Neuroendocrine Carcinoma of the Head and Neck

In Search for a Better Outcome

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In regione caecorum rex est luscus
Desiderius Erasmus's Adagia (1500)

Table of Contents

CHAPTER I

General Introduction

Head and neck cancer is the 7th most common form of cancer worldwide, with an estimated incidence of approximately half a million new cases per year globally and 3000 in the Netherlands alone.[1,2] Head and neck cancer arises from different subsites, most commonly the oral cavity, the oro- and hypopharynx, the larynx, and the nasal cavity and paranasal sinuses (also referred to as the sinonasal tract). The overwhelming proportion (90 - 95%) of head and neck tumors is of the squamous cell carcinoma (SCC) type.[3] Because of the high incidence of SCC, evidence based guidelines are focused almost exclusively on this specific histological type. In contrast, non-SCC lack specific diagnostic and therapeutic protocols. The choice of treatment for these tumors is often based on small case series, individual experiences, and more often than not treatment regiments developed for SCC, resulting in suboptimal treatment (e.g. the application of radiotherapy in tumors with poor radiosensitivity) of a substantial number of patients. This phenomenon is especially apparent in neuroendocrine carcinoma of the head and neck (NCHN).

Neuroendocrine tumors are neoplasms derived from cells of the endocrine and nervous systems. They include benign and malignant tumors and arise in different locations of the body, generally following the distribution of their progenitor cells, commonly Kulchitsky or similar enterochromograffin-like cells. Locations include the pituitary, adrenal, thyroid and parathyroid glands, the thymus, lungs, gastrointestinal tract, breast, genitourinary tract, (peripheral) nervous system and skin. However, they also present at sites devoid of their progenitor cells, in particular the larynx and the sinonasal tract. These rare tumors are thought to arise from pluripotent stem cells and are the topic of this thesis.

History

Neuroendocrine tumors were first described in the small intestine in 1907.[4] These tumors were named carcinoid tumors because their relatively benign nature was considered to be cancer-like rather than cancerous. In 1965, Raychowdhuri et al. were the first to describe a neuroendocrine carcinoma originating in the sinonasal tract[5], followed by the report of Goldman et al. on a carcinoid tumor of the larynx in 1969.[6] As more institutions reported on their experience with these tumors it became apparent that there were differences in their histopathological features and clinical behavior leading to the formulation of subtypes.[7]

In the larynx, a distinction was made between typical and atypical carcinoid tumors in order to account for the poorer prognosis of the latter.[8,9] Furthermore, poorly differentiated

subtypes consisting of small cells were designated oat cell or small cell (neuroendocrine) carcinoma, in recognition of their similarity to their pulmonary counterparts.[9,10] Additionally, a large cell variant was added.[11]

A comparable subdivision was made in the sinonasal tract. However, typical and atypical carcinoid tumors were grouped together under sinonasal neuroendocrine carcinoma (SNEC), while poorly differentiated tumors consisting of moderate to large cells were classified as undifferentiated sinonasal carcinoma (SNUC).[12]

Nomenclature

In 1991, the World Health Organization (WHO) published a classification scheme for neuroendocrine tumors.[13] Based on differentiation grade, three subtypes were delineated: well, moderately and poorly differentiated (or low, intermediate and high grade) neuroendocrine tumors. Adoption of this classification scheme to HNNC was variable. Some authors retained the legacy terminology, frequently supplementing it with a large cell neuroendocrine carcinoma subtype. Others embraced the WHO naming scheme, but extended it as they saw fit (e.a. by incorporated the location name in ever more complex growing abbreviations). Furthermore, no consensus was reached in the use of 'well, moderately and poorly differentiated' versus 'low, intermediate or high grade'. This led to a multitude of different naming schemes being used in the literature (Table 1). In 2017, the WHO classification was updated.[14] Large cell neuroendocrine carcinoma are now considered high grade (III) tumors instead of intermediatie (II), more appropriately reflecting their aggressive behavior and poor prognosis.

Incidence and Clinical Presentation

It is estimated that approximately 1% of all tumors arising from the larynx have neuroendocrine features, while 5% of all tumors of the sinonasal tract is of neuroendocrine origin.[15]

The clinical features are often similar to those associated with SCC of the same location. In the larynx, patients typically present with complaints of hoarseness, dyspnea, odynophagia, dysphagia and/or otalgia, while those with a sinonasal neuroendocrine carcinoma present with (unilateral) congestion, epistaxis and, more rarely, diplopia or proptosis.

