Treatment Outcomes and Prognostic Factors of Adult Sinonasal Sarcomas: A Single-Institution Case Series

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BE 1,2 Jianming Ding*
CD 3 Cuihong Wang*
BE 4 Jun Xiang
EF 1 Chunying Shen
CD 1 Chaosu Hu
CD 1 Tingting Xu
AF 1 Xueguan Lu

1 Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, P.R. China
2 Department of Radiation Oncology, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian, P.R. China
3 Department of Radiology, Fudan University Shanghai Cancer Center, Shanghai, P.R. China
4 Department of Head and Neck Surgery, Fudan University Shanghai Cancer Center, Shanghai, P.R. China

* The first 2 authors continued equally to this work

Corresponding Authors: Xueguan Lu, e-mail: luxueguan@163.com, Tingting Xu, e-mail: dr_tingtingxu@163.com
Source of support: This work was supported by a grant from the Science and Technology Commission of Shanghai Municipality (No. 17ZR1406100)

Background: The purpose of this study was to investigate the treatment outcomes and evaluate the prognostic factors of adult sinonasal sarcomas.

Material/Methods: A retrospective review was performed on consecutive patients with adult sinonasal sarcomas treated in our institution from 2005 to 2016. The Kaplan-Meier method was used to evaluate local recurrence-free survival (LRFS), distant metastases-free survival (DMFS), and overall survival (OS). Univariate and multivariate analyses using Cox proportional hazard models were performed to determine the prognostic factors associated with survival outcomes.

Results: A total of 49 patients were followed up for 6–122 months, with a median time of 36 months. The 5-year LRFS, DMFS, and OS rates of all patients were 68.3%, 62.8%, and 43.2%, respectively. The results of univariate analysis revealed that patients with an advanced stage of primary tumor and those who received incomplete surgical resection had worse LRFS ($p=0.013$; $p=0.026$). Patients with the histological type rhabdomyosarcoma (RMS) and existing regional lymph node metastasis had worse DMFS ($p=0.000$; $p=0.001$). The histological type RMS, advanced stage of primary tumor, existing regional lymph node metastasis, and receiving incomplete surgical resection had an unfavorable effect on OS ($p=0.001$; $p=0.002$; $p=0.008$; $p=0.011$). The results of multivariate analysis showed that histological type and degree of surgical resection were the independent prognostic factors for OS.

Conclusions: Our results suggest that the histological type RMS and receiving incomplete surgical resection are independent prognostic factors for worse OS.

MeSH Keywords: Adult • Prognosis • Rhabdomyosarcoma • Sarcoma

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/909116

📄 1843   ▦ 4   📊 1   📚 22

Background

Sarcoma originates from mesenchymal tissue and constitutes a heterogeneous group of rare malignancies, accounting for 1% of all adult and 15% of all pediatric malignant tumors. Among these, approximately 4–10% of primary sites are located in the head and neck region [1]. In general, sinonasal sarcomas are classified by the origin of the tumor cells, and various pathological subtypes are included [2]. About 80% originate from soft tissue, while the remaining 20% are from bone and cartilage. Rhabdomyosarcoma (RMS) is the most common histological subtype in the pediatric population, but not in adults [3]. Sinonasal RMS is usually unresectable, with involvement of the paranasal sinuses and cervical lymph nodes at the time of diagnosis, which results in a poor outcome [4,5]. Sinonasal teratocarcinosarcoma is an extremely rare and highly aggressive malignant neoplasm, with complex components of mesenchymal, epithelial, and neuroectodermal elements; it is not easy to forecast its trend of development and prognosis owing to its uncertain clinical behavior [6]. Other histological tumor types reported in the sinonasal tract include Ewing's sarcoma/PNET, malignant fibrous histiocytoma, chondrosarcoma and osteosarcoma, fibrosarcomas, leiomyosarcomas, and synovial sarcoma [7–11].

