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Review

Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: The importance of differentiation grade in determining treatment strategy

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ABSTRACT

The aim of this meta-analysis was to provide treatment guidelines for sinonasal neuroendocrine carcinoma (SNC) by combining all available data in the literature.

A literature search for all studies concerning SNC was performed against the MEDLINE and EMBASE databases. Available clinical data was normalized, pooled, and statistically analyzed.

A total of 701 cases of SNC were available for analysis, comprising 127 well or moderately differentiated sinonasal neuroendocrine carcinomas (SNEC), 459 sinonasal undifferentiated carcinoma (SNUC) and 115 sinonasal small cell carcinoma (SmCC). Tumor type was the most important predictor of survival, with a 5-year disease-specific survival (DSS) of 70.2% for SNEC, 35.9% for SNUC and 46.1% for SmCC. Tumor stage on presentation was of limited value in predicting survival or response to treatment. Overall, the application of surgery yielded significantly better results (5-year DSS 52.2% versus 30.1%, $p < 0.001$). In SNUC, radiotherapy was a beneficial supplement to surgery (5-year DSS 54.7% versus 15.7%, $p = 0.027$), while radiotherapy as monotherapy performed poorly (5-year DSS 17.9%). Chemotherapy did not appear to contribute to survival.

Based on these findings, we can conclude that the most important predictors of survival in SNC are differentiation grade and the associated choice of treatment modality. In contrast to other head and neck cancers, tumor staging appears of limited value in predicting survival or deciding on a treatment strategy. Surgery should be the cornerstone of treatment, supplemented by radiotherapy in poorly differentiated subtypes (SNUC, SmCC). Chemotherapy does not appear to contribute to survival.

Introduction

Sinonasal tumors with neuroendocrine differentiation are a rare group of neoplasms that account for only 5% of all sinonasal malignancies [1]. A broad distinction is made between tumors of neuroectodermal origin - esthesioneuroblastoma - and those of epithelial origin - sinonasal neuroendocrine carcinoma (SNC). The latter can be subdivided based on differentiation grade into well, moderately and poorly differentiated SNC. Poorly differentiated SNC are further subdivided into a small and large cell variants.

In the literature an ambiguous nomenclature is maintained. Confusingly, in contrast to well and moderately differentiated SNC, large cell poorly differentiated SNC are denoted by sinonasal undifferentiated carcinoma (SNUC) and small cell poorly differentiated SNC by sinonasal small cell carcinoma (SmCC), discounting their neuroendocrine nature. In order to prevent further ambiguity, well and moderately differentiated SNC are referred to by their common abbreviation, SNEC, in this article.

Previous studies have shown tumor behavior to differ markedly between the various entities of sinonasal tumors with neuroendocrine differentiation [2]. For esthesioneuroblastoma a well-defined treatment strategy is available that, in part due to their

Abbreviations: SNC, sinonasal neuroendocrine carcinoma; SNEC, well or moderately differentiated sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SmCC, sinonasal small cell carcinoma; DSS, Disease-Specific Survival.

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more benign nature, yields reasonable results [3]. However, for SNC no clear guidelines are available and treatment outcome remains both variable and poor. Individual studies have shown large differences in response to treatment and prognosis between SNEC, SNUC, and SmCC and, more recently, have advocated the use of multimodality therapy in order to improve survival [4,5]. While valuable, these studies suffer from small sample size due to the rare nature of these tumors. This makes it hard to estimate the contribution of individual treatment modalities to treatment outcome, especially considering the possibility that treatment response might differ between tumor subtypes.

The aim of this meta-analysis was to provide treatment guidelines for SNC by combining all available data concerning factors influencing treatment response and survival in the literature.

Material and methods

A literature search for all clinical research concerning SNC was performed against the MEDLINE and EMBASE databases. The following combination of search terms was used: 'neuroendocrine carcinoma/tumor', 'undifferentiated carcinoma/tumor', 'small cell carcinoma/tumor', 'oat cell carcinoma/tumor', or 'carcinoid (tumor)' in combination with either 'nasal', 'sinonasal', 'paranasal (sinuses)', 'sinus(es)', 'ethmoid (sinus)', 'frontal (sinus)', 'maxillary (sinus)' or ' sphenoid (sinus)'. Full text copies of all relevant articles in English were retrieved and checked for references. When available, English abstracts of non-English articles containing relevant data were included. Articles and abstracts not containing (original) clinical data or compound data were discarded. The following variables were extracted from the remainder: age at diagnosis, gender, tumor type, tumor stage, ectopic hormone production, treatment and survival. If not reported, the tumor stage was determined using the TNM staging system. Duplicate cases were removed. Cases were divided in two cohorts in order to allow for analysis of trends over time: those reported before 2006 and those reported thereafter, effectively dividing the number of cases per cohort in two equal proportions. Statistical analysis was performed using IBM SPSS Statistics 22 for Microsoft Windows (Armonk, NY). Age was compared using the median test. Categorical data were analyzed using the exact chi-square test. Survival data were calculated using the Kaplan-Meier estimator. Uni- and multivariate analysis was performed using the Cox proportional hazards model (enter method). Alpha was set at 0.05. Reported confidence intervals are for 95% probability.