TABLE 1 Nomenclature of Neuroendocrine Tumors of the Head and Neck

Legacy Terminology	WHO	Sinonasal Neuroendocrine Carcinoma
(Typical) Carcinoid	Well differentiated/Low grade neuroendocrine carcinoma	Sinonasal neuroendocrine carcinoma
Atypical carcinoid	Moderately differentiated/ Intermediate grade neuroendocrine carcinoma	
Small cell (neuroendocrine) carcinoma/oat cell carcinoma	Poorly differentiated or high grade neuroendocrine carcinoma	Sinonasal small cell carcinoma
-		Sinonasal undifferentiated carcinoma

The tumor stage on presentation for neuroendocrine carcinoma of the larynx varies per subtype, with patients with a moderately or poorly differentiated subtype presenting with higher stage disease. Patients with a sinonasal neuroendocrine carcinoma typically present with advanced disease regardless of differentiation grade.[16] This phenomenon is the result of a lack of disconcerting symptoms and the close anatomical proximity of adjacent structures (skull base, orbita), leading to early upstaging using the TNM classification system.

Treatment and Prognosis

There are no clear guidelines for the treatment of NCHN. Consequently, the choice of treatment differs between institutions. Most studies employ treatment protocols developed for SCC in a one-size-fits-all fashion. These usually consist of (some combination of) surgery and radiotherapy, with the odd addition of chemotherapy. However, from the sparse data available from case reports and series we can deduce that there are large differences in prognosis and response to therapy between the subtypes of NCHN.[17] For example, the reported 5-year survival ranges from approximately 80% to 15% for well and poorly differentiated subtypes respectively. Furthermore, some subtypes appear to be poor responders to radiotherapy. Therefore, a customized treatment approach, taking into account the histological subtype, tumor location and, to a lesser extent, stage on presentation is of great importance.

HPV

Little is known about the carcinogenesis of NCHN. While we can assume common etiological factors, like smoking and alcohol abuse, are involved, the role of human papillomavirus (HPV) is unclear. High-risk HPV (hr-HPV), including HPV 16, 18, 31, 33 and 45, is well known for its involvement in the carcinogenesis of cervical and head and neck cancer.[17,18,19,20] A classical site in the head and neck area affected by HPV is the larynx. This mainly involves benign laryngeal papillomatosis, which is associated with low-risk HPV types 6 and 11. The presence of hrHPV in SCC of the larynx varies between studies from 7.4 to 58.8%.[20] It has been shown that hrHPV plays an etiological role in the carcinogenesis of a significant proportion of oropharyngeal cancer.[18,19] Furthermore, patients with HPV-positive oropharyngeal cancer have a significantly more favorable prognosis compared to those with HPV-negative tumors (3-year disease-specific survival 40% vs 93%, respectively)[21,22,23], making HPV the first clinically relevant prognostic tumor marker in head and neck oncology.

As HPV has already been shown to be involved in the carcinogenesis of neuroendocrine carcinoma of the cervix[24,25], one could assume that HPV may also be implicated in some patients with NCHN. Previous to this thesis, only one study investigated the presence of HPV in a neuroendocrine carcinoma of the larynx, which tested negative.[26] A better understanding of the possible role of HPV in the carcinogenesis of NCHN could lead to better treatment selection and outcome.

The Aim of the Thesis

Due to their rare nature, the literature concerning NCHN is fragmented over several hundreds of case reports and series. While these studies include valuable information, few are of sufficient sample size to make generalizations.

The aim of this thesis is to offer a better understanding of the clinical behavior of NCHN and to provide treatment guidelines in order to improve outcome of patients affected, by studying both our own experience and by reviewing the literature. Furthermore, we aim to evaluate the role of HPV in the carcinogenesis of NCHN and its implication in treatment selection.

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PART I

Institutional Experience

CHAPTER II

Neuroendocrine Carcinoma of the Larynx

An Extraordinary Malignancy With High Recurrence Rate and Long Survival: How We Do It

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Abstract

Introduction Neuroendocrine Carcinoma of the Larynx (NCL) Form a Heterogenous Group of Tumors With Clinical Characteristics Different From Squamous Cell Carcinoma (SCC). Our Understanding of Their Behavior and Response to Therapy Is Hampered by Their Rare Nature.

Material and Methods Clinical data, including age at diagnosis, gender, tumor subtype and stage, treatment, recurrence, salvage treatment and survival of patients with a neuroendocrine carcinoma of the larynx, diagnosed at our department between 1988 and 2010 were collected and retrospectively analyzed.

Results Eleven patients were available for analysis: six with an atypical carcinoid tumor, three with a large cell neuroendocrine carcinoma, one with a typical carcinoid tumor and one with a small cell neuroendocrine carcinoma. Treatment consisted of surgery (5), radiotherapy (4), a combination of radiotherapy and chemotherapy (1) and surgery with postoperative radiotherapy (1). Nine patients developed a recurrence. Prognosis appeared to be determined by histological subtype instead of tumor stage on presentation. Four patients died of their disease after a median follow-up of 29 months (range, 11 - 74). The other seven patients were followed for a median time of 48 months (range, 19 - 215). At the last follow-up, four were without evidence of disease, two were alive with disease and one patient had died of a pulmonary tumor unrelated to his laryngeal cancer.