Sinonasal sarcomas are highly malignant and locally aggressive, with a high recurrence rate. Distant organ failure due to hematogenous metastases is often observed. Its low incidence has led to lack of consensus on high-grade evidence-based treatment for these diseases and an absence of large clinical studies focusing on treatment optimization. In the clinic, multidisciplinary treatments involving surgery, radiotherapy, and chemotherapy are necessary to improve the outcomes of patients with these diseases. Given that the site is adjacent to important organs and complex anatomical structures, surgical resection with negative margins can be difficult, but there are cases where lack of orbital or brain involvement facilitates negative margins using endoscopic or open craniofacial resection. Endoscopic surgery is widely used in selected patients to reduce postoperative complications, preserve function, and achieve an aesthetic outcome [12]. Radiotherapy and chemotherapy are commonly used to improve local control and treat occult metastases.

To provide further information on the prognostic factors in adult patients with sinonasal sarcomas, and further to optimize the treatment strategies, this study investigated the treatment outcomes and evaluated the prognostic factors for these adult patients.

Material and Methods

Patient demographics

From January 2005 to June 2016, a total of 51 consecutive adult patients with sinonasal sarcomas were treated at the Fudan University Shanghai Cancer Center. Two patients were lost to follow-up and 49 patients were included in the analysis. The clinical features, treatment information, and outcome data were collected through a retrospective review of medical records. The TNM staging system of the Intergroup Rhabdomyosarcoma Staging Group (IRSG) was used to categorize patients with RMS. Given that there was no widely accepted staging system for sinonasal non-rhabdomyosarcoma (non-RMS), we used the 2006 AJCC TNM staging classification system for cancer of the nasal cavity and paranasal sinuses to stage the non-RMS tumors. The early stage of a primary tumor was defined as T1 in IRSG and T1+T2 in non-RMS, and the advanced stage was defined as T2 in IRSG and T3+T4 in non-RMS. The patients' characteristics are shown in Table 1.

Treatment modalities

The patients received various treatment modalities (Table 2). Chemotherapy combined with radiotherapy (63%) was the main modality for patients with RMS, followed by surgery combined with chemoradiotherapy (25.9%). With regard to non-RMS tumors, surgery combined with radiotherapy (77.3%) was the primary therapeutic regimen.

For surgery, an endoscopic technique was used in 22 cases, while open surgery was used in another 10. Intra-operative findings and postoperative imaging were used to evaluate the degree of surgical resection. Eighteen patients underwent complete tumor resection and 13 patients had residual disease. Radiotherapy was delivered by intensity-modulated radiation therapy (IMRT) technology. A total dose of 50–70 Gy for RMS and 66–70 Gy for non-RMS tumors was used, with conventional fractions. The most commonly used chemotherapeutic regimen was VAC (n=17, 56.7%), which comprises vincristine, dactinomycin, and cyclophosphamide. The other 2 regimens (n=13, 43.3%) were ifosfamide + epirubicin + vincristine and ifosfamide + cisplatin + epirubicin.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0. The local recurrence-free survival (LRFS), distant metastases-free survival (DMFS), and overall survival (OS) rates for these patients were calculated. The LRFS and DMFS were defined as the time from initial treatment to locoregional recurrence and distant metastasis, respectively. The OS was defined as the time from initial treatment to death from any cause,

Table 1. The clinical characteristics of 49 patients with sinonasal sarcoma.

Patient characteristic	n (%)	
Age,y		
Mean (SD)	37.5	(14.6)
Median (range)	35	(16–75)
Gender		
Male	28	(57.1)
Female	21	(42.9)
Stage of primary tumor		
Early	24	(49.0)
Advanced	25	(51.0)
Regional lymph node metastasis		
Negative	33	(67.3)
Positive	16	(32.6)
Histological types		
Rhabdomyosarcoma	27	(55.1)
Teratocarcinosacroma	8	(16.3)
Malignant fibrous histocytoma	3	(6.1)
Chondrosarcoma	3	(6.1)
Leiomyosarcoma	2	(4.1)
Ewing sarcoma/PNET	2	(4.1)
Osteosarcoma	1	(2.0)
Synovial sarcoma	1	(2.0)
Fibrosarcoma	1	(2.0)
Not otherwise classified	1	(2.0)

Table 2. The treatment modalities for 49 patients with sinonasal sarcoma.

