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Treatment of Sinonasal Teratocarcinosarcoma: A Systematic Review and Survival Analysis

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Abstract

Background: Sinonasal teratocarcinosarcoma (SNTCS) is a rare malignancy of the anterior skull base with only 127 cases described in the English literature. Given the rarity of this tumor, new cases and analysis of published reports may assist in future management of SNTCS.

Objectives: 1) Describe findings from a systematic review of all available literature for malignant SNTCS including the clinical presentation, treatment modalities and outcomes. 2) Present two new cases of this rare anterior skull base tumor. 3) Compare treatment outcomes with respect to recurrence and mortality.

Methods: A systematic review of all English literature available in 2 comprehensive databases was conducted by two independent reviewers using PRISMA guidelines. 85 publications were identified. Each case was reviewed for demographics, treatment and survival, and aggregate treatment outcomes were compared using Kaplan-Meier analysis.

Results: A total of 64 articles meeting inclusion criteria were reported in the literature between 1977-2018. This represented a total of 127 patients, with a strong male predominance (83%) and mean age of 50 years (range 10–82). Mean follow-up was 21 months. Recurrence rate was 38%, with mean survival at 2 years of 55%. Almost all patients underwent surgery as a primary treatment modality (90%). The majority of cases were treated with multimodal therapy, with 55% receiving surgery and radiation and 20% receiving surgery with adjuvant chemoradiation. Kaplan-Meier analysis demonstrated a significant survival advantage for patients treated with combined therapy compared to surgery alone ($p < 0.001$) but did not show differences in recurrence ($p = 0.085$).

Conclusion: Two-year survival rates for SNTCS are 55%. Multimodality treatment outcomes appear to be superior to surgery alone based on the published data of this rare skull base tumor, although heterogeneity of treatment methods and reporting bias limits the generalizability of these findings.

Keywords

anterior skull base, sarcoma, sinonasal teratocarcino sinus malignancy, systematic review, teratomasarcoma

Introduction

Sinonasal teratocarcinosarcoma (SNTCS) is a unique and aggressive malignancy of the anterior skull base.[1] Typically arising in the paranasal or ethmoid sinuses, this neoplasm poses substantial diagnostic challenges given its heterogeneous composition.[2] SNTCS tumors are diverse in nature and are composed of epithelial, neuroepithelial and mesenchymal tissue.[3] In order to establish the diagnosis of SNTCS a tumor must possess malignant epithelial components as well as two or more malignant mesenchymal fragments—i.e. fibroblasts,

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cartilage, bone, and/or smooth muscle.[4] Given this heterogeneity, biopsies can be misleading and predisposed to misdiagnosis, resulting in a delay in treatment.[3]

The first sinonasal teratocarcinosarcoma was documented in 1966 as a malignant teratoma of the ethmoid sinus.[5] Descriptions and eventual naming of SNTCS were established by Shanmugaratnum and Heffner in 1983 and 1984, respectively.[6,7] To date, only 127 cases have been reported in the English literature.

While rare, the aggressive nature of this malignancy demands a high index of suspicion. In this study we describe our findings from the largest systematic review of all available literature on SNTCS. Additionally, in order to determine potential significant survival advantages based on treatment type, we compared reported outcomes across three modalities of treatment: surgery alone, surgery and adjuvant radiotherapy, and surgery with adjuvant chemo-radiation therapy.

Methods

This systematic review and analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria included papers with full English language text that provided descriptions of individual patient data, including description of disease and treatment course. Exclusion criteria included: non-English literature manuscripts, cases not involving the sinonasal pathways, cases that, upon further review, were without pathologic confirmation of teratocarcinosarcoma. The initial search used two comprehensive online databases: MEDLINE/PubMed and Google Scholar. Searches were conducted independently by two separate reviewers using key words: "sinonasal teratocarcinosarcoma," "teratocarcinosarcoma," "teratocarcinoma," "malignant teratoma," and "sinonasal teratoma." Duplicates described in separate articles were removed. Articles were assessed for a primary outcome of disease-free survival and secondary outcomes of recurrence rate and treatment modality utilized. Additional data reviewed included demographics, tumor location, and clinical presentation. A total of 62 original articles and two review articles meeting inclusion criteria were reported in the literature from 1977–2018 and included in the study, representing a total of 127 unique patients (Figure 1).[1–64] In addition to these reported cases, we also present two new cases of SNTCS treated at our institution with review of imaging, pathology and treatment outcome.