Conclusion Prognosis in NCL appears to be determined by histological subtype instead of tumor stage on presentation. There is an exceptionally high rate of recurrence. A better delineation of the differences between NCL and SCC of the larynx is necessary in order to improve treatment outcome of patients affected.

Introduction

Laryngeal neuroendocrine carcinomas are rare tumors that are believed to originate from pluripotent stem cells located in the submucosa of the larynx.[1] Constituting less than 1% of all tumors originating from the larynx, they still form the second most common group of neoplasms at this location, after laryngeal squamous cell carcinoma.[2] The World Health Organization classification divides laryngeal neuroendocrine carcinomas in four groups; typical carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, and paragangliomas.[3] Recently an aggressive subtype of the atypical carcinoid group was identified as a separate entity; the large cell neuroendocrine carcinoma.[4]

Identification of the right tumor type is of importance as tumor behavior and response to therapy are closely related to the histological diagnosis.[2,4] There are several pitfalls in the diagnostic and staging process of laryngeal neuroendocrine carcinoma. The different subtypes show considerable overlap in histological and immunohistochemical features, and neuroendocrine tumors can be a part of composite tumors, consisting of both a neuroendocrine neoplasm and a squamous cell carcinoma, impeding or delaying appropriate treatment.[1]

Due to the rarity of these tumors, only small series have been published. Therefore, it remains important that institutions report on their experience with these neoplasms. The aim of this study was to increase the understanding of the clinicopathological behavior by reviewing the medical files of patients diagnosed with a laryngeal neuroendocrine carcinoma at our institution.

Material and Methods

The Dutch nation wide digital database of histo- and cytopathology (PALGA) was searched for patients with a laryngeal neuroendocrine carcinoma who were diagnosed at the Department of Otolaryngology, Head and Neck Surgery of the University Medical Center Groningen between 1988 and 2010. Available data on gender, age, clinical presentation, smoking history, alcohol use, tumor site, tumor subtype, tumor stage, paraneoplastic syndrome, treatment, treatment outcome (loco-regional recurrence, distant metastases), additional treatment, follow-up and survival time in months (disease-specific and overall) were extracted from the patient charts. Staging was performed according to the 7th Edition

of the American Joint Committee on Cancer Staging Manual. Statistical analysis was performed in SPSS 18.0 for Mac OSX. Survival times were calculated using the Kaplan-Meier method. Reported confidence intervals (CI) are for 95% probability.

Results

A total of 11 cases of laryngeal neuroendocrine carcinoma were available for analysis. The clinical characteristics of these cases are summarized in Table 1. Eight patients were male, three were female. The median age at the time of diagnosis was 67 years (range, 40 - 81). Eight patients had a smoking history (two denied, one unknown). Complaints at presentation were in order of frequency: hoarseness, sore throat, otalgia, a lump sensation, and persistent cough. The primary tumor location was supraglottic in nine patients and subglottic in two. The tumor was interpreted as an atypical carcinoid in six cases and as a large cell neuroendocrine carcinoma in three. The two remaining patients presented with a typical carcinoid and a small cell neuroendocrine carcinoma. The tumor stage on presentation was stage I in three, stage II in another three, stage III in one and stage IVa in the remaining four cases.

Primary treatment consisted of surgery (5), radiotherapy (4), a combination of chemo- & radiotherapy (1) or surgery & postoperative radiotherapy (1). Surgery varied from laryngeal preservation techniques using transoral CO_2-laser surgery (2), or partial horizontal laryngectomy (1) to total laryngectomy (3). Resection margins were free of tumor cells in patients who underwent total laryngectomy or partial horizontal laryngectomy, surgical margins were not definable in cases of laser surgery due to carbonization. The patients who received radiotherapy were treated with a median total dose of 64Gy (range: 37.5 - 70). One patient received concomitant chemotherapy consisting of a combination of etoposide and carboplatin.

Eight patients developed loco-regional recurrence. Five patients developed distant metastases, most of them cutaneous. One patient developed bone metastases beside the skin metastases. One patient with a small cell neuroendocrine carcinoma developed multiple brain and liver metastases. Average time to recurrence was 30 months (CI, 9 - 52).

