A Comprehensive Comparative Analysis of Treatment Modalities for Sinonasal Malignancies

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Abstract

BACKGROUND: Sinonasal malignancies are a rare and heterogeneous group of tumors for which there is a paucity of robust data with which to guide management decisions. The authors used the National Cancer Data Base to better understand the presenting characteristics of these tumors and to compare outcomes by treatment modality.

METHODS: The National Cancer Data Base was queried for sinonasal malignancies diagnosed between 2004 and 2012. Overall survival was assessed using multivariate analyses and propensity score matching.

RESULTS: A total of 11,160 patients were identified for the initial analysis. The majority were male, aged 40 to 69 years, with tumors of the nasal cavity or maxillary sinus. Squamous cell histology was most common. The majority of patients presented with advanced tumor stage but without locoregional lymph node or distant metastases. Treatment modalities were compared for squamous cell carcinomas. In multivariate analysis, compared with surgery alone, patients who received adjuvant radiotherapy (hazard ratio [HR], 0.658 [*P*<.001]), adjuvant chemoradiotherapy (HR, 0.696 [*P*=.002]), or neoadjuvant therapy (HR, 0.656 [*P* = .007]) had improved overall survival. Patients who received radiotherapy alone (HR, 1.294 [*P*=.001]) or chemotherapy alone (HR, 1.834 [*P*<.001]) had worse outcomes. These findings were validated in propensity score

matching. It is important to note that neoadjuvant chemoradiotherapy was associated with achieving a negative surgical margin (odds ratio, 2.641 [*P*=.045]).

CONCLUSIONS: Surgery is the mainstay of therapy for patients with sinonasal malignancies, but multimodality therapy is associated with improved overall survival.

Keywords

chemoradiotherapy; head and neck cancer; National Cancer Data Base (NCDB); radiotherapy; sinonasal malignancy

INTRODUCTION

Cancers of the nasal and paranasal sinuses are rare, aggressive tumors that generally are diagnosed at an advanced stage because patients often remain asymptomatic until the tumor becomes large enough to manifest symptoms.[1] Although surgery is the mainstay of treatment for patients with these tumors,[2] to the best of our knowledge there is limited scientific rationale and weak clinical evidence supporting treatment guidelines in this field. Therapy encompassing a multimodality approach has been shown to improve treatment outcomes.[3–8]

Although it has been established that maximal safe surgical resection yields the best overall survival (OS) outcomes,[2] the role of postoperative radiotherapy is less well defined in the treatment of this disease. Some older series found no survival benefit with adjuvant therapy, [9–11] whereas others demonstrated that combined radiotherapy and surgery yield better survival rates.[3–7] Older radiotherapy techniques most likely contributed to the lack of therapeutic advantage to chemoradiotherapy, as demonstrated by the high rates of severe long-term toxicities.[7] Significant treatment-related toxicity is less common with modern radiotherapy techniques. It is interesting to note that recent advances in radiotherapy have demonstrated significantly improved outcomes with minimal long-term toxicity.[3,12–16]

The optimal sequencing of chemotherapy and radiotherapy for patients with sinonasal carcinoma remains controversial.[17] Small reports have shown a benefit for induction chemotherapy,[8,18–22] and numerous institutional and multi-institutional series have shown a benefit for adjuvant therapy.[3–6,8,23] To our knowledge, definitive concurrent chemoradiotherapy has been less studied in this disease, with a few series demonstrating low survival outcomes and in-field failures with biologically equivalent doses <65 grays.[24] Comparisons of surgery with or without adjuvant chemoradiotherapy reported in retrospective series have emphasized the importance of surgical resection.[25] Similarly, other series have shown surgery followed by radiotherapy to be superior to radiotherapy alone. [26,27] However, the small cohorts in these retrospective series coupled with heterogeneous histologies significantly limit the broad application of these findings.

In the current study, we used the high number and breadth of cases available in the National Cancer Data Base (NCDB) to investigate outcomes in a modern patient cohort. We specifically examined the presenting characteristics of these tumors according to histology and subsite and compared outcomes by treatment modality for squamous cell carcinomas

(SCC). To the best of our knowledge, this is the largest and most comprehensive assessment of sinonasal malignancies reported to date.

MATERIALS AND METHODS

The deidentified NCDB was used for the current study. The NCDB collects data from >1500 community and academic cancer centers and has been reported to represent approximately 70% of all cancer cases in the United States. The NCDB is the result of a collaboration between the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology used, or the conclusions drawn from these data by the investigator. The NCDB has established criteria to ensure the data submitted meet specific quality benchmarks. The following NCDB analysis was performed with the approval of our local Institutional Review Board.