Treatment modalities	n (%)	
RMS	27	
Chemo + RT	17	(63.0)
Surgery + Chemo + RT	7	(25.9)
Surgery + RT	1	(3.7)
Surgery + Chemo	1	(3.7)
Chemo + RT + Surgery	1	(3.7)
NON-RMS	22	
Surgery + RT	17	(77.3)
Surgery + Chemo + RT	3	(13.6)
Chemo + RT	1	(4.6)
Surgery only	1	(4.6)

Chemo – chemotherapy; RT – radiotherapy.

and distant metastasis was found in 16 patients. One patient had both local failure and distant metastasis. The 5-year LRFS, DMFS, and OS rates of all the patients were 68.3%, 62.8%, and 43.2%, respectively (Figure 1).

Prognostic factors

The results of univariate analysis revealed that the patients with an advanced stage of primary tumor and those who received incomplete surgical resection had worse LRFS (p=0.013; p=0.026). Patients with the histological type RMS and existing regional lymph node metastasis had worse DMFS (p=0.000; p=0.001). The histological type RMS, advanced stage of primary tumor, existing regional lymph node metastasis, and receiving incomplete surgical resection had an unfavorable effect on OS (p=0.001; p=0.002; p=0.008; p=0.011) (Table 3). The results of multivariate analysis showed that histological type and degree of surgical resection were the independent prognostic factors for OS (Table 4).

Discussions

The incidence of sinonasal sarcomas is very low and the prevalence of sinonasal sarcoma, especially RMS, is lower in adults than in the pediatric population. Therefore, there are few clinical studies that evaluated the optimization of treatment strategies in adult patients. It is well known that pediatric patients with sinonasal sarcoma have better prognosis than the corresponding adult patients. Wu et al. analyzed 352 patients with sinonasal sarcomas from 1973 to 2008 in the Surveillance,

or the last follow-up. The Kaplan-Meier method was used to evaluate LRFS, DMFS, and OS. Univariate and multivariate analyses using Cox proportional hazard models were performed to investigate the factors associated with survival outcomes. For all tests, two-sided p<0.05 was considered to be significant.

Results

Treatment outcomes

A total of 49 patients were followed up for 6–122 months, with a median time of 36 months. Among them, 29 patients had disease recurrence and 26 patients eventually died by the time of the last follow-up. Local failure occurred in 12 patients
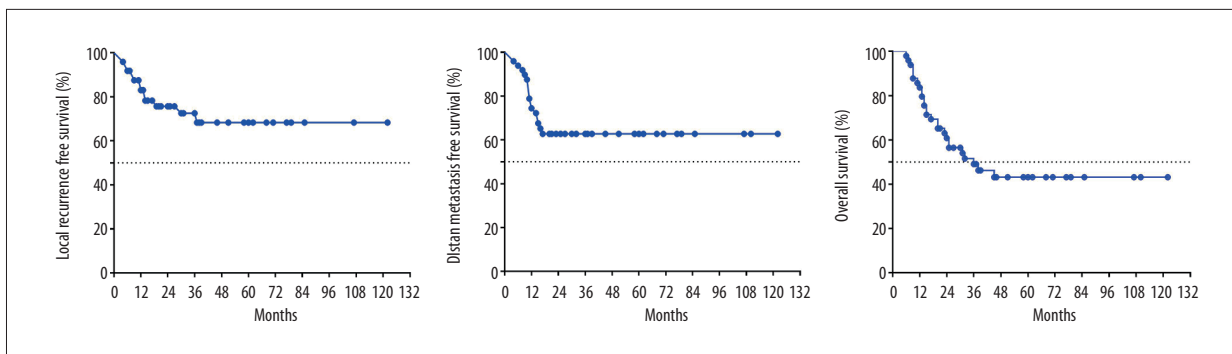
Figure 1. Kaplan-Meier curves of LRFS, DMFS, and OS for all patients with sinonasal sarcoma.