Statistical analysis was performed using Minitab (Minitab LLC, State College, PA) and R (R Foundation for Statistical Computing, Vienna, Austria). Descriptive analyses included prevalence by age, sex, geographic location, follow up, treatment choice, and recurrence/mortality outcomes. Data from studies reporting individual case details were then pooled to perform a Kaplan-Meier survival analysis of overall survival and time to recurrence stratified by treatment choice. Time to survival was also

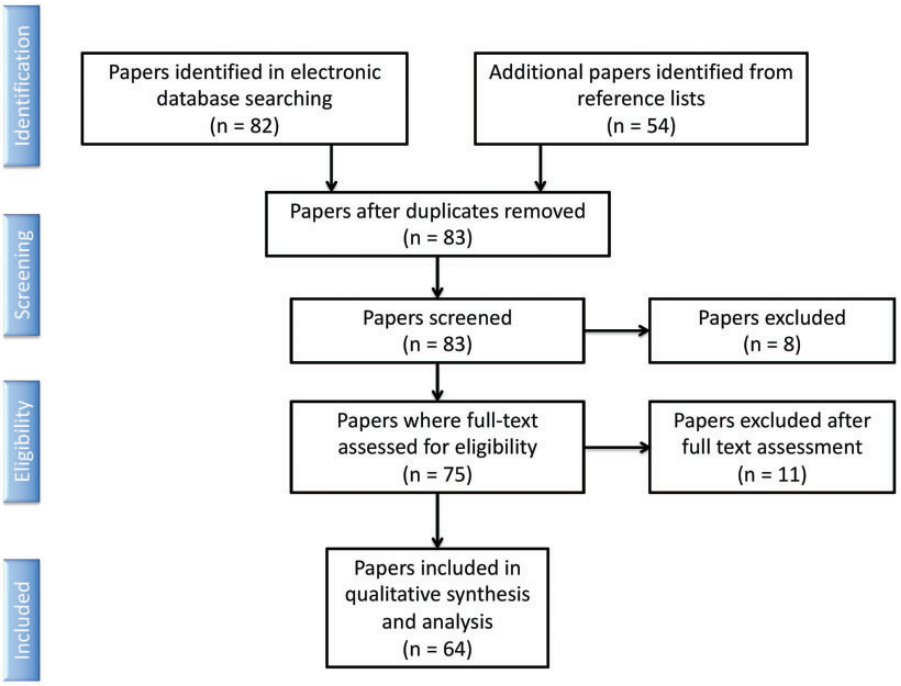


Figure 1. Flow diagram of studies identified by search and reference lists, studies excluded due to no cases of sinonasal teratocarcinosarcoma or no full English-language text, and studies included in final analysis.

assessed across three time periods (1968–1999, 2000–2009, 2010–2018). Pairwise testing between survival curves was then performed using the log-rank test to assess the relationship between treatment choice and outcome. A log-rank test was also used to assess the relationship between publication time period and survival to assess treatment outcome trends over time. An alpha level of 0.05 was prespecified as a threshold for statistical significance.

Case Reviews

Case 1. 44-year-old female presented 3 weeks of facial pain, nasal obstruction and blurry vision. Non-contrast sinus CT scan demonstrated left sided nasal mass with extension into ethmoid and frontal sinuses (Figure 2). Magnetic resonance imaging (MRI) confirmed presence of a locally destructive 3.5 cm soft tissue mass with which involved the cribriform plate and with focal extension into the anterior cranial fossa (Figure 3). Biopsy of