We queried the deidentified NCDB file for all patients with primary sinonasal malignancies diagnosed between 2004 and 2012 based on primary site codes C300 to C319 (ICD-0-3). This included the following subsites for initial analysis: maxillary sinus, ethmoid sinus, frontal sinus, sphenoid sinus, nasal cavity, paranasal sinuses, and middle ear. As detailed in Figure 1, our approach to develop a comprehensive and complete cohort for multivariate analysis (MVA) eliminated multiple subsites from our analysis. Ultimately, the subsites included on MVA were maxillary sinus, ethmoid sinus, and nasal cavity. For tumor (T) and lymph node (N) classification, clinical staging information was used primarily when available; otherwise pathologic staging information was applied. Metastases at the time of diagnosis were determined from provided overall stage and "CS mets at diagnosis." Overall stage was derived from TNM stages using the seventh edition of the AJCC staging manual. [28] "Microscopic residual tumor," "macroscopic residual tumor," and "residual tumor, NOS [not otherwise specified]" were categorized as positive surgical margins. The additional variables accounted for in the primary analysis included age, sex, race/ethnicity, year of diagnosis, specific disease site, Charlson/Deyo combined comorbidity score (CDCC),[29,30] and therapy received. We included the following histologies for our initial analysis of presentation and outcomes: SCC, adenosquamous carcinoma, adenocarcinoma, esthesioneuroblastoma, sinonasal undifferentiated carcinoma (SNUC), adenoid cystic carcinoma (ACC), mucosal melanoma, and mucoepidermoid carcinoma. SNUC was defined by histology code 8020 ("carcinoma, undifferentiated type, NOS"). Sarcomas were excluded from the current analysis. We limited our analysis of outcomes by modality to SCCs. Therapy was categorized into the following groups: surgery alone, radiotherapy alone, chemotherapy alone, definitive chemoradiotherapy, surgery with adjuvant radiotherapy, surgery with adjuvant chemoradiotherapy, and neoadjuvant therapy. The neoadjuvant therapy group was defined to include neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy because there were limited numbers of patients available for robust comparison from each individual neoadjuvant approach.

Surgery was defined as site code 30 or higher. For patients who were coded as receiving "debulking" or "surgery, NOS," if the surgical margin was negative or microscopic positive, then the patient was coded as having undergone surgery. Ifthe surgical margin was

macroscopic positive or unknown, then the patient was excluded because we were unable to determine whether the surgical procedure was oncologic. Concurrent chemotherapy was defined as a chemotherapy start date within 14 days of the radiotherapy start date.[31] If patients received definitive radiotherapy and received chemotherapy at some point but outside of this 14-day window, they were classified as having received definitive radiotherapy only. Neoadjuvant chemotherapy was defined as starting 7 days before surgery. Adjuvant chemotherapy was defined as starting within 30 days after surgery. Patients not meeting either of these criteria were considered to have undergone surgery alone for primary treatment. Ultimately, very few patients were treated with surgery followed by chemotherapy alone and were excluded from analyses. To categorize patients who received neoadjuvant or adjuvant radiotherapy, we first used the information provided under "RX_SUMM_SURGRAD_SEQ." If this information was not provided, this information then was derived from the days from diagnosis to surgery and the days from diagnosis to radiotherapy.

Our initial query as described above was limited to patients' first or second lifetime neoplasm. For our initial analysis, we in addition excluded patients with histologies other than those listed above. This yielded 11,160 patients for our primary analysis. To address the impact of differing treatment modalities, we excluded patients with unknown values for predetermined variables, such as staging and surgical margin status. Patients with distant metastatic disease and those with treatment paradigms other than those described above (or for whom we were unable to define the treatment received) were excluded as well. To account for immortal time bias in this retrospective analysis, we also excluded patients with follow-up of <2 months. This yielded 3331 patients for the primary MVA in the current study (Fig. 1).

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version 23.0; IBM Corporation, Armonk, NY). We performed Kaplan-Meier survival analysis with log-rank comparison. Multivariate Cox regression analysis was performed using OS as the outcome with a significance level of $P<.05$. The proportional hazards assumption was assessed with a test of Schoenfeld residuals for covariates in all final models as previously described,[32] and it returned no significant results. Propensity score matching also was performed for each treatment modality compared with surgery alone. The same variables used in the multivariate analysis were accounted for, including age, sex, CDCC score, race/ ethnicity, year of diagnosis, site, T classification, N classification, facility volume, and surgical margin status. One-to-1 matching without replacement was completed using the nearest neighbor match on the logit of the propensity score for treatment approach with the caliper width set to 0.05 times the standard deviation of the logit of the propensity score, as previously described.[33] Univariate cox hazard ratios (HRs) are reported. Logistic regression models were used to assess the association between patient characteristics and treatment. GraphPad Prism (version 5.03; GraphPad Software Inc, La Jolla, Calif) was used for the creation of the Kaplan-Meier curves presented.

