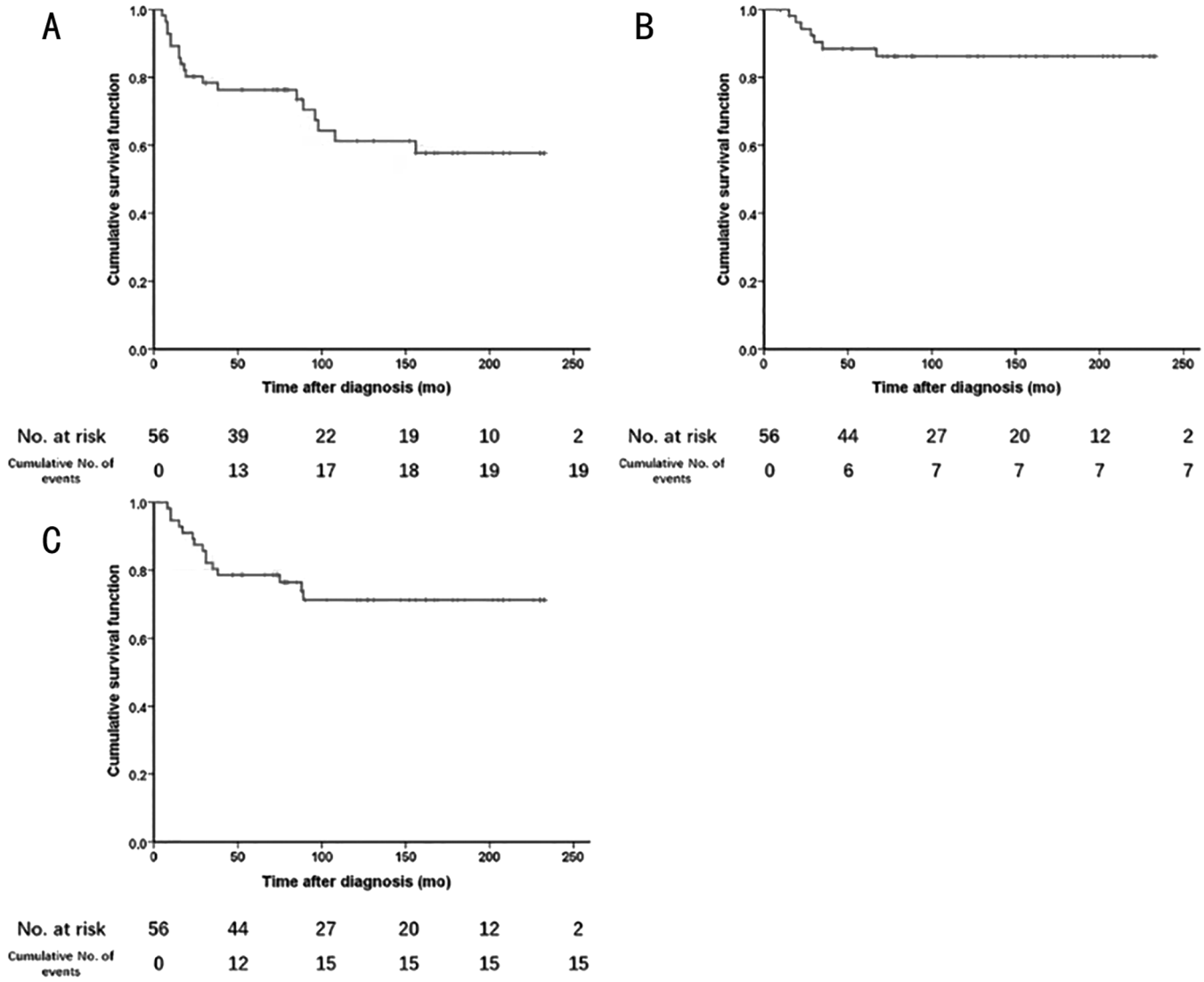

Figure 1 Kaplan-Meier curves for time to outcome for the whole study cohort A: Local-recurrence free survival; B: Distant metastasis free survival; C: Overall survival.

positive margins due to the extension of the tumor into the cavernous sinus. All the 9 patients invading adjacent tissues received combined multidiscipline radical surgery once diagnosed NRSTSs. Concerning the tumor margins, there were 18 (32.1%) in R0, 19 (33.9%) in R1, and 19 (33.9%) in Rx. Tumor pathological characteristics are also shown in Table 1. The FNCLCC grading distributions were as follows: 14 (25%) patients were G1, 36 (64.3%) patients were G2, while 6 (10.7%) patients were G3. WHO pathological distributions, demonstrated in Table 1, showed fibroblastic/myofibroblastic (30.4%) as the majority histologic subtype.