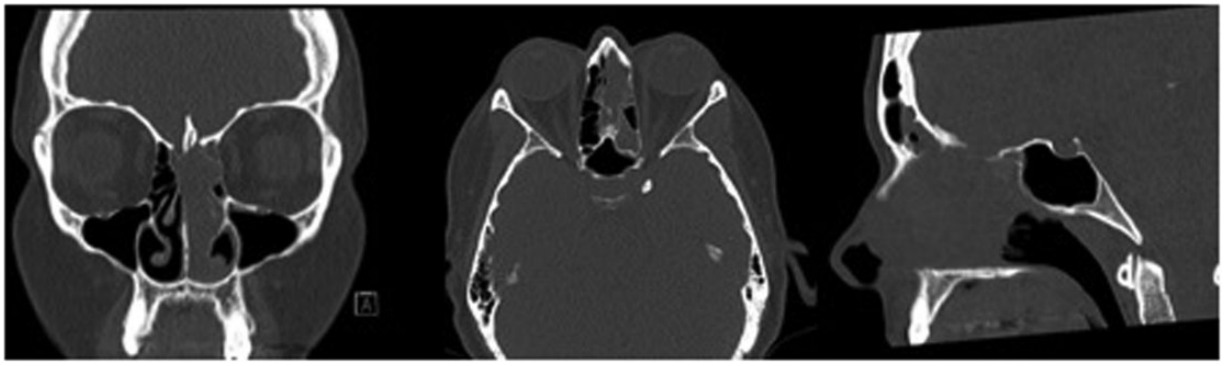


Figure 2. CT sinus demonstrating soft tissue sinonasal mass in case 1.

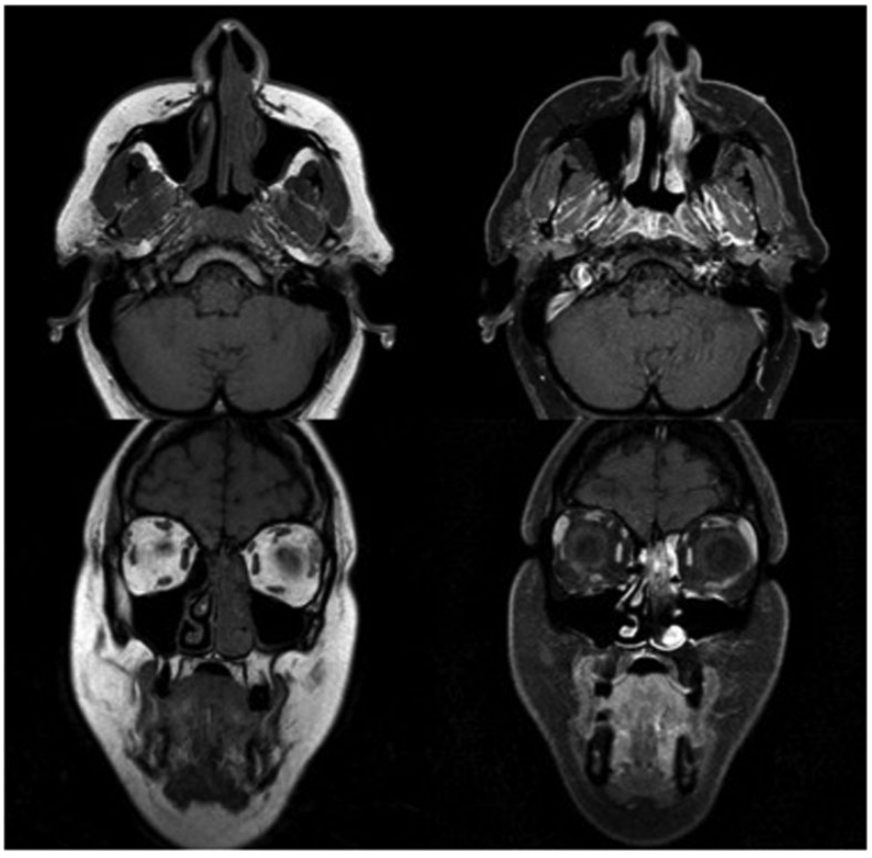


Figure 3. MRI with T2 hyperintense, enhancing 3.5 cm SNTCS involving the cribiform plateand anterior cranial fossa in case 1.

this mass confirmed SNTCS and subsequent anterior endoscopic skull base resection was performed (Figure 4). Surgical resection involved a superior septectomy connecting and widening frontal sinuses toward the cribriform plate. A posterior septectomy connected the sphenoid sinuses. The tumor was present on the left nasal cavity and was resected up towards the skull base. The anterior skull base was subsequently drilled to expose tumor and dura. At this point, several areas of the cribriform plate were removed to expose normal dura around the tumor, which was then incised and resected along with the residual tumor. Circumferential margins from the mucosa of the skull base, sphenoid sinus, frontal sinus, and nasal septum were all negative for malignancy. Skull base reconstruction utilized a multilayer technique with Biodesign inlay (Cook Medical, Bloomington, IN) and nasal septal flap overlay.

