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Meta-analysis of Treatment Outcomes for Sinonasal Undifferentiated Carcinoma

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Abstract

Objectives. This study reviews the published outcomes regarding sinonasal undifferentiated carcinoma (SNUC) since the initial description in 1986. This article attempts to (1) understand and better describe the benefit and survival advantages associated with using radiation, chemotherapy, and surgical treatment and (2) support the recommendations of a treatment regimen with current available data in the literature.

Data Sources. Published English-language literature.

Review Methods. A PubMed search for articles related to SNUC, along with the bibliographies of those articles to avoid missing articles. All articles were examined for an independent patient data meta-analysis. Thirty studies with 167 cases from 1986 to October 2009 were identified. Demographics, disease extent, treatment, follow-up, and survival were analyzed. Patient cohorts mirroring Kadish staging were created. Kaplan-Meier curves were constructed.

Results. Follow-up range was 1 to 195 months (mean 23.4 months, median 15 months). At last follow-up, 26.3% of patients were alive with no evidence of disease, 21.0% were alive with disease, and 52.7% were dead of disease. The use of surgery was found to be the best single modality, but chemotherapy and radiation were important as adjuncts in extensive and aggressive disease. The presence of neck metastases was a poor prognostic sign.

Conclusion. This study, containing the largest pool of SNUC patients, confirms a poor overall prognosis. The data suggest that the optimal treatment should include surgery, with radiation and/or chemotherapy as adjunct treatments. Neck disease in advanced local disease is a poor prognostic sign and merits aggressive treatment with multimodality therapy.

Keywords

sinonasal undifferentiated carcinoma, SNUC, meta-analysis, survival, metastases, cervical, treatment, review, skull base, surgery, chemotherapy, radiation, radiotherapy, open, endoscopic

Sinonasal undifferentiated carcinoma (SNUC) is characterized by poor differentiation and can be difficult to distinguish from other tumors of the sinonasal tract. The diagnosis is made by microscopic and immunohistochemical criteria. This disease is associated with a particularly aggressive course and often presents initially with extensive local invasion, commonly involving the orbit and skull base.[1-10] Sinonasal undifferentiated carcinoma has the ability to spread regionally and with distant metastasis. Patients often present late in the course of disease with nonspecific symptoms of epistaxis and obstruction.[2,3,5] Given the aggressive nature of the disease and poor specificity in symptom presentation, the overall mortality is high.

Since Frierson et al[1] initially described SNUC in 1986, various case studies and small case series have appeared in the literature examining outcomes in this disease. The rarity and aggressive nature of SNUC have limited the amount of information regarding the optimal treatment of this disease. Comparisons of outcomes of different studies have also been limited by the heterogeneous disease patterns, evolving staging systems, and varying treatment regimens used. However, examination of data across studies looking at treatment modalities may yield important trends that will help guide modern decision making in such a rare disease. This study attempts to systematically analyze and review the data available in the literature since the initial description in 1986 for these trends.

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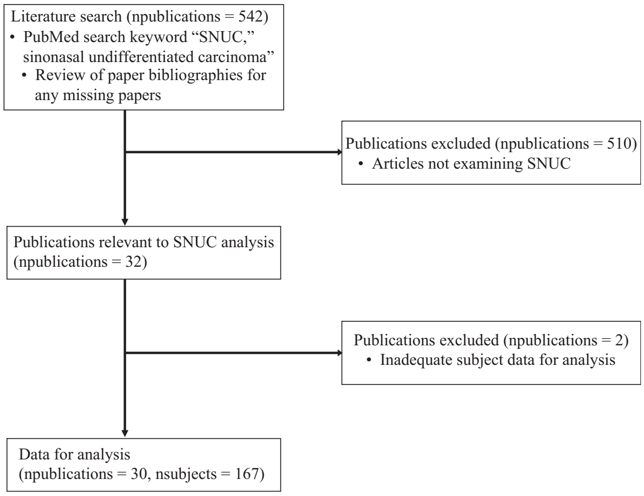

Figure 1. Flowchart for literature review. The search terms, methods, and pathway for selection of studies are illustrated. SNUC, sinonasal undifferentiated carcinoma.