TABLE 1 Clinical characteristics of eleven cases of laryngeal neuroendocrine carcinoma

Case no.	Age/ Gender	SH	Presentation	Tumor Site	Tumor Type	TNM Stage	Initial Treatment	Disease Free Period	Recurrence Type	Location Metastases	Salvage Therapy	Follow-up/Status
1	69/M	Y	Hoarseness, sore throat, otalgia	Supraglottic	AC	T1N0M0	TLE	29	Regional, distant	Skin	MRND	74/DOD
2	57/M	Y	Dysphagia	Supraglottic	SCNEC	T2N2cM0	Chemotherapy (Etoposide, Carboplatin), Radiotherapy (37.5Gy)	4	Distant	Brain, liver	Palliative chemotherapy (Carboplatin/ Paclitaxel)	11/DOD
3	57/F	N	Cough	Subglottic	TC	T1N0M0	Radiotherapy (70Gy)	96	-	-	-	96/NED
4	40/M	Y	Dysphagia, otalgia	Supraglottic	AC	T4N0M0	Partial horizontal laryngectomy	17	Regional, distant	Skin, bone, cervical lymph nodes	Miltefosine	28/DOD
5	51/F	NA	Hoarseness	Supraglottic	AC	T2N0M0	TLE	9	Regional	Cervical lymph node	RND	215/NED
6	81/M	Y	Otalgia	Supraglottic	LCNEC	T4aN2bM0	Radiotherapy (70Gy)	34	Regional	Cervical lymph nodes	TLE, MRND	48/AWD
7	75/F	N	Sore throat, otalgia	Supraglottic	AC	T2N0M0	Supraglottic laryngectomy by CO2 laser	14	Regional, distant	Skin	TLE	26/AWD
8	73/M	Y	Sore throat, otalgia	Supraglottic	LCNEC	T2N0M0	Radiotherapy (70Gy)	3	Regional, distant	Skin	TLE, Etoposide	30/DOD
9	67/M	Y	Hoarseness, sore throat	Supraglottic	AC	T3N0M0	Radiotherapy (70Gy)	12	Regional	NA	TLE	27/NED

TABLE 1 Clinical characteristics of eleven cases of laryngeal neuroendocrine carcinoma

Case no.	Age/ Gender	SH	Presentation	Tumor Site	Tumor Type	TNM Stage	Initial Treatment	Disease Free Period	Recurrence Type	Location Metastases	Salvage Therapy	Follow-up/Status
10	75/M	Y	Hoarseness	Subglottic	AC	T1N0M0	Endolaryngeal CO2 laser resection	1	Regional	NA	-	19/DOOC
11	53/M	Y	Dysphonia, dysphagia	Supraglottic	LCNEC	T3N2bM0	TLE, MRND, Radiotherapy (60Gy)	105	-	-	-	105/NED

SH, smoking history; DOD, dead of disease; NED, no evidence of disease; AWD, alive with disease; DOOC, dead of other cause; AC, atypical carcinoid; TC, typical carcinoid; SCNEC, small cell neuroendocrine carcinoma; TLE, total laryngectomy; MRND, modified radical neck dissection; RND, radical neck dissection. Regional includes recurrence of the primary tumor and, if noted under location, cervical lymphnode metastases. Disease free period and follow-up in months.

Salvage therapy was performed in all but one case. This patient had a second primary pulmonary tumor at the time which was deemed irresectable and the patient abstained from further treatment. Six patients underwent salvage surgery. Four patients were laryngectomized (one with neck dissection and another one with postoperative chemotherapy), two patients underwent a neck dissection and one patient received chemotherapy. The patient with small cell neuroendocrine carcinoma received palliative chemotherapy consisting of a combination of carboplatin and paclitaxel. Resection margins were free of tumor cells in all of the patients who underwent surgery. None of the patients with a typical carcinoid developed loco-regional recurrence. No relationship was found between tumor stage or choice of initial treatment and recurrence.

Four of the eleven patients died of their disease after a median follow-up of 29 months (range, 11 - 74). The other seven patients were followed for a median time of 48 months (range, 19 - 215). At the last follow-up, four were without evidence of disease, two were alive with disease and one patient had died of a pulmonary tumor unrelated to his laryngeal cancer. The mean overall and disease-specific survival were 115 (CI, 54 - 175) and 125 months (CI, 61 - 189), respectively. Tumor type, stage, location and or initial treatment were not significantly related to either overall or disease-specific survival.

Discussion

Treatment of Laryngeal Neuroendocrine Carcinoma

Due to the variation in clinical behavior, treatment guidelines are different for each laryngeal neuroendocrine carcinoma subtype.[2,5] Typical carcinoids rarely metastasize and are thought to be best treated by surgical excision alone. Atypical carcinoids are known to be more aggressive and metastasize more frequently and thus, depending on the size and extension of the tumor, partial or total laryngectomy is recommended. Most authors consider an elective neck dissection justified in these patients.[2,5,6] The radiosensitivity of these tumors is debated, with various results being reported.[1,2,6] Small cell neuroendocrine carcinoma should be considered systemic diseases, believed to be best treated by a combination of radio- & chemotherapy.[5] The best treatment of large cell neuroendocrine carcinoma is still debated. Most of our patients were primarily treated conform to the international recommendations. Although the literature seems to be coherent regarding the

primary treatment; little is published about salvage or palliative treatment of laryngeal neuroendocrine carcinoma.