The mean follow-up time was 111.8mo (range, 8-233mo). During follow-up, 15 patients (26.8%) had death from disease, 19 (33.9%) had local recurrence, and 7 (12.5%) had distant metastasis (Figure 1), with the lung as the most common metastatic site. Survival rates considering the whole study group was 78.57% at 5y, and 72.16% at 10y after the initial diagnosis. External-beam radiation therapy was administered to 34 (60.7%) patients, postoperatively. The mean dose was 59.5 Gy (range, 50-65.8 Gy). One patient with chondrosarcoma which received proton therapy was also included in RT group. As for severe irradiation complication, there were one patient with pleomorphic liposarcoma suffered osteosarcoma at the radiation region 10y after irradiation, who is presently alive after secondary surgery; one patient with fibrosarcoma suffered radiation retinopathy leading enucleation, and one patient with chondrosarcoma also suffered radiation retinopathy treated by intra-vitreous injection of anti-vascular endothelial growth factor (VEGF) drugs. Others complained mild to moderate discomforts, such as skin damage, dry eye, cataract, *etc*. Chemotherapy was administered to 22 (39.3%) patients, some of patients presented endurable fatigue. One patient received chemotherapy both preoperatively and postoperatively, the others received chemotherapy only postoperatively.

There was no statistically significant difference of clinicopathological characteristics between RT and chemotherapy groups, except