Methods

A systematic review of the literature was performed by searching MEDLINE and PubMed with the keywords *SNUC* and *sinonasal undifferentiated carcinoma* (**Figure 1**). Of 542 studies, 32 were found to have patient information regarding SNUC. Two were excluded for insufficient patient information necessary for an independent patient analysis.[11-13] The remaining 30 studies were reviewed for a total of 167 cases of SNUC reported in the literature. The data collected included information regarding the extent of disease, treatments (surgery, radiation, chemotherapy, or multimodal therapy), outcomes, and time of follow-up. This data collection was done and reviewed for accuracy by the first and senior authors (DAR and AKD).

The database, created in Excel (Microsoft, Seattle, Washington), included specific patient information, including age, sex, sinus involvement, extension beyond the sinuses, orbital involvement, extension into the cranial cavity, brain involvement, lymph node involvement, regional metastasis, and distant metastasis. The compiled data of disease extent reported in the cases present in the literature are heterogeneous due to the evolution of staging SNUC over time. The data describe the extent of disease through surgical description, radiography, American Joint Committee on Cancer (AJCC) staging, and Kadish staging. Given the heterogeneous nature of the staging, it was necessary to categorize the patients based on the extent of disease described in a manner that mirrors Kadish staging. This was done to avoid excluding any patients. Stage A consisted of tumors confined to the sinuses. Stage B extended beyond the sinuses. Stage C involved the apex of the orbit, the skull base, or the brain. The outcomes were listed in terms of survival and disease status followed by time of last follow-up. The information in this database was used to create a series of Kaplan-Meier survival curves with the use of SAS (Statistical Analysis Software v9.1; SAS Institute, Cary, North Carolina).

Table 1. Summary of the Literature That Yielded Data Eligible for Meta-Analysis

Lead Author	Year	No. of Patients
Frierson[1]	1986	8
Greger[19]	1990	1
Deutsch[3]	1993	1
Kapadia[20]	1993	1
Ascaso[21]	1994	1
Gallo[22]	1995	13
Leung[23]	1995	1
Pitman[24]	1995	1
Righi[4]	1996	7
Houston[25]	1998	2
Kerrebijn[5]	1998	1
Gorelick[6]	2000	4
Miyamoto[26]	2000	14
Smith[7]	2000	6
Sakamoto[27]	2001	2
Sharara[15]	2001	3
Ghosh[28]	2001	1
Jeng[10]	2002	36
Musy[17]	2002	20
Kim[29]	2004	8
Kramer[30]	2004	4
Rischin[31]	2008	10
Michael[32]	2005	1
Solares[33]	2005	1
Kumar[16]	2006	1
Tamhankar[34]	2007	1
Schmidt[35]	2008	1
Tanzler[18]	2008	15
Wallace[36]	2008	1
Sohsman[37]	2010	1
	Total	167

Results

Between January 1986 and October 2009, 30 studies with 167 patients were identified (**Table 1**). Demographics, follow-up, and disease characteristics by stage are displayed in **Table 2**. The patients represented in the study ranged in age from 12 to 84 years of age with a mean age of 53 years (median age 54 years). Sex was available for 136 of the 167 patients; 72.5% were male.

One hundred of the 167 patients (59.8%) had disease that spread beyond the paranasal sinuses. Of those 100 patients, 53 had orbital involvement, 41 had skull base involvement, and 13 had brain involvement. When all patients were classified using Kadish staging, 52 of 167 (31.1%) of the patients had disease contained within the sinuses, 35 of 167 (21.0%) had disease that invaded beyond the sinuses, and 65 of 167 (38.9%) had disease involving the apex of the orbit, the skull base, or the brain.