RESULTS

We identified 11,160 patients for our primary analysis inclusive of all patients with known follow-up. The majority of patients were aged 40 to 69 years (60.8%); 59.9% were male and 77.9% were non-Hispanic white. SCC was the most represented histology (54.1%). Approximately 16.2% of patients presented with T1 tumors, 9.9% with T2 tumors, 13.8% with T3 tumors, and 31.4% with T4 tumors. Approximately 58.5% of patients had N0 disease and only 5.1% had distant metastases at the time of diagnosis (Table 1). We compared OS by site (Fig. 2A) and histology (Fig. 2B). The median OS by site was 86.2 months for the nasal cavity, 51.2 months for the ethmoid sinus, 35.7 months for the middle ear, 35.2 months for the paranasal sinuses, 29.4 months for the maxillary sinus, 27.6 months for the sphenoid sinus, and 24.8 months for the frontal sinus. The median OS by histology was 98.6 months for adenocarcinoma, 86.1 months for ACC, 52.8 months for SCC, 33.4 months for SNUC, and 22.4 months for melanoma. The median OS was not reached for mucoepidermoid carcinoma, esthesioneuroblastoma, or adenosquamous cell carcinoma histologies.

For comparison of treatment modalities, we limited the current study cohort to patients with SCC histology and included only those patients with known values for the predefined variables for MVA, including TNM and overall stage and surgical margin status. We also excluded patients with metastatic disease at the time of diagnosis and those with treatment paradigms other than those of interest and in cases in which the treatment was unable to be defined. Finally, we excluded patients with <2 months follow-up from the current analysis. Using the above criteria, we identified a total of 3331 patients suitable for analysis. In MVA, we found that age (HR, 1.029 [P<.001]), increasing CDCC score (CDCC of 1: HR, 1.099 [P =.182]; and CDCC of 2: HR, 1.637 [P<.001]), and African American race (vs white: HR, 1.248 [P = .004]) all were associated with worse OS. Hispanic patients had an improved OS (HR, 0.739 [P = .015]) compared with non-Hispanic white patients. By tumor site, patients with nasal cavity tumors were found to have significantly improved OS compared with patients with maxillary sinus tumors (HR, 0.620 [P<.001]); the OS for patients with ethmoid sinus tumors did not differ significantly from that of patients with maxillary sinus tumors. Increasing T classification was associated with worse OS (T2: HR, 1.212 [P = .056]; T3: HR, 1.659 [P<.001]; andT4: HR, 2.035 [P<.001]). Increasing N classification also was associated with worse OS (N1: HR, 1.555 [P<.001]; and N2/N3: HR, 1.600 [P<.001]). Middle tertile-volume facilities had improved outcomes compared with low tertile-volume facilities (HR, 0.844 [P = .006]), and a trend toward improved OS was observed for high tertile-volume centers compared with low tertile-volume centers (HR, 0.888; 95% confidence interval [95% CI], 0.783-1.007 [P = .064]). When comparing treatment modalities, radiotherapy alone (HR, 1.294 [P = .001]) and chemotherapy alone (HR, 1.834 [P<.001]) were associated with worse OS, but patients treated with adjuvant radiotherapy (HR, 0.658 [P<.001]) and adjuvant chemoradiotherapy (HR, 0.696 [P = .002]) had improved outcomes compared with patients treated with single-modality surgery. OS did not differ between definitive chemoradiotherapy and surgery alone (HR, 1.076; 95% CI, 0.899-1.289 [P = .425]). Neoadjuvant therapy, including neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy, was associated with improved OS (HR, 0.656 [P = .007]) (Table 2).

Propensity score-matched analyses with 1-to-1 matching were performed to validate survival outcomes by treatment modality observed in multivariate analyses. Patient characteristics were well balanced between groups (see Supporting Information Table 1). Results were confirmed in propensity score-matched groups with HRs for OS compared with surgery as follows: radiotherapy alone (HR, 1.326; 95% CI, 1.108-1.587 [P = .002]), chemotherapy alone (HR, 1.473; 95% CI, 1.048-2.070 [P = .026]), chemoradiotherapy (HR, 1.136; 95% CI, 0.910-1.417 [P = .260]), adjuvant radiotherapy (HR, 0.762; 95% CI, 0.626-0.929 [P = .007]), adjuvant chemoradiotherapy (HR, 0.689; 95% CI, 0.523-0.909 [P = .008]), and neoadjuvant therapy (HR, 0.681; 95% CI, 0.465-0.996 [P = .048]).