The patient then underwent adjuvant concurrent chemoradiation with carboplatin and etoposide as chemotherapeutic agents. Radiotherapy was performed using intensity-modulated radiation therapy of 60 Gray (Gy) in 30 fractions. Initial surveillance consisted of an MRI every six months. After one year with no signs of disease, the interval between scans was increased to one year. The patient has no evidence of disease on endoscopic exam or surveillance imaging 2 years following completion of therapy.

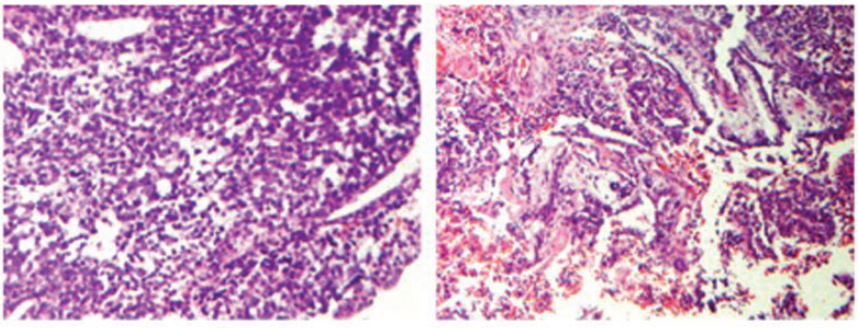
Case 2. 60-year old male with past medical history of two plasmacytomas: one of the right nasal cavity for which he received 46 Gy of radiation when he was 43 years of age and a second in the right neck which was excised and treated with adjuvant 45 Gy radiotherapy at age 59. The patient subsequently developed symptoms of nasal obstruction for which he underwent endoscopic resection of a presumed nasal polyp at an outside facility with final pathology consistent with teratocarcinosarcoma and was referred to our center for definitive treatment.

He subsequently underwent right endoscopic medial maxillectomy with negative margins on final pathology. No adjuvant treatment was given as the patient had previously received two courses of radiotherapy and was not considered a candidate for further radiation therapy. Post-operative cancer surveillance included semiannual endoscopic exams for six years postoperatively and annually thereafter. The patient also underwent MRI imaging at two and three years postoperatively with no evidence of disease. Further imaging was deferred in favor of clinical exam due to patient preference. He remains disease free nine years postoperatively with no evidence of disease.

Results

A total of 62 original articles and two review articles meeting inclusion criteria were reported in the literature between 1977–2019 and included in the study (Table 1). Fourteen cases were case series while 49 were individual case reports. This represented a total of 127 patients. This patient population had a strong male predominance (83%). The mean patient age was 50 years (range 10–82). The vast majority of patients (90%) underwent surgery as the primary treatment modality, typically followed with secondary adjuvant therapy. The majority of cases were treated with multimodal therapy, notably with surgery and radiation (55%), while surgery with adjuvant chemo-RT was also commonly used (20%; Table 1). More studies describing SNTCS have been published in the United States than any other nation (34%) followed by India (23%) and Japan (11%). Mean follow-up across all studies was 21 months. Mean time to recurrence was 19.5 months. Recurrence rate was 38%, with mean survival at 2 years of 55%.

Of the 127 reported cases in the literature, full outcome data was only available for only 58 cases (Table 1). Surgery alone was performed in 4 cases while 36 cases received adjuvant radiotherapy following surgery and 16



H&E (40x) high power view showing Blastemal component of the tumor

H&E (40x) high power view showing carcinoma component

Figure 4. H&E histology showing blastemal (A) and carcinomatous (B) components of SNTCS from case 1.

