



## Review

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



Tom P. van der Laan MD<sup>a,b</sup>, René Iepsma BSc<sup>a</sup>, Max J.H. Witjes MD, PhD<sup>c</sup>,  
Bernard F.A.M. van der Laan MD, PhD<sup>a,b</sup>, Boudewijn E.C. Plaat MD, PhD<sup>a</sup>, Gyorgy B. Halmos MD, PhD<sup>a,\*</sup>

<sup>a</sup> University of Groningen, University Medical Center Groningen, Dept. of Otorhinolaryngology/Head and Neck Surgery, The Netherlands

<sup>b</sup> University of Groningen, Graduate School of Medical Sciences (Damage and Repair in Cancer Development and Cancer Treatment), The Netherlands

<sup>c</sup> University of Groningen, University Medical Center Groningen, Department of Oral and Maxillofacial Surgery, The Netherlands

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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.

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## 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.

\* Corresponding author at: Department of Otorhinolaryngology/Head and Neck Surgery, University of Groningen, University Medical Center Groningen, P.O. Box 30.001, 9700RB Groningen, The Netherlands.

E-mail address: [g.b.halmos@umcg.nl](mailto:g.b.halmos@umcg.nl) (G.B. Halmos).

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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)	<b>0.023</b>
Gender (male, %)	378 (64.6)	70 (56.9)	239 (68.7)	69 (60.5)	<b>0.038</b>
Tumor stage (%)					
Stage I	25 (5.0)	8 (10.4)	8 (2.5)	9 (9.2)	<b>0.002</b>
Stage II	38 (7.6)	15 (19.5)	10 (3.1)	13 (13.3)	<b>&lt;0.001</b>
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)	<b>&lt;0.001</b>
Stage IVA	116 (23.3)	16 (20.8)	67 (20.7)	33 (33.7)	<b>0.025</b>
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)	<b>&lt;0.001</b>
Radiotherapy	52 (9.5)	4 (4.4)	43 (12.4)	5 (4.6)	<b>0.011</b>
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)	<b>0.033</b>
Surgery & Chemotherapy	12 (2.2)	3 (3.3)	2 (0.6)	7 (6.4)	<b>0.006</b>
Surgery & Radiotherapy & Chemotherapy	150 (27.5)	16 (17.8)	110 (31.7)	24 (22.0)	<b>0.015</b>
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)	<b>0.044</b>
Median disease specific survival	36 (27–45)	174 (69–279)	28 (23–33)	22 (6–38)	<b>&lt;0.001</b>
Median overall survival	32 (25–39)	120 (55–185)	25 (21–29)	22 (14–30)	<b>&lt;0.001</b>

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

and 4.6% respectively,  $p = 0.011$ ), while SNEC were more frequently treated with surgery combined with radiotherapy (24.4% versus 15.6% for SNUC and 11.0% for SmCC,  $p = 0.033$ ). SNUC was rarely managed with a combination of surgery and chemotherapy (0.6% versus 3.3% for SNEC and 6.4% for SmCC,  $p = 0.006$ ), but more often treated with a trimodality approach compared to the other groups (31.7% versus 17.8% for SNEC and 22.0% for SmCC,  $p = 0.015$ ).

#### Ectopic hormone production

Ectopic hormone production was described in ten cases (1.4%) [9,15,29,57,75,91,110,172]. These cases concerned patients with SNEC or SmCC with elevated levels of ACTH, beta-MSH, calcitonin, serotonin or ADH.

#### Survival

The median disease-specific survival (DSS) for SNEC was 36 months (CI 27–45) and the overall survival 32 months (CI, 25–39). Fig. 1A displays the influence of tumor type on DSS. SNEC performed significantly better with a 5-year DSS of 70.2% compared to 35.9% for SNUC and 46.1% for SmCC ( $p < 0.001$ ). There was no significant difference between the 5-year DSS of SNUC and SmCC ( $p = 0.792$ ). Comparable results were produced by the univariate analysis presented in Table 2. Overall, tumor stage did not significantly affect survival as shown in Fig. 1B. Similar results were produced when correcting for tumor type. The univariate analysis yielded varying results, with no significant difference in odds ratio (OR) between stage IVA and stage I disease (CI OR, 0.0871–5.607,  $p = 0.095$ ).

Fig. 2 displays an exploratory analysis of the influence of different treatment modalities on DSS. Overall, only surgery had a significant effect on 5-year DSS with 52.2% for patients treated with surgery versus 30.1% for those without ( $p < 0.001$ ).