Finally, we examined factors predictive of achieving a negative surgical margin in patients receiving neoadjuvant therapy. With increasing T classification, patients were less likely to have a negative surgical margin (T2: OR for a negative surgical margin ($_{neg\ margin}$), 0.824 [P = .589]; T3: OR$_{neg\ margin}$, 0.254 [P<.001]; and T4: OR$_{neg\ margin}$, 0.189 [P<.001]). Patients who received neoadjuvant chemotherapy (OR$_{neg\ margin}$, 1.388; 95% CI, 0.755-2.553 [P = .291]) or neoadjuvant radiotherapy alone (OR$_{neg\ margin}$, 1.496; 95% CI, 0.587-3.810 [P = .399]) were not found to have a statistically significant increased likelihood of achieving a negative surgical margin, but for patients who received neoadjuvant chemoradiotherapy, there was a statistically significant association with negative surgical margin status (OR$_{neg\ margin}$. 2.641 [P = .045]) (Table 3).

DISCUSSION

Sinonasal malignancies present a challenging situation for cancer providers based on their complex anatomic location and the lack of randomized data to guide management. In the current study, we used the NCDB to compile what is to our knowledge the largest study of sinonasal malignancies presented to date. We examined disease prognosis based on histology, subsite, and stage of disease, and assessed outcomes by treatment modality and sequencing for patients with SCC, who comprised the largest subset of patients.

Consistent with published retrospective series, the majority of patients presenting with sinonasal cancer were male, were non-Hispanic white, and had squamous cell histology.[5,9] The results of the current study also demonstrated worse outcomes for African American patients and improved outcomes for Hispanic patients compared with non-Hispanic white patients. It is interesting to note that parallel findings have been shown previously in patients with head and neck cancers,[34] as well as in patients with non–small cell lung cancer and cervical cancer.[35,36]

The majority of patients in the NCDB presented with a high T classification but without lymph node metastases, and only approximately 5% of patients had distant metastatic disease at the time of diagnosis. Such a locally aggressive disease emphasizes the importance of improving local therapy. Local disease recurrence has been reported as a predominant treatment failure pattern in the literature.[5,17] This also is supported by the findings presented herein that patients with surgically accessible tumors fared better. Patients with tumors of the nasal cavity were found to have far superior OS compared with patients with tumors of other sites. The anatomy of the region, with the proximity of several

important structures, adds further complexity to treatment planning. Although both surgical and radiotherapy approaches have advanced in recent years, with endoscopic resections[37] and intensity-modulated radiotherapy,[38,39] we did not see this translate into an improvement in OS over the time period assessed in MVA in the current study. It is likely that we did not observe an improvement in survival over time in the current study because many of these advancements predate our study period.

A recently reported Surveillance, Epidemiology, and End Results (SEER) analysis exclusive to paranasal sinus squamous cell carcinoma showed similar age and race distributions, although higher rates of lymph node metastases compared with our initial analysis inclusive of additional histologies.[40] Patients with mucosal melanoma were found to have the poorest OS, whereas those with esthesioneuroblastoma had the best OS. This finding is consistent with prior studies of mucosal melanoma of the head and neck.[41] The 5-year OS rate (approximately 21%) compared similarly with that reported in other studies of mucosal melanoma.[42] However, a major confounder in this comparison is the mutational analysis and receipt of targeted therapy and immunotherapy. A major limitation of the NCDB is that neither information regarding driver mutations nor any information concerning the receipt of targeted or immunotherapy is available for analysis.

To the best of our knowledge, the optimal therapeutic protocol for patients with sinonasal cancer remains a controversial entity. Although a multimodality approach has been shown to yield improved survival in some series,[3–8] the optimal combination and sequencing remain unanswered. In concordance with the literature, the results of the current study demonstrate that radiotherapy alone was inferior to surgery alone[9] and definitive chemoradiation performed similarly to surgery alone.[43] However, patients who received multimodality therapy, in the form of adjuvant radiotherapy, adjuvant chemoradiation, or neoadjuvant therapy, were found to have significantly improved outcomes. This is consistent with some published reports. For example, several series have shown improved survival in patients undergoing surgery and adjuvant radiotherapy or chemoradiotherapy compared with patients receiving radiotherapy alone.[6,7,19] Guntinas-Lichius et al demonstrated improved local control and disease-free survival for patients receiving multimodality therapy, including both preoperative and postoperative radiotherapy.[26] Another small series presented by Lee et al showed excellent outcomes in a retrospective cohort of 19 patients treated with induction chemotherapy, surgical resection, and adjuvant radiotherapy or chemoradiotherapy.[8] In all, the findings from these small series are supported by the findings in the current large cancer registry cohort.