Table 1. List and Description of Papers Reviewed.

Author	Year	Article Type	Number of Novel Patients	Included in K-M Analysis	Time to Recurrence (Months, avg if >1)	Follow-up Duration (Months, avg if >1)
Abt	1970	Case Report	1	Yes	1	72
Agrawal N	2012	Case Report	1	Yes	–	45
Batsakis JG	1995	Review	–	No	–	–
Bhalla V	2016	Case Series	2	No	–	–
Budrukkar A	2010	Case Series	22	No	–	34
Carrizo F	2006	Case Series	2	Yes	24	30
Chakraborty S	2016	Case Report	1	No	–	0
Chao KK	2004	Case Report	1	Yes	–	6
Devgan BK	1978	Case Report	1	No	0	N/A
Dicke TE	1970	Case Report	1	Yes	3	14
Endo H	2001	Case Report	1	Yes	54	84
Fatima SS	2013	Case Series	6	Yes	–	24
Fernandez PL	1995	Case Report	1	Yes	7	7
Foong YC	2017	Case Report	1	Yes	24	24
Fukuoka K	2000	Case Report	1	Yes	30	30
Heffner DK	1984	Case Series	15	No	–	33
Jin W	2018	Case Report	1	Yes	6	7
Joshi A	2014	Case Series	2	Yes	3	3
Joshi A	2015	Case Report	1	Yes	5	72
Kane SV	2009	Case Report	1	No	–	10
Kim JH	2011	Case Report	1	Yes	2	18
Krishna KK	2007	Case Report	1	Yes	6	12
Kurmi DJ	2017	Case Report	1	Yes	6	6
Leelamma JP	2018	Case Report	1	No	–	–
Lim CCT	2008	Case Report	1	Yes	7	8
Liu JK	2012	Case Report	1	No	–	–
McKean EL	2014	Case Report	1	No	–	–
Misra P	2014	Review	–	No	–	–
Mohanty S	2013	Case Report	1	Yes	12	12
Mondal SK	2012	Case Report	1	Yes	24	24
Nitsche M	2005	Case Report	1	Yes	36	36
Ogawa T	2000	Case Report	1	Yes	9	9
Oka K	2007	Case Report	1	Yes	12	12
Pai SA	1998	Case Series	4	Yes	18	15
Palled S	2015	Case Report	1	Yes	60	60
Patchefsky A	1968	Case Report	1	Yes	0.25	3
Peng G	2011	Case Series	2	Yes	–	25
Petrovich Z	1977	Case Report	1	Yes	60	60
Prasad KC	2003	Case Report	1	Yes	13	13
Rotenberg	2002	Case Report	1	Yes	6	6
Sable M	2017	Case Report	1	No	–	1
Salem F	2008	Case Series	3	No	12	12
Seo E	2017	Case Report	1	No	–	–
Shanmugaratnam	1983	Case Series	3	Yes	23	35
Sharma HS	1998	Case Report	1	No	9	12
Shemen L	1995	Case Report	1	Yes	60	60
Shimazaki	2000	Case Report	1	No	–	22
Shorter C	2010	Case Report	1	Yes	6	6
Smith SL	2008	Case Series	10	Yes	–	131
Sobani ZA	2012	Case Report	1	Yes	6	6
Su YY	2010	Case Report	1	Yes	18	43
Szudek J	2005	Case Report	1	No	–	–
Takasaki K	2006	Case Report	1	Yes	41	41
Terasaka S	1998	Case Report	1	Yes	31	31

(continued)

Table 1. Continued.

Author	Year	Article Type	Number of Novel Patients	Included in K-M Analysis	Time to Recurrence (Months, avg if >1)	Follow-up Duration (Months, avg if >1)
Thomas J	2011	Case Report	1	No	–	–
Tokunaga T	2012	Case Report	1	Yes	24	24
Vranic S	2008	Case Report	1	No	8	–
Wahid FI	2012	Case Report	1	No	–	–
Wang SY	2007	Case Series	5	No	70	–
Wassef SN	2012	Case Report	1	Yes	48	48
Wei S	2008	Case Report	1	Yes	12	12
Weinberg BD	2014	Case Report	1	Yes	24	32
Wellman M	2002	Case Report	1	No	48	48
Yang S	2013	Case Series	2	No	–	24

"K-M" refers to Kaplan-Meier analysis. A "Yes" in this category demonstrates that some or all cases reported in this manuscript presented enough case information for inclusion survival analysis. Time to recurrence and follow-up duration were averaged if more than one case applied per article.