While there was a trend favoring surgery in SNEC, no significant difference could be observed ( $p = 0.077$ ). Radiotherapy did not yield better results in these patients ( $p = 0.199$ ), while the application of chemotherapy was associated with a significantly unfavorable outcome (5-year DSS of 55.7% versus 82.2%,  $p = 0.029$ ).

Both surgery and radiotherapy were associated with significantly better outcome in patients with SNUC (5-year DSS of 42.2% versus 26.9%,  $p < 0.001$ , and 38.0% versus 10.6%,  $p = 0.008$ , respectively). The application of chemotherapy did not improve survival in these patient (5-year DSS of 36.6% versus 33.3%,  $p = 0.782$ ).

**Table 2**

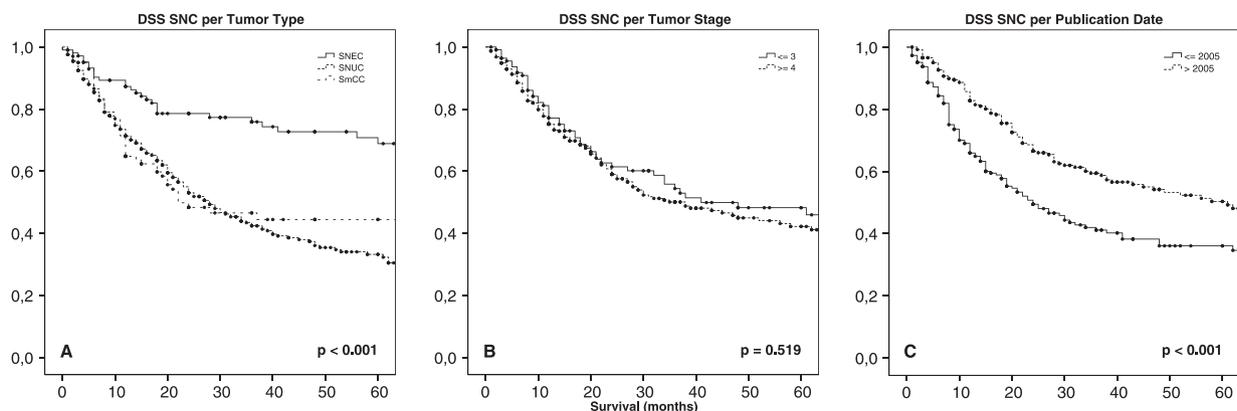
Univariate analysis of factors influencing the disease-specific survival of sinonasal neuroendocrine carcinoma. Bold numbers represent significant P-values ( $P < 0.05$ ).

Factor	OR (95% CI)	P-value
Age	1.009 (1.001–1.017)	<b>0.019</b>
Gender (male as reference)	0.874 (0.660–1.159)	0.351
Tumor type		
SNEC	1 (reference)	
SNUC	2.601 (1.783–3.794)	<b>&lt;0.001</b>
SmCC	2.410 (1.539–3.774)	<b>&lt;0.001</b>
Tumor stage		
Stage I	1 (reference)	
Stage II	2.152 (0.781–5.930)	0.139
Stage III	3.672 (1.425–9.460)	<b>0.007</b>
Stage IV	3.663 (1.462–9.180)	<b>0.006</b>
Stage IVA	2.210 (0.871–5.607)	0.095
Stage IVB	3.050 (1.224–7.597)	<b>0.017</b>
Stage IVC	7.612 (2.695–21.499)	<b>&lt;0.001</b>
Treatment (decoupled, no as reference)		
Surgery	0.521 (0.400–0.677)	<b>0.000</b>
Radiotherapy	0.898 (0.631–1.279)	0.898
Chemotherapy	1.243 (0.944–1.636)	0.121
Treatment		
Surgery	1 (reference)	
Radiotherapy	2.261 (1.329–3.847)	<b>0.003</b>
Chemotherapy	6.182 (2.803–13.633)	<b>&lt;0.001</b>
Surgery & Radiotherapy	0.779 (0.444–1.366)	0.383
Surgery & Chemotherapy	1.810 (0.801–4.090)	0.154
Surgery & Radiotherapy & Chemotherapy	1.052 (0.638–1.735)	0.905
Radiotherapy & Chemotherapy	1.712 (1.050–2.791)	<b>0.031</b>
Palliative care	15.769 (7.408–33.567)	<b>&lt;0.001</b>