Table 2. Patient Demographics

	Sex, No.[a]			Age Range, y			Neck Disease			Metastases at Presentation[b]				
	Male	Female	M:F Ratio	Min	Max	Mean Age	Yes, No.	No, No.	%	Yes, No.	No, No.	%	Mean Length of Follow Up, mo	Overall Survival, %
Group A	33	15	2.2:1	14	84	56	0	3	0.00	0	3	0.00	31	57.44
Group B	14	6	1.5:1	22	83	52	3	32	8.57	2	38	0.05	23	34.21
Group C	48	15	3.2:1	12	77	51	11	118	8.53	28	81	25.69	17	47.56
Total	95	36	2.64:1	12	84	53	14	153	8.38	30	122	19.74	23	47.31

Included are demographic and disease characteristics for the patients included in the study.
[a]Musy et. al. (20 patients), Deutsch et. al. (1 patient), and Tanzler et. al (15 patients) did not include sex demographics.
[b]One study, Tanzler et. al., did not include enough information to determine whether metastases were present at presentation or developed after initial diagnosis.

Table 3. Summary of Treatment and Extent of Disease

	Staging			
Treatment	A	B	C	Total, No. (%)
Chemotherapy alone	0	1	5	6 (3.6)
Radiation alone	5	5	11	21 (12.6)
Radiation and chemotherapy	7	11	18	36 (21.6)
Surgery alone	4	3	8	15 (9.0)
Surgery and chemotherapy	0	0	1	1 (0.6)
Surgery and radiation	22	6	18	46 (27.5)
Surgery, radiation, and chemotherapy	7	9	18	34 (20.4)
No treatment	2	3	3	8 (4.8)
Total	47	38	82	167

The patients in the study are listed according to extent of disease and type of treatment.

Follow-up ranged from 1 to 195 months (mean 23.4 months, median 15 months). **Table 3** shows the distribution of patients in the described cohorts and their treatment. Cyclophosphamide, doxorubicin, and vincristine (CAV) were the chemotherapeutics most often used. With regard to radiation therapy, fractionated radiation to the extent of 50 to 65 Gy was most commonly described in the literature. Variations of pre- and postoperative chemotherapy and radiotherapy strategies were used in different patients and across studies.

Kaplan-Meier survival curves (**Figures 2-4**) were created to compare outcomes by treatment modalities (surgery, radiation, chemotherapy, or combination). Seven patients reported in the literature had no evidence of disease with a final follow-up time of less than 12 months.[4,7,10,14-16] These patients were excluded from survival analysis due to insufficient follow-up. Overall survival at last follow-up: 26.3% of the patients were alive with no evidence of disease, 21.0% were alive with disease, and 52.7% were dead of disease. By comparing the survival plots for each treatment modality for each stage of disease, we were less likely to misinterpret the increased survival associated with having surgically resectable disease with that of the increased survival from having the disease surgically resected (**Figures 3-5**).

On further examination, stage C patients had a statistically significant difference in overall survival when comparing the use of different modalities; this is further analyzed in **Table 4**. Of the single-modality treatments, surgery appeared to confer higher survival, but the comparisons were limited as the number of patients in single-modality treatment cohorts was limited. There was evidence that adjuvant therapy improves survival. Analysis indicates that adding radiation and/or chemotherapy would confer a survival benefit, but statistically it would appear that there is no significant difference between adding either one or both treatment modalities in stage C patients, but it is possible that the relatively low numbers of patients may not allow for discerning this difference (type II error).

Review of patients who presented with neck disease (excluding those with distant metastases) showed that the presence of neck disease is a poor prognostic sign. **Table 5** lists the patients with neck disease as identified in the literature. The corresponding demographics, disease characteristics, follow-up, and survival have been included. Stages B and C both had patients with neck disease. When plotted to compare those in each stage with and without neck disease (**Figures 6** and **7**), there was a statistically significant difference in survival only in stage C. The presence of neck