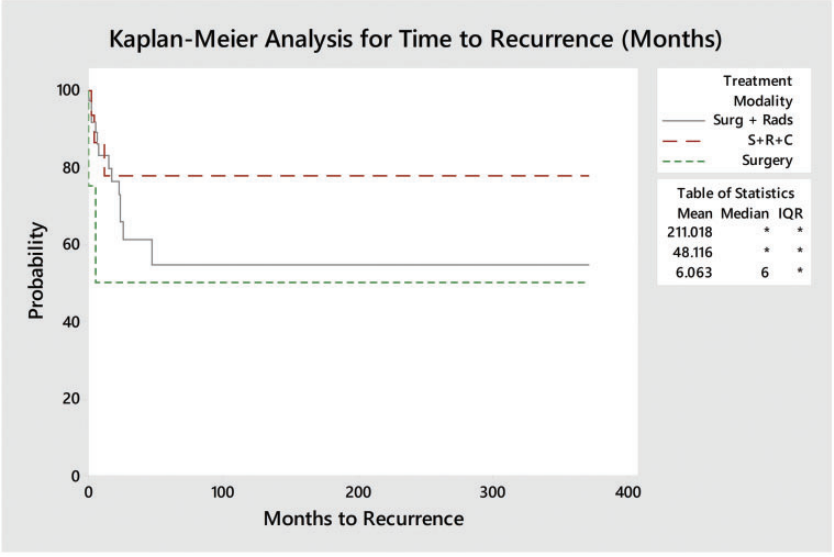


Figure 5. Kaplan-Meier plot with recurrence events for each cohort based on modality of treatment vs time (months). Log-Rank test was not significant between treatment modalities ($p = 0.085$). Time to recurrence was defined as the time from the end of treatment to recurrence.

cases received adjuvant radiotherapy and chemotherapy. One patient each received radiotherapy in isolation and surgery with adjuvant chemotherapy (without radiotherapy). Kaplan-Meier curves were plotted based on treatment modality – single (surgery), bimodality (surgery and radiation), and trimodality (surgery and adjuvant chemo-radiation) by time to recurrence and mortality from the end of treatment (Figures 5 and 6). No deaths occurred amongst the 16 trimodality cases while 13 of 36 (36.1%) bimodality cases and 2 of 4 (50%) surgery cases resulted in death. Log-rank tests demonstrated significant differences between time to mortality between the three main courses of treatment ($p < 0.001$; surgery, bimodality, and trimodality) but did not identify a significant difference in time to recurrence ($p = 0.085$). A pairwise log-rank test for time to death identified significant differences in survival between specific modes of treatment. Trimodality was found to be associated with significantly delayed time to death as compared to bimodality ($p = 0.05$) and surgery without adjuvant treatment ($p = 0.004$). Similarly, patients receiving bimodality were also found to have improved survival compared those receiving surgery alone ($p = 0.004$). A Kaplan-Meier survival plot was also performed to compare time to mortality across three time periods (1968–1999, 2000–2009, 2010–2018; Figure 7). A log-rank test found no significant difference in time to survival between these time points ($p = 0.8$).