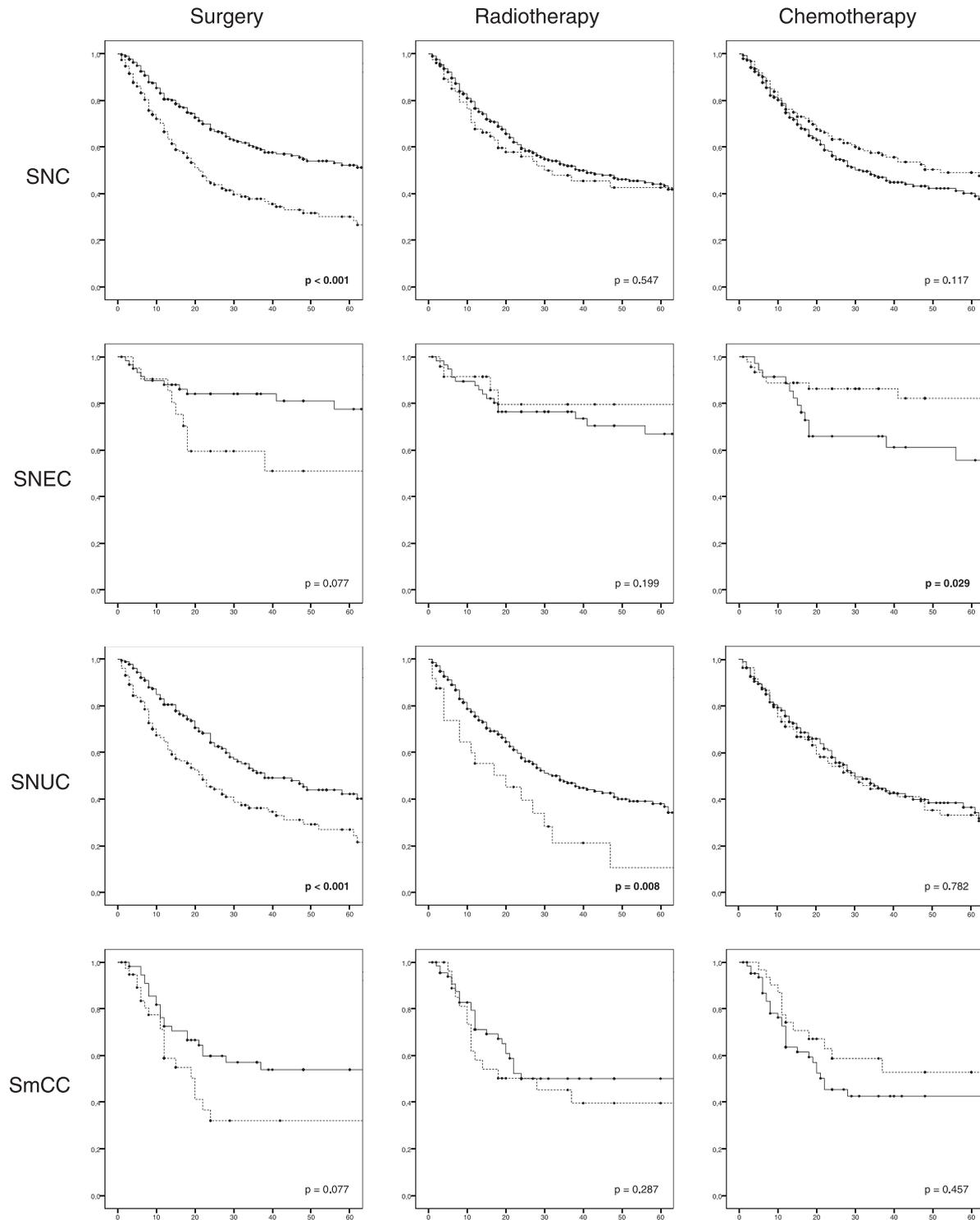
OR, odds ratio; CI, confidence interval; SNEC, well or moderately differentiated sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SmCC, sinonasal small cell carcinoma.

While not significant, surgery appeared to have a beneficial effect on treatment outcome in patients with SmCC (5-year DSS of 53.9% versus 32.0%,  $p = 0.077$ ), while no difference in outcome could be observed for radiotherapy and chemotherapy (5-year DSS of 50.1% for patients treated with radiotherapy versus 39.6% for those without,  $p = 0.287$  and 42.6% for patients treated with chemotherapy versus 52.9% for those without,  $p = 0.287$  respectively).