Table 3. Univariate analysis for clinical factors on prognosis of patients with sinonasal sarcoma.

Clinical factors	5-year LRFS			5-year DMFS			5-year OS		
	(%)	χ^2	*P* value	(%)	χ^2	*P* value	(%)	χ^2	*P* value
Age (years)									
<35	67.7	0.028	0.866	56.5	0.721	0.396	39.1	0.581	0.446
≥35	68.0			68.8			52.2		
Gender									
Female	59.0	0.251	0.616	53.5	1.397	0.237	27.1	1.824	0.177
Male	72.7			69.4			52.9		
Histological types									
RMS	69.0	0.221	0.638	39.9	12.231	0.000	20.6	10.445	0.001
Non-RMS	71.1			89.9			66.9		
Stage of primary tumor									
Early	86.4	6.211	0.013	66.7	0.281	0.596	63.2	9.239	0.002
Advanced	46.4			57.3			22.4		
Regional lymph node metastasis									
Negative	68.6	0.075	0.784	77.6	11.031	0.001	55.1	7.121	0.008
Positive	69.2			29.4			17.9		
Degree of surgical resection									
Complete	88.1	7.319	0.026	76.7	1.879	0.391	69.9	9.211	0.011
Incomplete	48.4			56.4			23.1		
No receiving surgery	55.7			53.1			25.6		

Epidemiology, and End Result (SEER) database [13]. They found that the 5-year OS rate for patients younger than 10 years was 63.1%, whereas it was 48.9% for patients aged 10 to 49 years and 53.8% for patients aged 50 to 69 years. Cases of RMS were more aggressive and such patients had a worse OS rate than those with any other sinonasal sarcoma. In a recent series of 286 patients who were diagnosed with sinonasal RMS

from 1973 to 2013 in the SEER database, the 5-year OS rate for patients younger than 10 years was 69.3%, whereas it was 39.7% for patients aged 10 to 19 years and 20% for patients aged over 20 years [14]. In the present study, the 5-year OS rate was 43.2% for all patients and 20.6% for patients with RMS. The results of univariate analysis demonstrated that the patients with the histological type RMS had worse DMFS and

Table 4. Multivariate analysis for clinical factors on prognosis of patients with sinonasal sarcoma.

Clinical factors	OS		
	HR	95% CI	*p* Value
Stage of primary tumor			
Early	1.0	–	–
Advanced	2.332	0.747–7.283	0.145
Regional lymph node metastasis			
Negative	1.0	–	–
Positive	1.837	0.726–4.684	0.199
Degree of surgical resection			
Incomplete	1.0	–	–
Complete	0.109	0.034–0.346	0.000
No receiving surgery	0.216	0.061–0.766	0.018
Histological types			
RMS	1.0	–	–
Non-RMS	0.191	0.055–0.658	0.009

OS. The results of multivariate analysis showed that histological type was one of the independent prognostic factors for OS.

In this study, 16 patients had regional lymph node metastasis, including 15 patients (55.6%) in the RMS group and 1 patient (4.5%) in the non-RMS group. Aykut et al. found regional lymph node involvement in 54.3% of patients with RMS at diagnosis, but positive lymph node involvement did not significantly affect survival [14]. However, Wu et al. reported that the patients with lymph node involvement had worse survival [15]. Similarly, our univariate analysis revealed that patients with lymph node metastasis had worse DMFS and OS. However, lymph node involvement was not an independent prognostic factor for OS in the multivariate analysis. Therefore, the prognostic value of regional lymph node involvement was not clarified.