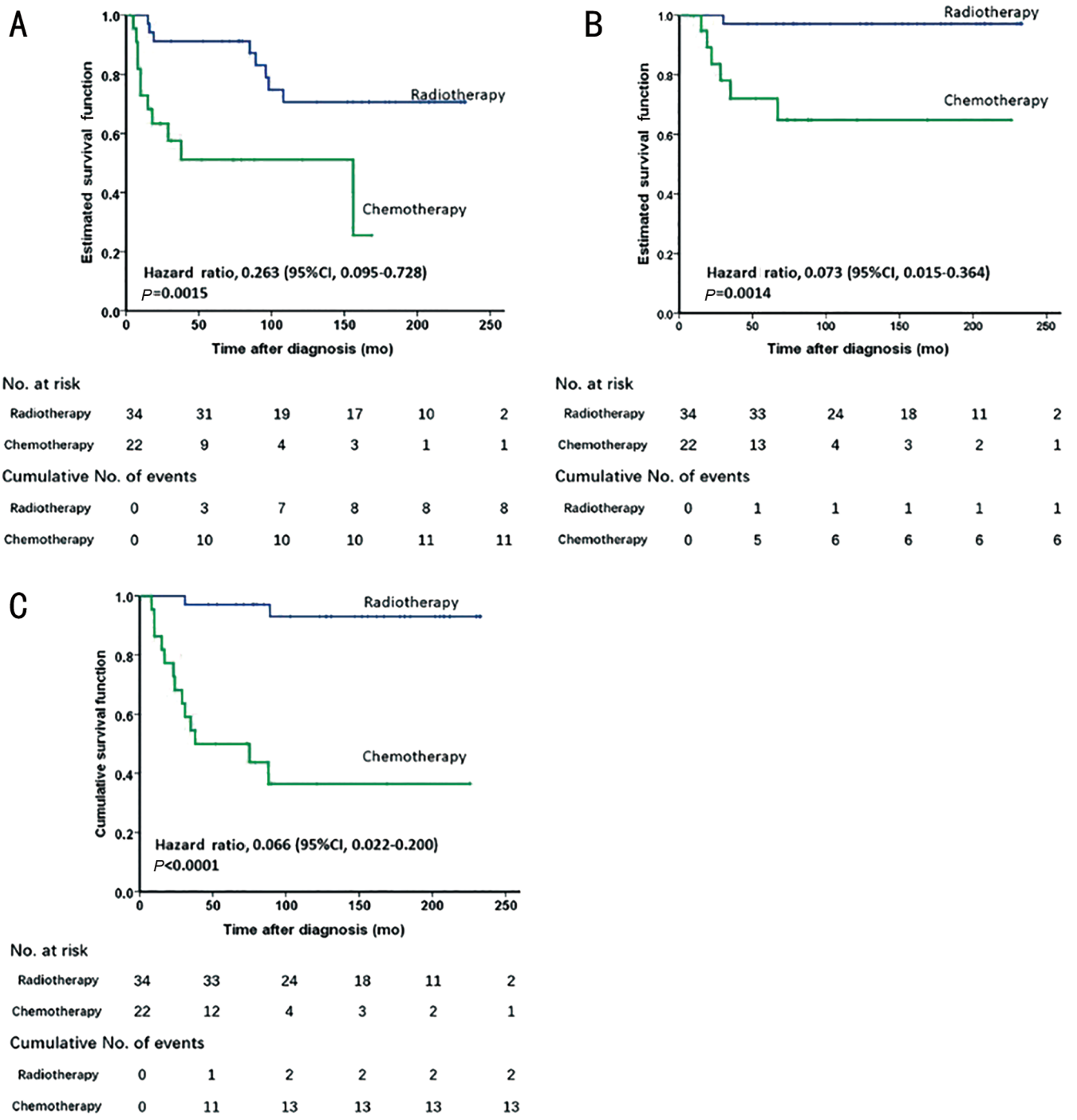

Figure 2 Kaplan-Meier curves for time to outcome by the adjuvant therapy (radiotherapy or chemotherapy) A: Local-recurrence free survival; B: Distant metastasis free survival; C: Overall survival.

for ocular laterality (P=0.013; Table 1). RT was associated with lower risk of local recurrence [hazard ratio for RT *vs* chemotherapy, 0.263, 95% confidence interval (CI), 0.095-0.728, P=0.0015]; with lower risk of distant metastasis (hazard ratio for RT *vs* chemotherapy, 0.073, 95%CI, 0.015-0.364, P=0.0014); and with lower risk of death from disease (hazard ratio for RT *vs* chemotherapy, 0.066, 95%CI, 0.022-0.200, P<0.0001), as well. The 5-year survival rate for RT group was 97.06% compared to 50% in patients with chemotherapy (P<0.0001). The survival analysis for local recurrence, distant metastasis and over survival of RT and chemotherapy group were illustrated in Figure 2. As shown in Table 1, the chemotherapy group had a mildly lower proportion of FNCLCC grade 1 and a mildly higher proportion of grade 3 compared to the RT group. The further overall survival analysis of the patients suffered grade 2 tumors between RT and chemotherapy group was conducted in Figure 3. In grade 2 cases, RT was also associated with lower risk of death from disease (hazard ratio for RT *vs* chemotherapy, 0.056, 95%CI, 0.028-0.116, P<0.0001).

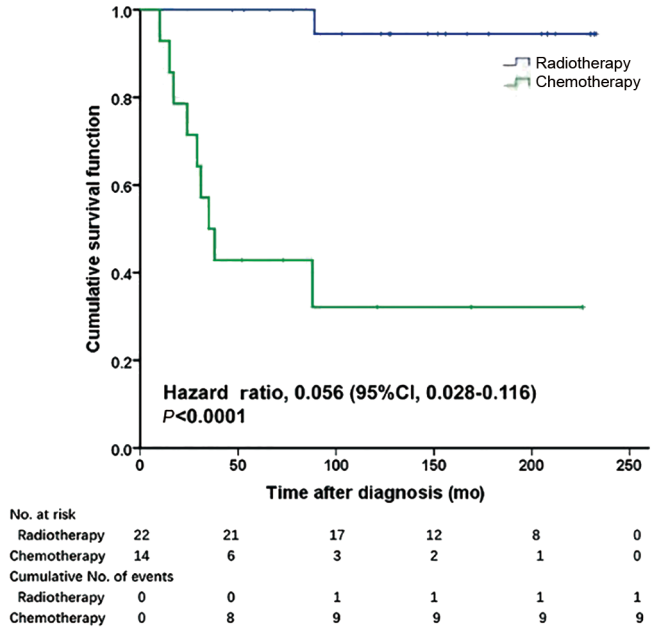

Figure 3 Kaplan-Meier curves for time to death from disease by the adjuvant therapy (radiotherapy or chemotherapy) in grade 2 tumors.