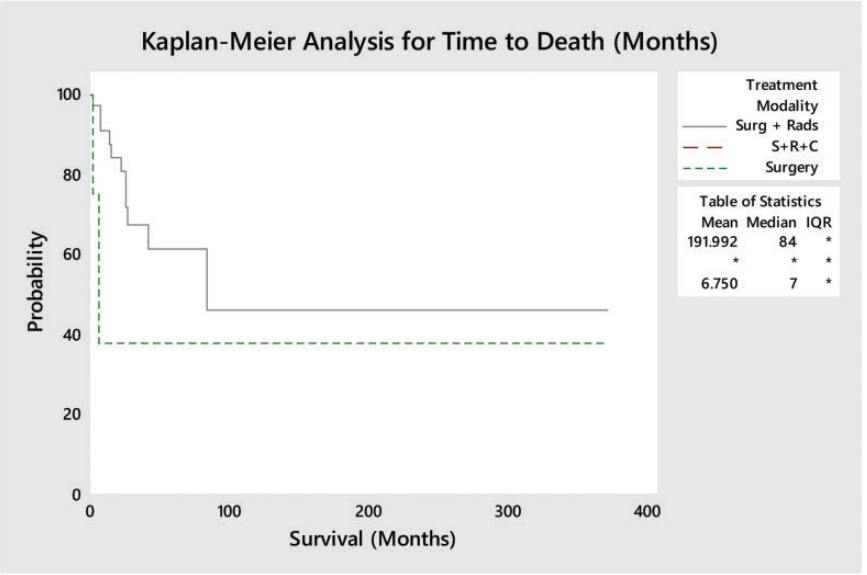


Figure 6. Kaplan-Meier survival analysis based on modality of treatment vs. months to death for cases were survival data was available. Log-Rank test was significant between treatment modalities ($p < 0.001$). Survival was defined as the time from the end of treatment to death. Note that no deaths were reported in patients who underwent trimodality with surgery followed by adjuvant radiotherapy and chemotherapy.

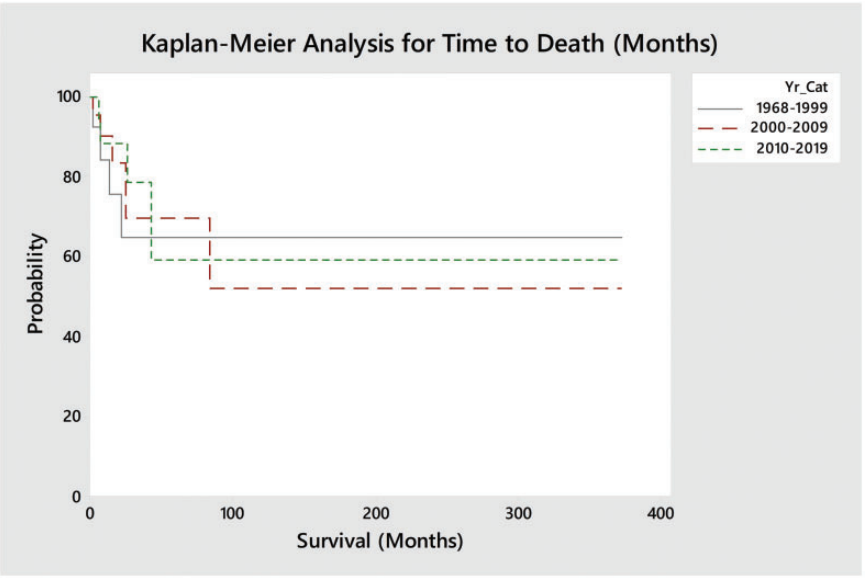


Figure 7. Kaplan-Meier survival analysis based on era and months to death for cases where survival data was available. Log-rank test did not identify a significant difference between time to survival by era ($p = 0.8$). Survival was defined as the time from the end of treatment to death.

Discussion

Sinonasal teratocarcinosarcoma is an exceptionally rare and aggressive disease with a poor prognosis. Due to its rarity and the heterogeneous nature of the neoplasm itself, there is vast variation in disease presentation and management. The neoplasm itself features both teratoma and carcinosarcoma components, including epithelial and mesenchymal tissue (Figure 4).[29] The epithelial tissue may be highly variable with both benign and malignant squamous and glandular components and may include columnar and/or cuboidal cells with or without cilia. Mesenchymal components may appear as various muscle types, cartilage, and/or bone tissue.