A multivariate analysis of the influence of treatment (combinations) correcting for age on diagnosis and tumor stage on presentation is presented in Table 3. Patients with SNEC treated without



**Fig. 1.** Disease-specific survival (DSS) of sinonasal neuroendocrine carcinoma (SNC) per tumor type, stage and publication date. SNEC, well or moderately differentiated sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SmCC, sinonasal small cell carcinoma.



**Fig. 2.** Disease-specific survival of sinonasal neuroendocrine carcinoma (SNC) per tumor type and treatment modality. The straight line represents the cohort in which the treatment modality was applied. Survival in months. SNEC, well or moderately differentiated sinonasal neuroendocrine carcinoma; SNUC, sinonasal undifferentiated carcinoma; SmCC, sinonasal small cell carcinoma.

surgery had a significantly higher change of dying of disease (OR 11.464, CI 1.125–116.796,  $p = 0.039$ ). No advantage from multimodality therapy could be inferred from this analysis. For SNUC, patients treated with a combination of surgery and radiotherapy, with or without chemotherapy, had better outcome than those treated with surgery alone (OR 0.337, CI 0.0125–0.908,  $p = 0.032$  and OR 0.368, CI 0.147–0.921,  $p = 0.033$  respectively). Chemotherapy as monotherapy yielded a significantly higher OR in patients

with SmCC (6.964, CI 1.104–43.930), while none of the other treatment (combinations) significantly differed from surgery as monotherapy.

5-Year DSS estimates per tumor type and treatment (combination) are presented in Table 4. Overall, the highest 5-year DSS was observed for the combination of surgery and radiotherapy (64.0%). For SNEC surgery as monotherapy produced the most favorable results (5-year DSS 83.3%). SNUC and SmCC responded best to a

**Table 3**

Multivariate analysis of factors<sup>a</sup> influencing the disease-specific survival of sinonasal neuroendocrine carcinoma treated with curative intent per tumor type. Bold numbers represent significant P-values (P < 0.05).

Factor	OR (95% CI)	P-value
<i>Well or moderately differentiated sinonasal neuroendocrine carcinoma</i>		
Surgery	1 (reference)	
Radiotherapy	–	–
Chemotherapy	–	–
Surgery & Radiotherapy	4.604 (0.514–41.212)	0.172
Surgery & Chemotherapy	6.950 (0.355–135.961)	0.201
Surgery & Radiotherapy & Chemotherapy	4.804 (0.370–62.430)	0.230
Radiotherapy & Chemotherapy	11.464 (1.125–116.796)	<b>0.039</b>
<i>Sinonasal undifferentiated carcinoma</i>		
Surgery	1 (reference)	
Radiotherapy	0.643 (0.254–1.632)	0.353
Chemotherapy	1.644 (0.443–6.105)	0.458
Surgery & Radiotherapy	0.337 (0.125–0.908)	<b>0.032</b>
Surgery & Chemotherapy	3.164 (0.359–27.890)	0.300
Surgery & Radiotherapy & Chemotherapy	0.368 (0.147–0.921)	<b>0.033</b>
Radiotherapy & Chemotherapy	0.471 (0.185–1.200)	0.115
<i>Sinonasal small cell carcinoma</i>		
Surgery	1 (reference)	
Radiotherapy	3.669 (0.677–19.900)	0.132
Chemotherapy	6.964 (1.104–43.930)	<b>0.039</b>
Surgery & Radiotherapy	0.529 (0.123–2.278)	0.393
Surgery & Chemotherapy	1.057 (0.239–4.669)	0.942
Surgery & Radiotherapy & Chemotherapy	0.811 (0.234–2.806)	0.741
Radiotherapy & Chemotherapy	1.078 (0.370–3.146)	0.890

OR, odds ratio; CI, confidence interval. Reported odds ratios for patient dying of disease.

<sup>a</sup> Not shown but included in the models are the factors age and tumor stage. Both of which did not reach significance in any of the models.

combination of surgery and radiotherapy (5-year DSS of 54.7% and 71.3% respectively).