DISCUSSION

Studies of NRSTS are challenging due to the disease rarity and heterogeneity of histologic subtypes. In the current study, we retrospectively analyzed a single-center orbital NRSTS cohort. We determined the outcome of orbital NRSTS patients after surgical treatment and compared efficacy of postoperative RT and chemotherapy. To the best of our knowledge, this is the most up-to-date report providing a prognostic evaluation of orbital NRSTS with comparison of RT versus chemotherapy.

As the rarity of research into orbital NRSTS, we had compared the data concerning local recurrence, distant metastasis and survival rate to tumors at other sites. The survival rate in our cohort was 78.57% at 5y, and 72.16% at 10y after surgery. The 5-year survival rate in our study is slightly lower than that in some other literatures. Sanfillipo *et al*[10] revealed a rate of 80% in a homogenous cohort of mostly myxofibrosarcoma patients. Whereas, the 5-year overall survival rate in our cohort is higher than the result of Harati *et al*'s[11], who indicated a 5-year overall survival rate of 65.3% in a comparable cohort of STS patients, and is higher than the result of a study indicating a 5-year overall survival rate of 68.9% in 119 STS patients who received postoperative RT[12]. A study of 58 head and neck cases revealed 10-year overall survival rates of 63.2%±7.1%[13]. As for orbital STS, Sa *et al*[5] revealed 22% patients died of disease at a median follow-up of 38.9mo, although, 48% of the patients in this study were rhabdomyosarcoma. Our survival result is approximating Sa *et al*'s[5] study, showing most death evens happened in the first 50mo[5]. The survival of STSs/NRSTSs depends on different parameters, such as grading, tumor size, distribution of pathologic subtypes, and resection margins; therefore, the study cohorts are difficult to compare in a mixed manner. We found that the majority of NRSTSs in orbital region were relatively small and grade 2, which may partially explain the difference of survival rate from research about tumors at other sites. In a report with a cohort of patients with NRSTS, up to 30% cases will develop metastatic disease up to 10y after primary diagnosis[14]. In our study cohort, however, only 12.5% patients developed metastatic disease at the last follow-up, revealing most of the orbital NRSTSs is associated with low risk of metastasis.

Complete resection with negative margins can decrease rates of local recurrence and improve survival in NRSTS patients. This was confirmed by previous pediatric and adult study cohort containing NRSTSs at other anatomic sites[13,15]. For most STSs, tumor-free margins of 1 to 2 cm has been recommended, while a margin of 3 cm or more is potentially required for highly invasive STSs[16]. Tumor resection with margins more than 2 cm in the orbit, however, is not easy to accomplish without disfigure and damage of vital structures. In our study, most of the NRSTSs had severe adhesion to orbital tissues, such as the muscle, optic nerve, and even the eyeball. When reviewing the surgical records, many of the masses had no or uncomplete capsule. These features leaded positive or unevaluable tumor margins, because these tumors had to be resected piece by piece. This underscores the importance of postoperative adjuvant treatments in patients with orbital sarcomas. Previous orbital STS cohort demonstrated 82% cases received surgery plus adjuvant therapy[5]. A recent study, which contained six patients, revealed that trimodality treatment (radiation therapy, chemotherapy, and surgery) maybe the best option for primary orbital mesenchymal chondrosarcoma[17].

Trials in both north America (COG ARST 0332)[18] and Europe (EpSSG NRSTS 2005)[19] have a suggestion of standardized treatment schema for different subtypes of NRSTS based on the well-defined prognostic factors. RT and chemotherapy are administered selectively based upon factors such as resectability, histologic grade, tumor size, chemotherapy responsiveness, and stage. Whereas the above guidelines do not mention how the RT or chemotherapy affects the survival of patients with NRSTS.

Savar *et al*[20] once reported a cohort of adult patients with orbital sarcomas treated in Anderson Cancer Center, and they revealed that adult patients with orbital sarcomas may benefit from preoperative chemotherapy with or without RT. There were few studies concerning the efficacy comparison between RT and chemotherapy. The randomized COG ARST1321 trial included separate "chemotherapy" (preoperative chemoradiation with or without pazopanib) and "non-chemotherapy" (preoperative RT with or without pazopanib)

cohorts initially. The "RT with or without pazopanib" arm was closed early due to poor accrual; however, the "chemotherapy" arm completed full accrual[21].