The importance of a negative surgical margin has been shown previously[7,9] and was again demonstrated in the current study. Neoadjuvant chemoradiotherapy was associated with an increased likelihood of achieving a negative surgical margin and neoadjuvant therapy (a group inclusive of neoadjuvant chemotherapy, radiotherapy, or chemoradiation) was associated with improved OS. In a small single-institution case series of neoadjuvant chemoradiotherapy for SNUC, 3 patients achieved a pathologic complete response, 2 patients had negative surgical margins, and another 3 patients had close surgical margins,[44] thereby supporting the benefit of neoadjuvant chemoradiotherapy for surgical margin status.

However, it is interesting to note that another small series of patients with SNUC demonstrated no difference in local control or OS based on surgical margin status.[45]

As discussed above, the current study supports the use of multimodality therapy for the treatment of these tumors, and we believe the study findings are hypothesis generating. For example, the results herein demonstrate that the addition of radiotherapy to surgery offers an OS benefit either in the neoadjuvant or adjuvant setting, but neither sequence appears to be superior over the other. We suspect that neoadjuvant radiotherapy is preferable in converting patients with unresectable disease to surgical candidates, but outside of that context adjuvant radiotherapy may be preferable given the complexities of operating in a radiated field. Unfortunately, this hypothesis cannot be fully tested in the NCDB due to lack of information regarding initial resectability and surgical complications, but this area of exploration is ripe for prospective assessment. Furthermore, it is not clear that the addition of concurrent chemotherapy to adjuvant radiotherapy further improves OS. This suggests that radiotherapy alone may be sufficient for the sterilization of microscopic disease for SCC in this setting. However, there is a key oncologic outcome that we were unable to assess with the NCDB: freedom from distant metastases. It is possible that chemotherapy improves freedom from distant metastases even if that does not translate into an OS benefit. This may be an important indication for chemotherapy and should be tested prospectively as well.

Overall, to the best of our knowledge, the majority of prior studies regarding this topic consist of small cohorts or case series. Some of these studies failed to demonstrate an advantage to multimodality therapy,[9–11] whereas others demonstrated improved survival outcomes, which is consistent with the findings of the current study.[3–8] One reason that earlier studies might have failed to demonstrate an improvement with multimodality therapy may be the radiotherapy techniques used, compared with the modern cohort of patients in the current study. Although another more contemporary national cancer registry study also did not demonstrate a benefit to adjuvant radiotherapy,[1] it does not appear that this study accounted for other confounding variables. Such outcomes may simply be the result of selection bias because patients with more advanced disease are likely to be offered more extensive therapy. It is important to note that we ultimately may have prospective data to help guide management because there currently are 2 ongoing Italian trials addressing multimodality therapy for sinonasal malignancies (ClinicalTrials.gov NCT02099175 and NCT02099188).[46,47] Nevertheless, for now, this large cancer registry cohort offers valuable information to help guide treatment decisions for these difficult cases.

The current study has limitations. It is important to note that the NCDB does not provide data regarding cause-specific survival. Furthermore, because it is a retrospective study, the results of the current study were prone to contamination by other factors for which we could not account. To mitigate as much confounding bias as possible herein, we used MVA and propensity score matching to account for available important variables. Furthermore, to reduce the contribution of immortal time bias, specifically within the context of our neoadjuvant therapy outcomes, we excluded all patients with <2 months of follow-up. Ultimately, we favor this approach but it is important to note that by excluding patients with short follow-up, we also may be selecting for patients who survive aggressive therapies. To better understand the influence of excluding patients with <2 months follow-up, we

performed a separate analysis inclusive of all patients and found no significant changes in the results (see Supporting Information Table 2). Another concern is that there is a subset of patients treated nonoperatively, but from the data provided in the NCDB, we cannot know whether these patients presented with resectable or unresectable disease, or the decision-making process that led to them being managed nonoperatively. Despite these limitations, the current study is a large study that asked pointed questions regarding specific treatment modalities to offer cancer providers additional information to help navigate the complex decision making involved in the management of patients with these rare diseases.