Prognostic Aspects of Laryngeal Neuroendocrine Carcinoma

Laryngeal neuroendocrine carcinoma, with the exception of typical carcinoid, are known to have a high propensity for recurrence.[8] This was confirmed by our data with 80 percent of patients developing recurrent disease. Interestingly, no relationship could be found between tumor stage and the development of recurrent disease, with most recurrences occurring in patients with stage II disease. A remarkable feature of laryngeal neuroendocrine carcinoma is their ability to produce distant metastases in the form of painful cutaneous nodules in several different locations.[2,6] Three of the four patients with distant metastases developed these lesions. Despite their high recurrence rate, very long overall and disease-specific survival were found, suggesting that patients with a laryngeal neuroendocrine carcinoma that develop recurrent disease can survive relatively long.

Commonly used prognostic indicators in laryngeal squamous cell carcinoma (e.a. recurrence rate and disease free survival) appear to be of less importance in estimating prognosis in laryngeal neuroendocrine carcinoma. Instead, the tumor subtype is a strong determinant of treatment outcome, with a generally good prognosis for patients with a typical carcinoid and a progressively worse prognosis for those with an atypical carcinoid, small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma. As patients with recurrence can survive relatively long, laryngeal neuroendocrine carcinoma require a different treatment philosophy. Based on our experiences, salvage surgery, including palliative metastasectomy has an important role in the treatment of laryngeal neuroendocrine carcinoma and reasonable overall survival can be achieved.

Conclusions

In conclusion, laryngeal neuroendocrine carcinoma form a rare and heterogeneous group of tumors displaying distinctly different behavior from laryngeal squamous cell carcinoma. It is important to be aware of the higher recurrence rate in laryngeal neuroendocrine carcinoma, both regional and distant, and the differences in optimal treatment as these differ not only between laryngeal neuroendocrine carcinoma and laryngeal squamous cell carcinoma, but also between the different subtypes of laryngeal neuroendocrine carcinoma. A radical surgical approach with neck dissection is warranted in patients with an atypical

carcinoid as loco-regional metastasis likely occurs at an early stage in these tumors. On the other hand, the surprisingly long overall and disease-specific survival in laryngeal neuroendocrine carcinoma suggests that salvage therapy plays extremely important role in the treatment of these malignancies. Moreover, in patients where radical treatment is contraindicated (based on high co-morbidity or other reason) long-term palliation should be considered.

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Supplementary Analyses

While not included in the original publication, we additionally performed a case control analysis, matching patients with a neuroendocrine carcinoma of the larynx with patients with a squamous cell carcinoma on age, primary tumor location and tumor stage. The results are presented in this supplement and will be discussed in Chapter VIII.

Results

An overview of the differences between the laryngeal neuroendocrine carcinoma (NC) group and the control group is given in Table 2. The control group consisted of twenty-two patients with a squamous cell carcinoma (SCC) of the larynx. Fourteen patients were male, eight were female. The median age at presentation was 67 years (range, 41 - 79). In contrast with patients with a NC, all patients with a SCC had a smoking history. Tumor site and stage were matched 1:1 with the NC group.

Only 4 of the 22 SCC patients were treated surgically. All four underwent a TLE. Two received adjuvant radiotherapy. Another was additionally treated with a selective neck dissection followed by adjuvant radiotherapy, because of positive resection margins. The other patients received radiotherapy with a median total dose of 70Gy (range, 64 - 70). One patient received concomitant chemotherapy. One patient was included in the ARCON trail. The choice of therapy was significantly different from the NC group with radiotherapy being the preferred initial treatment in patients with a SCC in contrast to a preference for surgery in the NC group ($p = .010$).

The number of recurrences was significantly lower in the SCC group with five patients developing loco-regional recurrence and only one patient developing distant metastases to the lung ($p = .005$). Mean time to recurrence for SCC was 96 months (95% CI, 75 - 117), which was significantly longer than that for NC ($p = .003$). Three patients received salvage surgery. All of them underwent TLE, two of them with a neck dissection. Free resection margins were obtained in all patients. Two patients received no further treatment.

No statistically significant difference was found between the Kaplan-Meier estimates of the mean time of overall ($p = .734$) and disease-specific ($p = .312$) survival between NC and SCC with 89 months (95% CI, 59 - 119) and 137 months (95% CI, 107 - 167) respectively.