#### Trends over time

As shown in Fig. 1C, cases reported after 2006 show improved outcome compared to those reported before this date (5-year DSS of 50.4% versus 36.1%,  $p < 0.001$ ). This trend was present for all tumor types, although only SNUC remained significant after sub-analysis ( $p = 0.001$ ). Patients with SNUC, reported before 2006, were more often treated with radiotherapy as monotherapy (21.1% versus 4.3%), while those reported after 2006 were more often treated with a combination of surgery and radiotherapy with or without chemotherapy (65.9% versus 40.6%).

## Discussion

### Synopsis

This study offers the most comprehensive overview of knowledge concerning SNC available today by pooling all available cases

published in the literature. It is clear from our data, that prognosis is primarily determined by histological subtype and thus differentiation grade, rather than by TNM classification. Overall, SNEC have a reasonable prognosis, with a 5-year DSS of about 70%, while SNUC and SmCC perform poorly with a 5-year DSS of approximately 40%. Surgery should be the cornerstone of treatment as it was associated with improved outcome, regardless of its combination with other treatment modalities or tumor subtype. Postoperative radiotherapy should be applied in patients with SNUC or SmCC.

### Classification

As noted in the introduction, the nomenclature of SNC applied in the literature is both confusing and ambiguous. This is a common problem concerning neuroendocrine carcinoma of the head and neck, as evidenced by the diverse terminology used for their more common laryngeal counterparts [175]. In 2002, Mills already recognized the similarities between (the subtypes of) neuroendocrine carcinoma of the head and neck of different locations and suggested that SNUC was probably best recognized as the equivalent of the large cell neuroendocrine carcinoma of the larynx [176]. While similar tumors in different locations may behave differently and require a different treatment approach, certain similarities are lost in translation. This is crucial problem, as it is clear from our data that the histological diagnosis is the single most important factor influencing response to treatment and survival.

In order to solve this problem in laryngeal neuroendocrine carcinoma (LNC), Lewis et al. proposed to adopt the classification system of pulmonary neuroendocrine carcinoma, in which neuroendocrine carcinoma are classified based on differentiation grade [175]. We suggest extending this classification to SNC as well, additionally labeling poorly differentiated SNC A for small and B for large cell features (Table 5). Unifying the classification system for neuroendocrine carcinoma of the head and neck would yield a more intuitive way of thinking about these neoplasms and prevent relevant data from not being taken into consideration due to semantic deficiencies.

### Tumor stage on presentation

Sinonasal malignancies often present at an advanced stage due to the lack of disconcerting symptoms. This reduces the value of the TNM classification system (or any other classification system for that matter) in predicting prognosis and aiding in treatment selection. This holds true for SNC as well, with 75.0% of patients presenting with stage IV disease. In patients presenting with early stage disease the TNM classification remains of poor value as univariate analysis revealed that patients with stage III disease had a higher OR for dying of disease compared to patients with stage IVA disease (3.672 versus 2.210), while no significant difference in OR could be observed between stage I and stage IVA disease. A similar

**Table 4**

5-year disease-specific survival estimates of sinonasal neuroendocrine carcinoma per tumor type and treatment (combination) of patients treated with curative intent.

Treatment	All	SNEC	SNUC	SmCC
All	43.9 (2.8)	70.2 (5.9)	35.9 (3.5)	46.1 (5.9)
Surgery	52.7 (8.3)	83.3 (9.0)	15.7 (13.1)	52.1 (13.9)
Radiotherapy	22.7 (7.3)	100.0 (–)	17.9 (7.1)	0.0 (0.0)
Chemotherapy	0.0 (0.0)	–	0.0 (0.0)	0.0 (0.0)
Surgery & Radiotherapy	64.0 (6.4)	77.9 (10.2)	54.7 (9.2)	71.3 (14.1)
Surgery & Chemotherapy	30.0 (14.0)	66.7 (27.2)	0.0 (0.0)	28.6 (17.1)
Surgery & Radiotherapy & Chemotherapy	47.0 (5.6)	73.8 (13.8)	40.2 (6.8)	57.6 (11.6)
Radiotherapy & Chemotherapy	36.3 (5.4)	39.2 (13.5)	40.2 (6.8)	39.9 (10.9)

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

**Table 5**  
Classification schemes for sinonasal neuroendocrine carcinoma.

Legacy terminology	Common abbreviation	Differentiation grade	Cell size	Proposed terminology
Carcinoid	SNEC	Well	–	Grade I
Atypical carcinoid	SNEC	Moderate	–	Grade II
Small cell (neuroendocrine) carcinoma	SmCC	Poor	Small	Grade IIIA
Sinonasal undifferentiated carcinoma	SNUC	Poor	Moderate to large	Grade IIIB

pattern is seen in LNC and can probably be attributed to a high propensity for recurrence and early distant metastasis [177]. Due to the nature of the data and the confusing outcome of the resulting analyses, the relationship between tumor stage on presentation and survival remains uncertain. However, as patients with limited disease potentially have a similar prognosis to those with advanced disease, we think that treatment strategy should not be influenced by this factor, except in specific cases in which isolated lesions can be excised and surgical margins evaluated properly.