Conclusions

Herein we present what is to our knowledge the largest study to date of sinonasal malignancies. We demonstrated an advantage of multimodality therapy even when accounting for surgical margin status. Overall, these data emphasize the importance of coordinated multidisciplinary care in the management of patients with sinonasal malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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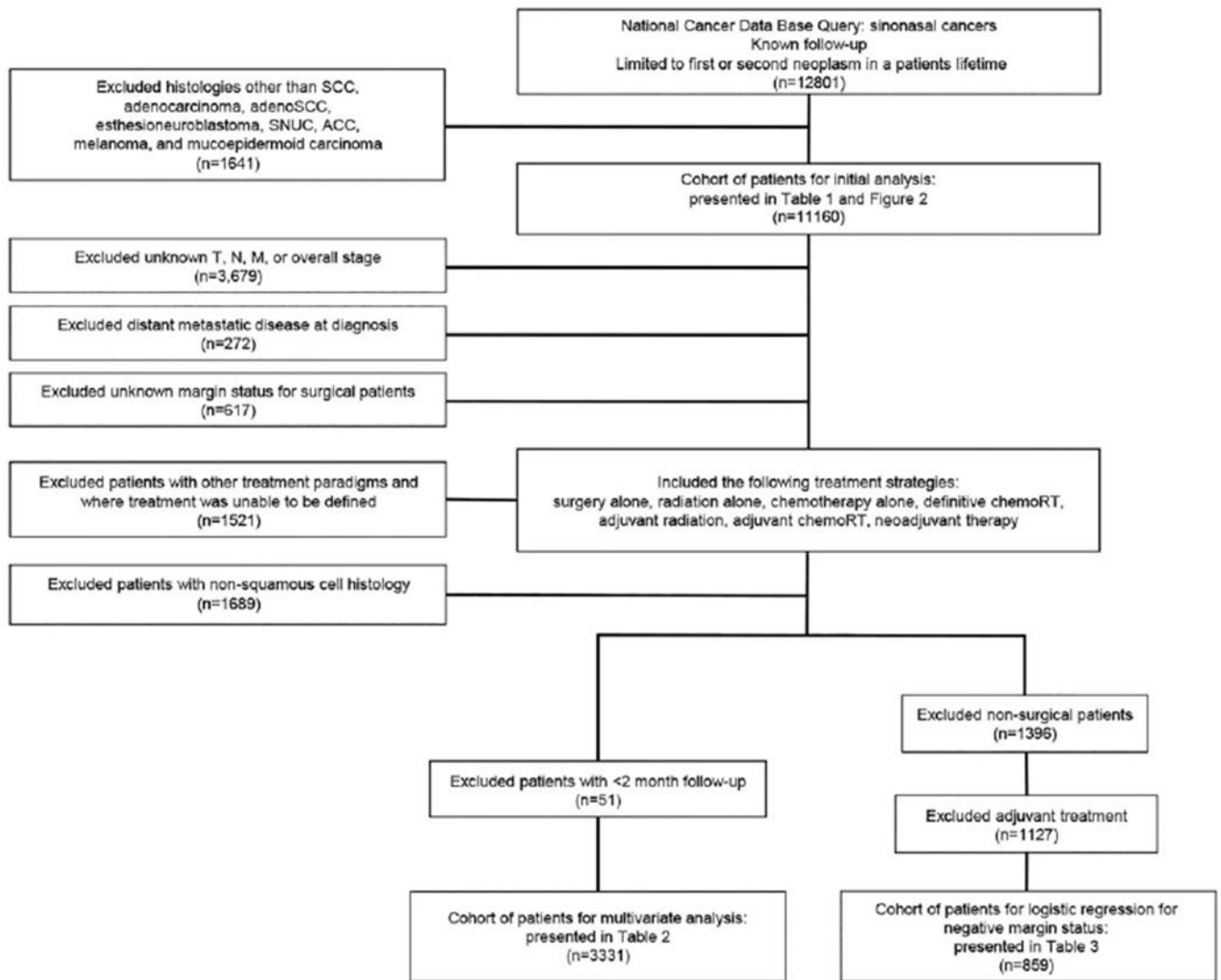
Figure 1.
Flowchart illustrating patient cohort selection criteria. ACC indicates adenoid cystic
carcinoma; adenoSCC, adenosquamous carcinoma; SCC, squamous cell carcinoma;
chemoRT, chemoradiotherapy; SNUC, sinonasal undifferentiated carcinoma.
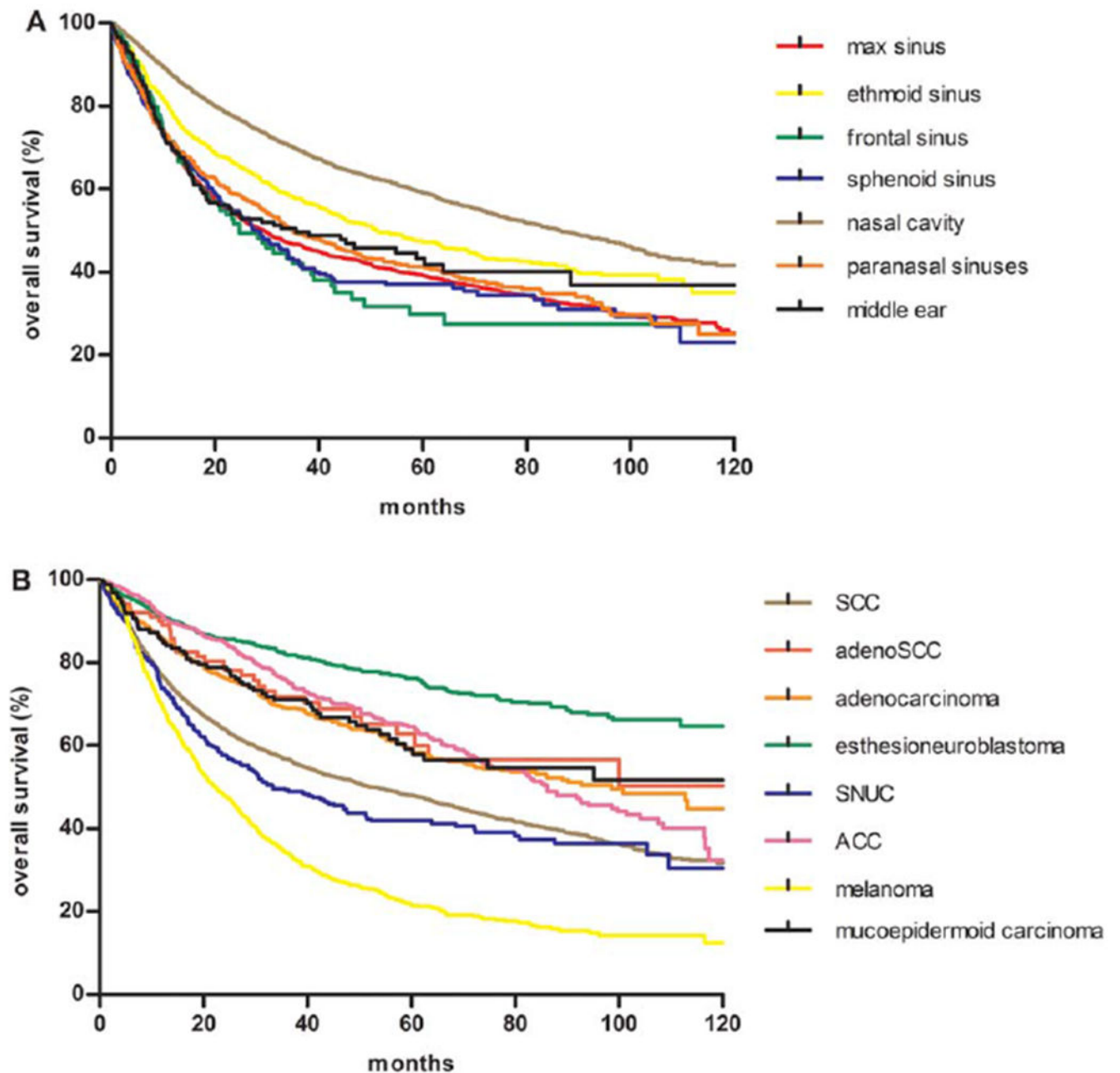
Figure 2.
Kaplan-Meier overall survival curves by (A) primary tumor site and (B) histology. ACC indicates adenoid cystic carcinoma; adenoSCC, adenosquamous carcinoma; max, maxillary sinus; SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.