TABLE 2 Comparison of neuroendocrine carcinoma and squaumous cell carcinoma of the larynx

	NC (n = 11)	SCC (n = 22)	P-value
Age (years)	63 ± 13	64 ± 12	.826
Sex (male), N (%)	8 (73)	14 (64)	.709
Smoking History, N (%)	8 (80)	22 (100)	.091
Tumor Stage, N (%)			
I	3 (27)	6 (27)	1
II	3 (27)	6 (27)	1
III	1 (9)	2 (9)	1
IVa	4 (36)	8 (36)	1
Initial Treatment, N (%)			
Surgery	5 (46)	1 (5)	.010
Radiotherapy	4 (36)	17 (77)	.052
Chemo- & Radiotherapy	1 (9)	1 (5)	1
Surgery & Radiotherapy	1 (9)	3 (14)	1
Radical Resection Margins Initial Therapy, N (%)	5 (83)**	3 (75)	1
Recurrence, N (%)	8 (80)	5 (23)	.005
Recurrence Location, N (%)			
Regional Only	4 (50)	4 (80)	.565
Regional & Distant	4 (50)	1 (20)	.565
Salvage Treatment, N (%)	7 (64)	3 (14)	.006
Management of Recurrent Disease, N (%)			
No Treatment	1 (13)	2 (40)	.510
Surgery	4 (50)	3 (60)	1
Chemotherapy	1 (13)	0 (0)	1
Surgery & Radiotherapy	1 (13)	0 (0)	1
Surgery & Chemotherapy	1 (13)	0 (0)	1
Radical Resection Margins Salvage Therapy, N (%)	6 (100)	3 (100)	-
Mean Time to Recurrence*, Months (CI)	33 (10-56)	96 (75-117)	.003
Mean Disease-specific Survival Time*, Months (CI)	137 (71-203)	137 (107-167)	.312
Mean Overal Survival Time*, Months (CI)	125 (62-188)	89 (59-119)	.734

* Kaplan-Meier Estimate
** One patient with CO2-laser resection, where resection margin determination was not possible

CHAPTER III

The Importance of Multimodality Therapy in the Treatment of Sinonasal Neuroendocrine Carcinoma

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Abstract

Introduction Sinonasal Carcinoma with Neuroendocrine Differentiation (SCND) are a rare group of tumors known for their aggressive behavior and poor response to treatment. The data in the literature is sparse and covers a wide range of therapeutic approaches over a protracted timeline. Therefore, it is important that institutions report on their experience with these rare neoplasms.

Material and Methods Clinical data, such as age at diagnosis, gender, tumor subtype and stage, treatment intention and modality, recurrence, salvage treatment, and survival of patients with a SCND, diagnosed at our department between 1980 and 2010, were retrospectively analyzed.

Results Fifteen patients were available for analysis; eight with a sinonasal undifferentiated carcinoma (SNUC), five with a sinonasal neuroendocrine carcinoma (SNEC), and two with a small cell neuroendocrine carcinoma (SmCC). The median age at the time of diagnosis was 68 years (range, 28 - 87). Treatment consisted of surgery (2), radiotherapy (4), a combination of these modalities (6) and palliation (3). The estimated 5-year overall survival was 60% for SNEC, 44% for SNUC and 0% for SmCC.

Conclusion According to our institutional experience, an aggressive multi-modality approach incorporating (neoadjuvant) chemoradiotherapy, radical surgery and elective treatment of the neck is the best treatment strategy for SCND. The high propensity for distant metastasis and poor prognosis of SmCC warrants consideration of the impact of treatment on the remaining quality of life in these patients.

Introduction

Sinonasal tumors with neuroendocrine differentiation (STND) form a group of rare neoplasms consisting of esthesioneuroblastoma (ENB), sinonasal neuroendocrine carcinoma (SNEC), sinonasal undifferentiated carcinoma (SNUC) and small cell neuroendocrine carcinoma (SmCC).[1,2] A broad distinction is made between STND of epithelial and neuroectodermal origin.[1]

STND of epithelial origin, i.e. Sinonasal Carcinoma with Neuroendocrine Differentiation (SCND), are further divided based on differentiation grade and cell size.[2] The well- and moderately differentiated tumors are grouped under SNEC, while the poorly differentiated neoplasms, depending on their cell size, are categorized as either SNUC or SmCC. The neuroectodermal group consists solely of ENB (Figure 1).

In contrast to ENB, SCND lack a well-defined treatment strategy, with various therapeutic approaches and results being reported by different institutions.[1, 3-10] Due to the rarity of these tumors, most of these series are small and describe a heterogeneous population,