Our univariate analysis results also demonstrated that the patients with advanced primary tumors had worse LRFS and OS. The primary tumor stage may be associated with the degree of surgical resection. Several studies have found that complete resection with a negative margin is an important prognostic factor in improved survival outcome for patients with sinonasal sarcomas [16]. However, complete resection of sinonasal sarcomas may be difficult because they are adjacent to important organs and complex anatomical structures. Nicolas et al. reviewed their experience of 28 cases and found that there was inadequate resection in 31.6% of patients and that inadequate resection was associated with poor outcome [17].

In the present study, 42% of patients undergoing surgery had incomplete resection and had worse LRFS and OS. Therefore, preoperative evaluation is required to select the optimal surgical procedure and ensure wide resection with negative margins.

Radiotherapy has been confirmed to significantly increase local control for patients with sinonasal RMS and non-RMS [18,19]. For non-RMS, Lucyna et al. found that the radiation dose had a considerable effect on the treatment outcome: a 1-Gy increase in the dose delivered decreased the risk of death and local failure by 3%. They suggested that a dose of >63 Gy should be used for postoperative adjuvant radiotherapy, and that radiation doses of 68 Gy or more should be provided for definitive therapy [20]. In the present study, a dose of 66–70 Gy was used for the gross tumor volume (GTV) of non-RMS cases. For RMS, a radiation dose of 40–59 Gy was used in the Intergroup Rhabdomyosarcoma Study (IRS) [21]. A wide range of doses, from 50 to 70 Gy, was applied in the present study for RMS. We did not analyze the difference in prognosis for patients with or without radiotherapy because almost all of the patients received radiotherapy. Differences in prognosis related to different radiation doses were also not analyzed in the RMS or non-RMS patients because of the relatively small number of patients.

RMS is considered to be more sensitive to chemotherapy than non-RMS tumors. In the present study, chemotherapy was received by 96.3% (26/27) of the patients with RMS and only 18.2% (4/22) of the patients with non-RMS. The IRS-IV study

showed that the objective response rate to chemotherapy was 77%: 21% complete response (CR) and 56% partial response (PR) [22]. Vincristine, dactinomycin, and cyclophosphamide (VAC) is the most commonly used chemotherapeutic regimen for RMS. However, the value of chemotherapy remains controversial for non-RMS tumors. Chemotherapy is considered to be ineffective for most sinonasal non-RMS. However, Ewing sarcoma/PNET is sensitive to chemotherapy and systemic chemotherapy plays a pivotal role in its treatment [7]. In our study, objective responses were observed in 2 patients with Ewing sarcoma/PNET treated by chemotherapy with the VAC regimen.

Conclusions

In conclusion, our results suggest that the histological type RMS and incomplete surgical resection were the most important prognostic factors for worse OS in adult patients with sinonasal sarcomas. The study has limitations in that it was a retrospective study with a relatively small number of patients. Further study is needed.

References:

1. Bai Y, Chen X, Yan Y et al: [Clinical efficacy analysis of adult sinonasal rhabdomyosarcoma]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi, 2015; 29(9): 804–10 [in Chinese]

2. Thompson LDR, Franchi A: New tumor entities in the 4th edition of the World Health Organization classification of head and neck tumors: Nasal cavity, paranasal sinuses and skull base. Virchows Arch, 2018; 472(3): 315–30

3. Perez EA, Kassira N, Cheung MC et al: Rhabdomyosarcoma in children: A SEER population-based study. J Surg Res, 2011; 170(2): e243–51

4. Stepan K, Konuthula N, Khan M et al: Outcomes in adult sinonasal rhabdomyosarcoma. Otolaryngol Head Neck Surg, 2017; 157(1): 135–41