Better prognosis is associated with smaller, nonmetastatic tumors, lower and more differentiated grade, and certain histologic type[22]. And, the AJCC 8th edition T classifications can accurately predict 5-year disease-specific survival of head and neck STSs, as reported previously[23]. In our study cohort, the clinicopathological parameters of NRSTS were compared between the RT and chemotherapy group. There were no significant differences between the two group on age, gender, tumor volume, TNM category, surgery margin, WHO pathological distribution and FNCLCC staging. The laterality distribution between the two group was significantly different. Considering the laterality of orbital tumors were not proved to predict overall survival by previous research, the RT group and chemotherapy group can be still comparable in our opinion in our view. The rate of local recurrence, distant metastasis and death from disease was significantly higher in chemotherapy cohort than in RT cohort. To further avoid bias, we conducted survival analysis in grade 2 cases separately, which also indicating higher rate of death from disease in chemotherapy cohort than in RT cohort. Our study confirms the efficacy of RT in head and neck NRSTS reported by Rastatter *et al*[22]. Tinkle *et al*'s[24] research has also reported excellent disease control with the use of brachytherapy in pediatric and young adult NRSTS patients. In contrast, Federico *et al*[13] failed to identify a positive effect of RT on overall survival of head and neck NRSTS. The differences in radiation sensitivity may related to tumor histology or orbit anatomic site.

The efficacy of adjuvant postoperative chemotherapy for localized NRSTS has also been questioned. In one cohort of patients with completely resected, high-grade tumors, the five-year survival rate was 41.5% in patients treated with multiagent chemotherapy. Compared with 23.8% in patients who did not receive chemotherapy, thus recommending postoperative chemotherapy in high-risk surgically-resected patients[25]. Additionally, increasing evidence showed targeted agents such as sunitinib, cediranib, pazopanib, tivantinib or bevacizumab may produce tumor response and prolong survival[26]. Neoadjuvant chemotherapy has also been reported in the treatment of periorbital angiosarcoma previously[27]. However, there were studies showing no improvement in outcomes associating with the use of chemotherapy[28]. In principle, adult-type NRSTS are usually assumed to be relatively insensitive to chemotherapy, with reported tumor response in the range of 40%-50%, or even less, and RT has a role in local control after incomplete resections and even after wide excisions in the case of large tumors[29]. Thus, our study further provides the evidence of RT and chemotherapy in the treatment of NRSTS, revealing RT is more appropriate for orbital NRSTS.

There were some limitations. First, the study cohort contained only 56 patients, although it is a relatively large cohort compared to other orbital tumor research due to the rarity of NRSTS in orbit region; second, we did not have sufficient NRSTS patients treated by surgery solely, so the study of radiation or chemotherapy versus surgery could not be conducted; third, this is a retrospective article containing patients treated 8 to 19 years ago, and we have no way to explain how the treatment was chosen for each patient; fourth, the detailed chemotherapy agents were not discussed in this article as most of patients cannot provide the chemotherapy detail who received chemotherapy in other institutions.

In conclusion, considering the extreme rarity of orbital NRSTS, it is difficult to design a prospective study of treatments for this disease. This study is limited by the retrospective nature, and the cohort was small compared to research in other parts of the body, however, it represents one of the largest series of orbital NRSTS in the literature. Most of orbital NRSTSs are small, low-moderate grade and non-metastasis, however, the resection with safe margin is not easy to achieve due to the specificity of orbital anatomy, underscoring the importance of adjuvant treatments in orbital NRSTS. We compared the efficacy of adjuvant RT and chemotherapy. In our study, the postoperative RT provides more benefits in local recurrence, distant metastasis and survival rated than chemotherapy, revealing it may be more appropriate to conduct postoperative RT in patients with orbital NRSTS. The determination of the minimum radiation dose and field size necessary for local control to reduce the toxicity associated with RT, and the development of more effective and/or less toxic chemotherapy regimens to improve oncologic outcomes and reduce morbidity, will be the further study emphasis[30].

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