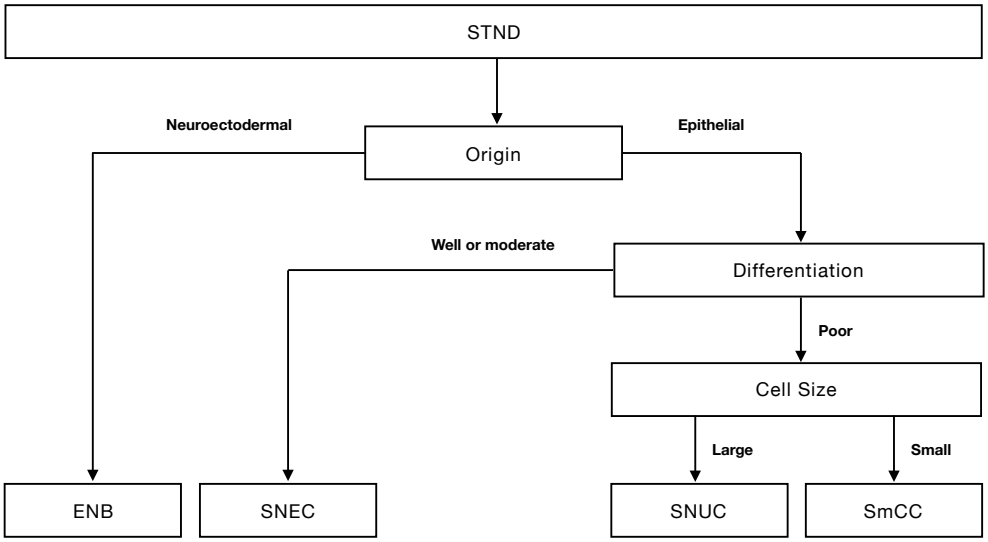

FIGURE 1
Classification of sinonasal tumors with neuroendocrine differentiation. STND, Sinonasal Tumors with Neuroendocrine Differentiation; ENB, Esthesioneuroblastoma; SNEC, Sinonasal Neuroendocrine Carcinoma; SNUC, Sinonasal Undifferentiated Carcinoma; SmCC, Small Cell neuroendocrine Carcinoma

limiting our ability to make definitive statements with regard to their behavior, response to therapy and prognosis.

This study reports on our institution's experience with SCND and reviews the literature on these rare neoplasms in order to advance our understanding of their characteristics and improve the treatment strategy and outcome of patients affected.

Patients and Methods

Patients

The Dutch nationwide digital database for histo- and cytopathology (PALGA) was searched for patients with a SCND that were diagnosed at the Department of Otolaryngology, Head and Neck Surgery of the University Medical Center Groningen between 1980 and 2010. All histology specimens were revised by an experienced head and neck pathologist.

Data

Demographic data such as age at diagnosis, gender, tumor subtype and stage, treatment, recurrence, salvage treatment, and survival were retrieved from the medical charts and electronic patient files of the Department of Otolaryngology, Head and Neck Surgery and retrospectively analyzed. Staging was performed according to the 7th Edition of the American Joint Committee on Cancer Staging Manual. Overall Survival (OS) estimates were calculated using the Kaplan-Meier method.

Ethical Considerations

The study was approved by the Institutional Review Board.

Results

Patients Characteristics

Fifteen cases of SCND were available for analysis. Ten patients were male. The median age at the time of diagnosis was 68 years (range, 28 - 87). The tumor type was SNUC in eight cases, SNEC in five, and SmCC in two. Eleven patients presented with stage IVa disease, two with stage I, one with stage III and another with stage IVb. In all cases, the tumor stage was related to the extension of the primary tumor (T classification) and not to regional or

distant metastasis. All patient characteristics, treatment and follow-up data are presented in Table 1.

Initial Treatment

Twelve patients were treated with curative intent. Eight of them with surgery. Five received post-operative radiotherapy. The remaining four were treated with primary radiotherapy. The other three patients were managed palliatively due to the extent of their disease and old age. Surgery consisted of a lateral rhinotomy in six cases, combined with a craniotomy in two, an orbital exenteration in another and a transnasal duraplasty in yet another. The remaining patient was treated with endoscopic surgery. Due to the nature of these procedures, en bloc resection of the tumor was not possible in most of the cases. Therefore, no reliable resection margins could be obtained upon pathological examination. However, macroscopic tumor has never been left behind (R1 margins). Primary and post-operative radiotherapy was performed using three-dimensional conformal radiotherapy in seven patients, intensity-modulated radiotherapy in two, and two-dimensional radiotherapy in one. The median total dose was 66.3Gy (range, 30 - 70.2).

Recurrence & Management

Five of the patients treated with curative intent developed a recurrence; two local, another two loco-regional and one distant. The median time to recurrence was five months (range, 4 - 37). Salvage treatment consisted of surgery with post-operative radiotherapy in two patients. Two patients received radiotherapy, one in combination with chemotherapy. The patient with distant metastasis was treated with palliation.

Follow-Up

The median follow-up duration for patients treated with curative intent was 30.5 months (range, 5 - 225). At the end of follow-up seven of them had died of their disease. One patient died of another cause. The remaining five patients were alive without evidence of disease with a median follow-up duration of 74 months (range, 27 - 225). Patients treated with palliative intent survived for a median duration of 2 months (range, 1 - 18). The estimated 5-year overall survival was 60% for SNEC, 44% for SNUC and 0% for SmCC.