TABLE 1.

Patient Characteristics

Characteristic	No.	%
Age, y		
Birth to 39	710	6.4
40-69	6781	60.8
70	3669	32.9
Sex		
Male	6690	59.9
Female	4470	40.1
CDCC score		
0	9240	82.8
1	1509	13.5
2	411	3.7
Race/ethnicity		
Non-Hispanic white	8691	77.9
Non-Hispanic African American	1164	10.4
Hispanic	679	6.1
Other/unknown	626	5.6
Y of diagnosis		
2004-2006	3410	30.5
2007-2009	3848	34.5
2010-2012	3902	35.0
Tumor site		
Maxillary sinus	3398	30.4
Ethmoid sinus	954	8.5
Frontal sinus	110	1.0
Sphenoid sinus	317	2.8
Nasal cavity	5524	49.5
Paranasal sinuses	682	6.1
Middle ear	175	1.6
Histology		
Squamous cell carcinoma	6039	54.1
Adenosquamous carcinoma	104	0.9
Adenocarcinoma	821	7.4
Esthesioneuroblastoma	1113	10.0
SNUC	417	3.7
Adenoid cystic carcinoma	779	7.0
Melanoma	1076	9.6
Mucoepidermoid carcinoma	163	1.5
NOS	648	5.8
Tumor classification		