#### *Ectopic hormone production*

The incidence of ectopic hormone production is likely higher than the reported 1.4% due to under-diagnosis and under-reporting. However, only a small number of patients presented with clinical features in the form of the associated paraneoplastic syndrome and it remains unclear whether routine tests should be incorporated in the work-up of these patients.

#### *Treatment and survival*

Due to the nature of the study care should be taken in interpreting the resulting analyses. Incomplete data results in some seemingly contradictory figures (e.a. an overall survival estimate that is lower than the disease-specific survival). However, by including these data points we utilize the available information to its fullest and are able to provide estimates that are as close to reality as possible.

While decoupling the combination of treatment modalities introduces an obvious bias, Fig. 2 allows for an exploratory analysis of the contribution of different treatment modalities to treatment outcome. Combined with the results from the uni- and multivariate analysis, and the 5-year DSS per tumor subtype and treatment (combination) presented in Table 4 a general pattern can be observed.

It appears clear that, irrespective of the histological diagnosis, surgery has a beneficial effect on survival and should be the cornerstone of any treatment strategy. This is supported by both the univariate and multivariate analyses in which treatment (combinations) incorporating surgery produced the best results with the exception of four patients with a SNEC who were successfully treated with radiotherapy as monotherapy. It is unfortunate that most authors do not make a distinction between well and moderately differentiated SNEC as the former could probably be treated by surgery alone while the latter may require a more aggressive approach incorporating postoperative radiotherapy.

Radiotherapy appeared especially beneficial in patients with SNUC, but only if combined with surgery. In fact, the combination of surgery and radiotherapy with or without chemotherapy yielded a significantly lower OR for patients dying of disease in the multivariate analysis (0.337, CI 0.125–0.908 and 0.368, CI 0.147–0.921 respectively), making it the de facto treatment strategy for this group. Radiotherapy as monotherapy performed poorly with the exception of the four patients mentioned above (5-year DSS of 17.9% for SNUC and 0.0% for SmCC) and should not be performed in curative setting.

No benefit from the application of chemotherapy could be deduced from our results. Chemotherapy as monotherapy had the worst 5-year DSS, with no patients surviving regardless of tumor subtype.

The improvement in treatment outcome over time is best explained by the shift towards multimodality therapy as advocated by several authors. Especially the abandonment of radiotherapy as monotherapy appears to have contributed to improved survival. Furthermore, the advance of treatment modalities, e.a. the introduction of image guided surgery, could have positively affected treatment outcome in the last decade.

#### *Conclusions*

This article presents a near complete overview of all available data concerning SNC. It offers a basic understanding of their clinical behavior and a general direction for deciding on a treatment strategy. While the nature of the data does not allow for definite treatment guidelines, certain overall conclusions and recommendations can be made.

It is clear that a proper histological diagnosis with emphasis on differentiation grade is of paramount importance in predicting prognosis and treatment response in SNC. Well and moderately differentiated SNC perform significantly better and may require a less aggressive treatment approach than their poorly differentiated counterparts. However, no strong recommendations can be made in this regard, due to semantic deficiencies in the literature. Therefore, we strongly advocate the application of a uniform classification system for neuroendocrine carcinoma of the head and neck.

As we are unable to reliably infer the relationship between tumor stage on presentation and survival from our data, we feel caution is justified in taking a more conservative approach in treating patients with early stage disease.

Surgery should be the cornerstone of any treatment strategy with curative intent, supplemented by radiotherapy in poorly (and perhaps moderately) differentiated subtypes. Chemotherapy does not appear to contribute to survival.

Overcoming the limitations of this study would require a long term multi-center clinical trial. Until such a study is performed we have to rely on fragmented data such as presented in this paper. Therefore, we encourage institutions to keep publishing their experiences with these rare neoplasms.

#### **Conflict of interest statement**

None declared.

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