Additionally, many cases include poorly differentiated neuroepithelial tissue with neural rosettes.[4] Given this large histologic heterogeneity, small biopsy samples are often inadequate for diagnostic purposes. Diagnosis may be assisted by the appearance of "fetal-appearing" squamous epithelium with large nucleoli and the absence of germ cell components, however this finding is not universal.[7,34] Immunohistochemistry often demonstrates expression of CD99, vimentin, and neuron-specific enolase, while STNCS cells are typically negative for leukocyte common antigen, beta-HCG, and neurofilament protein.[4,34]

Despite its rarity, SNTCS is an aggressive tumor with a mean 2-year survival rate of 55% and a recurrence rate of 38%. Both patients treated at our institution show no evidence of disease at 2 and 9 years post-operatively, respectively. Interestingly, our second patient had extensive radiation therapy to the ipsilateral head and neck area prior to identification of the SNTCS tumor. It is unclear if this represents an inciting event correlating to his disease etiology, however this is feasible given known associations of radiation induced skull base sarcomas.[65]

SNTCS patients most often present with signs and symptoms of nasal obstruction, as seen in the two patients described in this study, with possible tumor origination from a pluripotential progenitor cells.[10] While primarily a disease of middle age adults, SNTCS has been observed in patients 10–82 years of age. Interestingly, the literature demonstrates a male predilection for SNTCS, with men accounting for over 80% of patients in this review. The reasons for this are still unknown and may reflect gender disparities in access to care around the world leading to publication bias or a fundamental biological process that favors oncogenesis in men.

Only 85 prior studies have examined SNTCS. These have varied considerably from case reports to literature reviews with most focusing on basic science rather than clinical management.[46] Despite the limited sample, certain treatment trends are identifiable. Bimodality consisting of surgery with adjuvant radiation appears to be the most commonly selected treatment, used in 62% of cases for which treatment data is available, while trimodality with surgery, adjuvant radiotherapy, and adjuvant chemotherapy was the second most common treatment of choice, used in 28% of the cases. Using a pairwise log-rank test, both bimodality and trimodality were found to be associated with significantly longer time to death as compared to surgery alone. Interestingly, trimodality was also associated with significantly delayed time to death as compared to bimodality, despite being used less frequently. While not statistically significant, the Kaplan-Meier curves also demonstrate possible differences between treatment strategies with regard to time to recurrence, with multimodal therapy appearing to have a lower proportion of patients with post-treatment recurrence compared to surgery alone. Future meta-analyses with larger cohorts may be sufficiently powered to detect if this is a true difference. Time to survival, meanwhile, has not appeared to change over time, as demonstrated by a Kaplan-Meier analysis with a log-rank test comparing survival across different eras ($p = 0.8$), suggesting that treatment outcomes have been relatively stable over analysis period.

As with any individual patient data, survival analysis of rare disease based on case reports, this study is not without limitations. Historical trends in treatment are dependent on methods used in previous studies, and selection bias is inevitable as only a limited subset of cases may have been reported as a result of rare presentation or outcomes. Additionally, given the retrospective nature of this study, we were unable to control for functional status, comorbidities, or differences within management strategies. Length of follow-up varied considerably between studies as well, with the average duration of follow up exceeding average time to recurrence by 1.5 months (21 to 19.5 months). Consequently, studies with shorter length of follow-up may not have captured later recurrence. While a formal analysis of heterogeneity was unable to be performed, the variety of cases across time, age, and location suggests the cases were fairly heterogeneous. Furthermore, cases where surgery was performed without adjuvant therapy may reflect patient inability to tolerate further treatment, which may have contributed to the poor results in this cohort. The relatively few numbers of surgery only patients further limits direct comparison against other treatment modalities and generalization of this data should be undertaken with caution. Nevertheless, this study represents the largest and most complete systematic review of the literature regarding SNTCS to date, and further demonstrates the need for comprehensive multi-institutional databases to study outcomes of rare skull base pathologies.

Conclusion

Sinonasal teratocarcinosarcoma (SNTCS) is a rare and frequently misdiagnosed sinonasal neoplasm. Two-year survival rates for this aggressive skull base tumor appear to be 55% with a recurrence rate of 38%. Bimodality with surgery and adjuvant radiotherapy is the most common treatment modality utilized, followed by trimodality. While trimodality may be more effective than bimodality, both forms of adjuvant therapy appear more effective than surgery alone in managing SNTCS.

Declaration of Conflicting Interests

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