Characteristic	No.	%
T1	1805	16.2
T2	1104	9.9
T3	1538	13.8
T4	3500	31.4
Unknown	3213	28.8
Lymph node classification		
N0	6531	58.5
N1	453	4.1
N2/N3	684	6.1
Unknown	3492	31.3
Distant metastases at time of diagnosis		
No	10045	90.0
Yes	574	5.1
Unknown	541	4.8
Overall 7th ed AJCC stage		
I	1706	15.3
II	923	8.3
III	1465	13.1
IVA/IVB	3473	31.1
IVC	574	5.1
Unknown	3019	27.1

Abbreviations: AJCC, American Joint Committee on Cancer; CDCC, Charlson/Deyo combined comorbidity score; NOS, not otherwise specified; SNUC, sinonasal undifferentiated carcinoma.

TABLE 2.

Multivariate Cox Regression Analysis for OS Accounting For Relevant Variables In Patients With SCC Histology

Variable	No.	HR	P	95% CI
Age (continuous variable)	3331	1.029	<.001	1.024-1.033
Sex				
Male	2165	Reference		
Female	1166	0.924	.140	0.831-1.026
CDCC score				
0	2707	Reference		
1	477	1.099	.182	0.957-1.261
2	147	1.637	<.001	1.301-2.061
Race/ethnicity				
Non-Hispanic white	2621	Reference		
Non-Hispanic African American	376	1.248	.004	1.075-1.449
Hispanic	185	0.739	.015	0.579-0.943
Other/unknown	149	1.144	.271	0.900-1.456
Y of diagnosis				
2004-2006	944	Reference		
2007-2009	1176	0.909	.118	0.806-1.024
2010-2012	1211	0.903	.133	0.789-1.032
Tumor site				
Maxillary sinus	1579	Reference		
Ethmoid sinus	212	0.851	.127	0.692-1.047
Nasal cavity	1540	0.620	<.001	0.546-0.705
Tumor classification				
T1	713	Reference		
T2	540	1.212	.056	0.995-1.477
T3	574	1.659	<.001	1.358-2.027
T4	1504	2.035	<.001	1.700-2.436
Lymph node classification				
N0	2736	Reference		

Variable	No.	HR	P	95% CI
N1	238	1.555	<.001	1.306-1.852
N2/N3	357	1.600	<.001	1.379-1.855
Facility volume				
Low	1054	Reference		
Mid	1194	0.844	.006	0.748-0.952
High	1083	0.888	.064	0.783-1.007
Surgical margin (for 1959 surgical patients)				
Negative	1422	Reference		
Positive	537	1.575	<.001	1.349-1.839
Therapy				
Surgery alone	703	Reference		
RT alone	784	1.294	.001	1.107-1.511
Chemotherapy alone	123	1.834	<.001	1.421-2.367
Definitive chemoradiotherapy	465	1.076	.425	0.899-1.289
Surgery plus adjuvant RT	794	0.658	<.001	0.553-0.784
Surgery plus adjuvant chemoradiation	333	0.696	.002	0.555-0.874
Neoadjuvant therapy	129	0.656	.007	0.483-0.893

Abbreviations: 95% CI, 95% confidence interval; CDCC, Charlson/Deyo combined comorbidity score; HR, hazard ratio; OS, overall survival; RT, radiotherapy; SCC, squamous cell carcinoma.

TABLE 3.

Logistic Regression for Negative Surgical Margins in Patients With SCC Histology Treated With Surgery and Neoadjuvant Therapy

Variable	OR$_{(-)margin}$	P	95% CI
Tumor site			
Maxillary sinus	Reference		
Ethmoid sinus	0.440	.015	0.228-0.852
Nasal cavity	1.428	.104	0.929-2.194
Tumor classification			
T1	Reference		
T2	0.824	.589	0.408-1.663
T3	0.254	<.001	0.137-0.471
T4	0.189	<.001	0.108-0.330
Lymph node classification			
N0	Reference		
N1	0.485	.038	0.245-0.959
N2/N3	0.648	.161	0.353-1.188
Therapy			
Surgery alone	Reference		
Neoadjuvant chemotherapy plus surgery	1.388	.291	0.755-2.553
Neoadjuvant RT plus surgery	1.496	.399	0.587-3.810
Neoadjuvant chemoradiotherapy plus surgery	2.641	.045	1.024-6.812

Abbreviations: 95% CI, 95% confidence interval; OR(−)margin, odds ratio of having a negative surgical margin; RT, radiotherapy; SCC, squamous cell carcinoma.