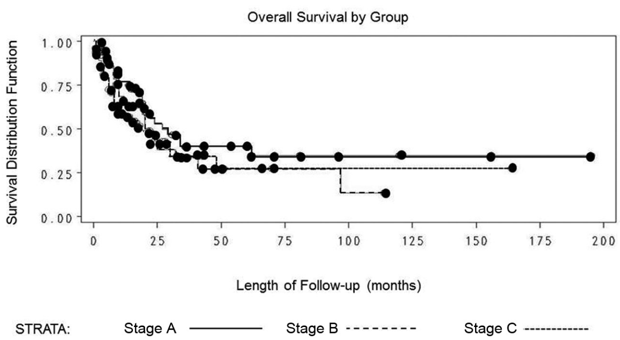

Figure 2. Overall survival by group. A Kaplan-Meier survival analysis is plotted here. Stage A consists of tumors confined to the sinuses, stage B consists of tumors extending beyond the sinuses, and stage C involves the apex of the orbit, the skull base, or the brain. (Mantel-Haenszel log rank; P = .1101)

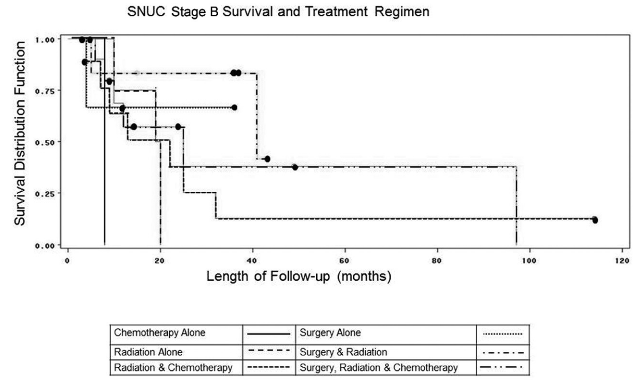

Figure 4. Stage B survival and treatment regimen. A Kaplan-Meier survival analysis for stage B based on treatment strategy is plotted here. SNUC, sinonasal undifferentiated carcinoma. (Mantel-Haenszel log rank; P = .1063)

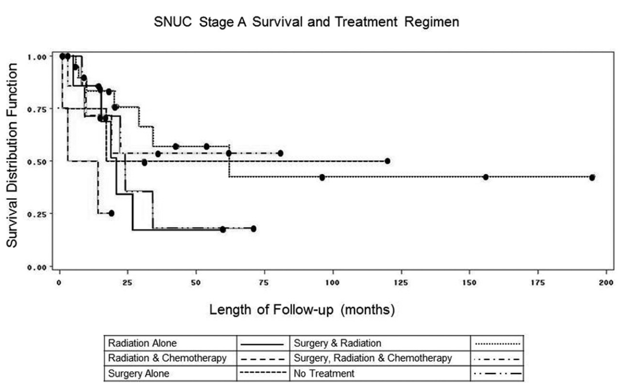

Figure 3. Stage A survival and treatment regimen. A Kaplan-Meier survival analysis for stage A based on treatment strategy is plotted here. SNUC, sinonasal undifferentiated carcinoma. (Mantel-Haenszel log rank; P = .0831)

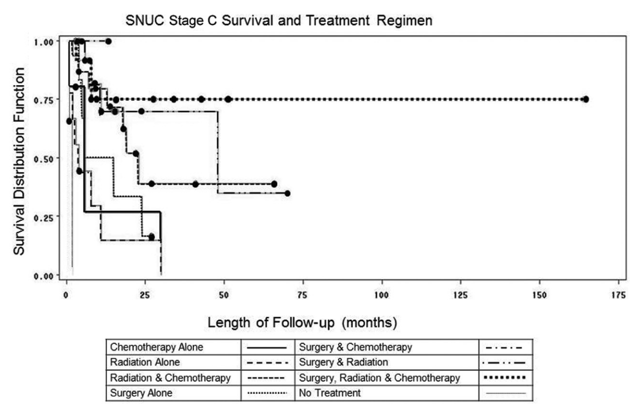

Figure 5. Stage C survival and treatment regimen. A Kaplan-Meier survival analysis for stage C based on treatment strategy is plotted here. SNUC, sinonasal undifferentiated carcinoma. (Mantel-Haenszel log rank; $P < .0001$)

disease is associated with lower survival (Wilcoxon rank-sum, stage B: P = .3798; stage C: P = .0146).