Results

After discarding articles not including original clinical data or compound data, a total of 171 articles remained available for analysis [4–174]. Full text copies were available for 167 of these. Abstracts containing clinical data were included for five articles not in English [39,73,92,159,162] and one in English [168], yielding a total of 701 cases.

Patient characteristics

Patient characteristics are presented in Table 1. Most cases were classified as SNUC (459, 65.5%), followed by SNEC (127, 18.1%) and SmCC (115, 16.4%). The median age on presentation for all SNC was 53 years (range 12–89). Overall there was a male gender predilection (64.6%). The tumor stage on presentation was stage IV in 75.0% of cases. However, this distribution significantly differed amongst tumor types, with SNEC presenting with stage IV in 57.1% of cases, SmCC in 70.4% and SNUC in 80.6% ($p < 0.001$). It was not possible to reliably infer the original tumor location from the available data as most patients presented with advanced disease.

Treatment consisted of multimodality therapy in the majority of cases treated with curative intent (73.7%). Overall, radiotherapy was the most frequently employed modality in these patients with 84.3%, followed by 61.4% for chemotherapy and 60.2% for surgery. Combination therapy most often consisted of trimodality therapy (38.7%) or a combination of radiotherapy and chemotherapy (36.6%). The combination of surgery and radiotherapy was less often applied (22.7%). Only a small minority of patients was treated with a combination of surgery and chemotherapy (3.1%). There were significant differences in choice of treatment between subtypes. Compared to SNUC, SNEC and SmCC were more often treated with surgery as monotherapy (4.3% versus 24.4% and 17.4% respectively, $p < 0.001$). SNUC were more often treated with radiotherapy as monotherapy compared to SNEC and SmCC (12.4% versus 4.4%

Table 1
Patient characteristics of sinonasal neuroendocrine carcinoma. Bold numbers represent significant P-values ($P < 0.05$).

Variable	All (n = 701)	SNEC (n = 127)	SNUC (n = 459)	SmCC (n = 115)	P-value
Age (median, range)	53 (12–89)	50 (13–84)	53 (12–88)	56 (16–89)	**0.023**
Gender (male, %)	378 (64.6)	70 (56.9)	239 (68.7)	69 (60.5)	**0.038**
Tumor stage (%)					
Stage I	25 (5.0)	8 (10.4)	8 (2.5)	9 (9.2)	**0.002**
Stage II	38 (7.6)	15 (19.5)	10 (3.1)	13 (13.3)	**<0.001**
Stage III	61 (12.2)	10 (13.0)	45 (13.8)	6 (6.1)	0.125
Stage IV	375 (75.0)	44 (57.1)	262 (80.6)	69 (70.4)	**<0.001**
Stage IVA	116 (23.3)	16 (20.8)	67 (20.7)	33 (33.7)	**0.025**
Stage IVB	147 (29.5)	22 (28.6)	104 (32.2)	21 (21.4)	0.116
Stage IVC	22 (4.4)	2 (2.6)	17 (5.2)	3 (3.1)	0.480
Treatment (%)					
Surgery	56 (10.3)	22 (24.4)	15 (4.3)	19 (17.4)	**<0.001**
Radiotherapy	52 (9.5)	4 (4.4)	43 (12.4)	5 (4.6)	**0.011**
Chemotherapy	12 (2.2)	0 (0.0)	7 (2.0)	5 (4.6)	0.080
Surgery & Radiotherapy	88 (16.1)	22 (24.4)	54 (15.6)	12 (11.0)	**0.033**
Surgery & Chemotherapy	12 (2.2)	3 (3.3)	2 (0.6)	7 (6.4)	**0.006**
Surgery & Radiotherapy & Chemotherapy	150 (27.5)	16 (17.8)	110 (31.7)	24 (22.0)	**0.015**
Radiotherapy & Chemotherapy	138 (25.3)	21 (23.3)	85 (24.5)	32 (29.4)	0.546
Palliative care	38 (7.0)	2 (2.2)	31 (8.9)	5 (4.6)	**0.044**
Median disease specific survival	36 (27–45)	174 (69–279)	28 (23–33)	22 (6–38)	**<0.001**
Median overall survival	32 (25–39)	120 (55–185)	25 (21–29)	22 (14–30)	**<0.001**

SNEC, well or moderately differentiated sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SmCC, sinonasal small cell carcinoma.