5. Sanghvi S, Misra P, Patel NR et al: Incidence trends and long-term survival analysis of sinonasal rhabdomyosarcoma. Am J Otolaryngol, 2013; 34(6): 682–89

6. Misra P, Husain Q, Svider PF et al: Management of sinonasal teratocarcinosarcoma: A systematic review. Am J Otolaryngol, 2014; 35(1): 5–11

7. Lombardi D, Mattavelli D, Redaelli De Zinis LO et al: Primary Ewing's sarcoma of the sinonasal tract in adults: A challenging disease. Head Neck, 2017; 39(3): E45–50

8. Papoian V, Yarlagadda BB, Devaiah AK: Multifocal, recurrent sinonasal leiomyosarcoma: Case report and review of literature. Am J Otolaryngol, 2014; 35(2): 254–56

9. Khan MN, Husain Q, Kanumuri VV et al: Management of sinonasal chondrosarcoma: A systematic review of 161 patients. Int Forum Allergy Rhinol, 2013; 3(8): 670–77

10. Mallen-St Clair J, Arshi A, Abemayor E, St John M: Factors associated with survival in patients with synovial cell sarcoma of the head and neck: An analysis of 167 cases using the SEER (Surveillance, Epidemiology, and End Results) database. JAMA Otolaryngol Head Neck Surg, 2016; 142(6): 576–83

11. Patel TD, Carniol ET, Vazquez A et al: Sinonasal fibrosarcoma: Analysis of the surveillance, epidemiology, and end results database. Int Forum Allergy Rhinol, 2016; 6(2): 201–5

12. Castelnuovo P, Dallan I, Battaglia P, Bignami M: Endoscopic endonasal skull base surgery: Past, present and future. Eur Arch Otorhinolaryngol, 2010; 267(5): 649–63

13. Wu AW, Suh JD, Metson R, Wang MB: Prognostic factors in sinonasal sarcomas: Analysis of the surveillance, epidemiology and end result database. Laryngoscope, 2012; 122(10): 2137–42

14. Unsal AA, Chung SY, Unsal AB et al: A Population-based analysis of survival for sinonasal rhabdomyosarcoma. Otolaryngol Head Neck Surg, 2017; 157(1): 142–49

15. Wu Y, Li C, Zhong Y et al: Head and neck rhabdomyosarcoma in adults. J Craniofac Surg, 2014; 25(3): 922–25

16. Rapidis AD: Sarcomas of the head and neck in adult patients: Current concepts and future perspectives. Expert Rev Anticancer Ther, 2008; 8(8): 1271–77

17. Penel N, Van Haverbeke C, Lartigau E et al: Head and neck soft tissue sarcomas of adult: Prognostic value of surgery in multimodal therapeutic approach. Oral Oncol, 2004; 40(9): 890–97

18. Wortman JR, Tirumani SH, Jagannathan JP et al: Radiation therapy for soft-tissue sarcomas: A primer for radiologists. Radiographics, 2016; 36(2): 554–72

19. Choi Y, Lim DH: The impact of radiotherapy on clinical outcomes in parameningeal rhabdomyosarcoma. Radiat Oncol J, 2016; 34(4): 290–96

20. Kepka L, DeLaney TF, Suit HD, Goldberg SI: Results of radiation therapy for unresected soft-tissue sarcomas. Int J Radiat Oncol Biol Phys, 2005; 63(3): 852–59

21. Raney RB, Meza J, Anderson JR et al: Treatment of children and adolescents with localized parameningeal sarcoma: Experience of the Intergroup Rhabdomyosarcoma Study Group protocols IRS-II through -IV, 1978–1997. Med Pediatr Oncol, 2002; 38(1): 22–32

22. Burke M, Anderson JR, Kao SC et al: Assessment of response to induction therapy and its influence on 5-year failure-free survival in group III rhabdomyosarcoma: the Intergroup Rhabdomyosarcoma Study-IV experience – a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. J Clin Oncol, 2007; 25(31): 4909–13