Results of the odds ratios from calculable case series are shown in **Table 6**. These odds ratios calculate the chance of survival throughout the observation period for those patients who had surgery vs those who did not have surgery. Results from studies with calculable data show increased survival for surgical patients, although the 95% confidence intervals are wide and show no significance. In our compiled database of all eligible studies, 58 of 96 surgery patients vs 23 of 71 were alive at the end of the observation period. Patients who had surgery, whether alone or in conjunction with chemotherapy and/or radiation, had a 210% increased chance of survival (odds ratio [OR] = 3.1; 95% confidence interval [CI], 1.63-5.89).

A similar forest plot examining survival of patients who had surgery with the addition of radiation and/or chemotherapy vs surgery alone is not possible because of insufficient patient data. Only one study, by Musy et al,[17] had sufficient data to calculate an odds ratio (OR = 1.6; 95% CI, 0.17-15.27) favoring surgery with the addition of radiation and/or chemotherapy over surgery alone. However, our individual patient data meta-analysis was able to demonstrate that patients who had surgery with the addition of radiation and/or chemotherapy had a 260% increased chance of survival compared with those who had surgery alone (OR = 2.6; 95% CI, 0.82-7.87).

Discussion

In our study, we found variability in the treatment regimens presented, but converging evidence suggests surgery with adjuvant therapy (radiation and/or chemotherapy) is the best option in the treatment of SNUC. The study of sinonasal undifferentiated carcinoma began with Frierson et al[1] in 1986, who reviewed the tumor registry at the University of Virginia from 1942 to 1985. Levine et al[2] and subsequently Deutsch et al,[3] then Musy et al,[17] carried on this study. These initial authors from the University of Virginia first demonstrated improved outcomes when treating with neoadjuvant chemotherapy and radiation (50-54 Gy) followed by surgical resection when possible. Improved survival in the

Table 4. Comparison of Stage C Survival by Treatment Modality

Comparison: Stage C	*P* Value[a]
All treatments	<.0001
Surgery, radiation, and chemotherapy (n = 18) vs surgery and radiation (n = 18)	.3093
Surgery, radiation, and chemotherapy (n = 18) vs radiation and chemotherapy (n = 18)	.5337
Surgery, radiation, and chemotherapy (n = 18) vs surgery and chemotherapy (n = 1)	.3093
Surgery, radiation, and chemotherapy (n = 18) vs surgery alone (n = 8)	.0015
Surgery, radiation, and chemotherapy (n = 18) vs radiation alone (n = 11)	.0001
Surgery, radiation, and chemotherapy (n = 18) vs chemotherapy alone (n = 5)	.0006

The *P* values demonstrating the statistical significance of survival analysis for stage C patients are listed for each treatment strategy.
[a]Mantel-Haenszel log rank.

Table 5. Neck Involvement

Lead Author	Year Published	Age	Sex	Stage	Treatment Modality	Status at End of Study	Length of Follow-Up, mo
Frierson[1]	1986	71	F	B	Surgery and radiation	DOD	41
Frierson[1]	1986	46	M	C	Radiation and chemotherapy	DOD	4
Leung[23]	1995	70	M	C	Radiation alone	DOD	3
Sakamoto[27]	2001	17	M	C	Chemotherapy alone	DOD	6
Ghosh[28]	2001	61	M	C	Surgery and radiation	AWD	24
Jeng[10]	2002	54	M	C	Radiation alone	DOD	5
Jeng[10]	2002	67	F	C	No treatment	DOD	2
Jeng[10]	2002	60	M	B	No treatment	DOD	14
Jeng[10]	2002	54	M	B	No treatment	DOD	3
Jeng[10]	2002	76	M	B	Radiation and chemotherapy	DOD	22
Jeng[10]	2002	34	M	B	Radiation alone	DOD	21
Tanzler[18]	2008	—	—	C	Surgery and radiation	DOD	11
Tanzler[18]	2008	—	—	C	Radiation and chemotherapy	DOD	18
Sohsman[37]	2010	58	F	C	Surgery, radiation, and chemotherapy	AWD	9

The patients with cervical lymphadenopathy in the absence of distant metastasis are listed in this table along with individual treatments and outcomes. Abbreviations: AWD, alive with disease; DOD, dead of disease; —, data not available.

studies using this aggressive treatment algorithm has led to other studies following similar treatment plans. The most common treatment regimens across the literature consisted of neoadjuvant chemotherapy using cyclophosphamide, doxorubicin, and vincristine (CAV) followed by craniofacial resection combined with either preoperative or postoperative radiotherapy (50-55 Gy).[3,5,14,17]

Musy et al[17] also provided important information regarding the effectiveness of the above described protocol of preoperative chemotherapy and radiation. The extent and reliability of the chemoradiation as a primary treatment was demonstrated by analysis of the surgical pathology specimen from the patients who received surgical resection after chemoradiation. Of the 10 patients who had craniofacial resection, 7 patients had a viable tumor in the surgical specimen. This helps support the need for more aggressive treatment than chemoradiation alone to eradicate the diseased tissue.

By far the largest case series of SNUC was performed by Jeng et al[10] in 2002 at the National Taiwan University. The study consisted of 36 patients, but no standardized treatment protocol was used in the treatment of these patients. In the study, 47% of the patients had treatment that included surgical resection of the tumor. These patients had improved prognosis compared with a nonsurgical group.

In our study, the patients treated with single modality suffered from increased recurrence and mortality when compared with patients with similarly staged disease. But when looking at single-modality treatment, there is a survival advantage for surgery over other treatments for SNUC. The certainty of this calculation is limited because there are too few patients in the population with single-modality treatment. The group treated surgically with at least 1 adjuvant therapy showed improved survival in the most extensive disease category (stage C). However, there was no statistically significant difference between surgery combined with chemoradiation, surgery combined only with radiation therapy, and surgery combined only with chemotherapy. However, the low numbers of patients may limit this conclusion.

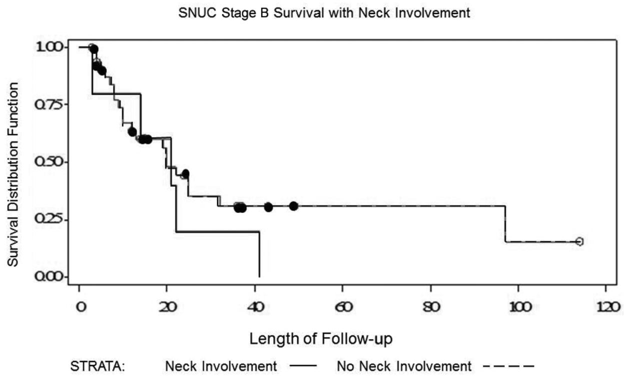

Figure 6. Stage B patients with neck involvement. A Kaplan-Meier survival analysis for stage B patients with and without neck disease is plotted here. SNUC, sinonasal undifferentiated carcinoma. (Mantel-Haenszel log rank; $P = .3798$)

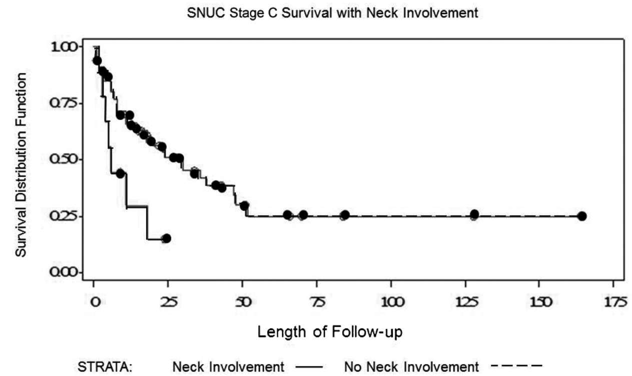

Figure 7. Stage C patients with neck involvement. A Kaplan-Meier survival analysis for stage C patients with and without neck disease is plotted here. SNUC, sinonasal undifferentiated carcinoma. (Mantel-Haenszel log rank; $P = .0146$)

Table 6. Odds Ratios for Available Case Series with 95% Confidence Intervals

Study	Surgery Patients Alive at End of Observation	Nonsurgery Patients Alive at End of Observation	OR (95% CI)
Frierson[1]	1/2	3/6	1.0 (0.04-24.55)
Righi[4]	2/4	1/3	2.0 (0.09-44.35)
Miyamoto[26]	3/9	2/5	0.25 (0.02-3.99)
Jeng[10]	10/17	5/19	1.7 (0.37-7.85)
Musy[17]	5/11	2/9	2.92 (0.40-20.78)
Tanzler[18]	7/11	1/4	5.25 (0.40-68.69)

Only a select number of studies had adequate numbers to calculate individual confidence intervals. Abbreviations: CI, confidence interval; OR, odds ratio.

Tanzler et al[18] reported results regarding the controversial question of whether to radiate an uninvolved neck. Given the morbidity of neck radiation, many argue against the practice. However, this University of Florida study showed that none of the 7 patients who received prophylactic neck irradiation developed regional disease compared with the 4 of 6 patients (66%) with clinically negative necks who declined prophylactic neck irradiation and developed regional disease. Overall, survival was higher in this series, particularly in the groups treated with surgery and radiation.

Of the patients included in this meta-analysis, only 14 of the 167 patients (8.4%) had clinically positive cervical lymphadenopathy without evidence of regional or distant metastases. Based on analysis of the data, cervical lymphadenopathy is a particular ominous sign. Patients with disease involving cervical lymph nodes had decreased survival when compared with other patients with similar levels of local disease.

There are potential confounders in a meta-analysis study. When assembling patients for an independent patient data meta-analysis, as in the current study, one must be careful to avoid biases and recognize that pooling data from different studies does not fully recapitulate a uniform treatment protocol. Patient and treatment variability can affect outcome, which may not be reported satisfactorily in the studies compiled. However, by taking independent patient information, keeping as much data resolution as possible, and assembling patients into reasonably homogeneous cohorts, we can create groups as uniform as the published studies will allow.

It was necessary to stage all patients included in this study under a single staging system to bring patients into specific strata based on the extent of disease. The Kadish staging system was used as opposed to the modern TNM staging. Not all patients included in this study were initially staged (in the cited articles) by the Kadish staging system. However, they were included if adequate descriptive information regarding anatomic involvement was available for reassignment to stages in the Kadish system. This action is reasonable; it allows for simple criteria to stratify the patients according to extent of disease. However, it is limited in its ability to predict prognosis.

Another limitation is the necessary combining of those who receive different orders of therapy (eg, pre- vs postoperative adjuvant therapies); we cannot make a reliable comment on whether the order would make a difference in survival as the numbers are too small to try and factor this out for comparison. Furthermore, patients with increased levels of comorbidities—and thus poor surgical candidates—may receive a different level of treatment than that of similarly staged counterparts. This can present as a confounder to the study, as these comorbidities may contribute to worse outcomes and bias against the use of nonsurgical treatment. Nonetheless, there is evidence that those treated with surgery fare better. Surgery as a part of the treatment regimen when possible is a reasonable recommendation based on the data.

Conclusion

This study concludes that data present in the literature support the use of surgery with the addition of radiation and/or chemotherapy. Radiation and/or chemotherapy should be considered in addition to surgical resection whenever patient comorbidities will allow. In addition, advanced local or cervical disease warrants aggressive therapy and appears to have the most benefit from adjuvant therapy.

The current data are inadequate to compare order of therapy. The superiority of either protocol (pre- or postoperative adjuvant therapy) has not been demonstrated, and both are acceptable until further studies are performed. Further information regarding optimal treatment for SNUC would best be done through a prospective, randomized trial. However, given the low incidence of SNUC combined with the high morbidity and mortality associated with the disease, it is unlikely that a properly powered randomized trial could be performed in the future.

Author Contributions

David A. Reiersen, conception, design, acquisition of data, analysis, interpretation, draft and revision of article, final approval; **M. Elaine Pahilan**, design, analysis, interpretation, draft and revision of article, final approval; **Anand K. Devaiah**, conception, design, acquisition of data, analysis, interpretation, draft and revision of article, final approval.

Disclosures

Competing interests: Anand K. Devaiah is a consultant and has a development agreement with OmniGuide, Inc and does medical expert legal case review.

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