TABLE 1 Patient and Treatment Characteristics of 15 Patients With a Sinonasal Carcinoma With Neuroendocrine Differentiation

Case no.	Gender	Age	Tumor Type	Stage	Initial Treatment	Recurrence	TTR	Recurrence management	Follow-up	Status
1	M	84	SNEC	IVA	LR + OE + 2D-RT (30Gy)	-	-	-	7	DOD
2	M	76	SNEC	IVA	LR + 3D-CRT (64Gy)	Distant	4	Palliation	6	DOD
3	M	36	SNEC	IVA	LR + TD	Regional	4	RND + 3D-CRT (60Gy)	225	NED
4	M	62	SNEC	IVA	C + LR + 3D-CRT (59.4Gy)	-	-	-	99	NED
5	M	54	SNEC	I	ED + 3D-CRT (59.4Gy)	Local	37	LR + Palliative 2D-RT (8Gy)	174	DOD
6	M	59	SNUC	I	LR + 3D-CRT (66.6Gy)	-	-	-	74	NED
7	M	28	SNUC	IVA	C + LR	Local	5	3D-CRT (63Gy)	20	DOD
8	F	78	SNUC	IVA	3D-CRT (70.2Gy)	-	-	-	23	DOD
9	F	60	SNUC	III	LR + 3D-CRT (66Gy)	Regional	12	IMRT (70Gy) + Cisplatin	34	DOD
10	F	87	SNUC	IVA	Palliative 3D-CRT (30Gy)	-	-	-	18	DOOC
11	F	81	SNUC	IVB	Palliation	-	-	-	1	DOD
12	M	79	SNUC	IVA	IMRT (70Gy)	-	-	-	27	NED
13	M	58	SNUC	IVA	IMRT (70Gy)	-	-	-	40	NED
14	M	68	SmCC	IVA	3D-CRT (70Gy)	-	-	-	5	DOD
15	F	81	SmCC	IVA	Palliative 3D-CRT (32.5Gy)	-	-	-	2	DOD

TTR; Time To Recurrence; M, Male; F, Female; SNEC, Sinonasal Neuroendocrine Carcinoma; SNUC, Sinonasal Undifferentiated Carcinoma; SmCC, Small Cell Neuroendocrine Carcinoma; LR, Lateral Rhinotomy; OE, Orbital Exenteration; 2D-RT, 2-Dimensional Radiotherapy; 3D-CRT, 3-Dimensional Conformal Radiotherapy; TD, Transnasal Duraplasty; RND, Radical Neck Dissection; C, Craniotomy; ED, Endoscopic Debulking; IMRT, Intensity-Modulated Radiotherapy; DOD, Dead Of Disease; NED, No Evidence of Disease; DOOC, Dead Of Other Cause. TTR and follow-up in months.

Discussion

General

The division of STND in ENB and non-ENB histological subtypes was introduced by Rosenthal et al. in 2004.[1] Their study revealed a large difference in the patterns of failure between both groups, making a common origin unlikely. While ENB generally show a consistent response to therapy, with local control rates of 86 - 96% routinely achieved in recent series, non-ENB STND prove to be more difficult to manage. It is hard to arrive at clear treatment guidelines for these tumors as the data in the literature is sparse and covers a wide range of therapeutic approaches over a protracted timeline. Therefore, it is important that institutions report on their experience with these rare neoplasms.

Incidence & Location

It is estimated that SCND account for approximately 5% of all tumors arising from the sinonasal tract.[4] They are most commonly located in the nasal cavity followed by the ethmoid sinuses.[4,10] Patients typically present during or after their 5th decade with locally advanced disease due to the non-specific nature of accompanying symptoms (nasal obstruction, epistaxis and/or nasal drainage).[1] There appears to be a male preponderance. For SNUC, it is estimated that 10 to 30% of patients have regional metastasis at presentation.[8] This figure is even higher for SmCC.[1] Our series confirms these observations, with twelve out of fifteen patients (80%) presenting with stage IV disease.

Treatment

The reported treatment strategies for SCND vary widely. Recent series have shown that a combination of surgery, radiotherapy and chemotherapy can improve survival over dual or single modality therapy.[1,3,4,9] Furthermore, it has been suggested that elective treatment of the neck will improve regional control.[5] In their 2012 study, Fried et al. advocate the use of neoadjuvant chemoradiotherapy.[3] Although no statistically significant benefit could be demonstrated from their series, they hypothesize that the early introduction of chemotherapeutic agents halts disease progression and, combined with radiotherapy, reduces tumor volume, improving surgical outcome. While SCND appear to be sensitive to chemo- and radiotherapy, gross total tumor resection has repeatedly been identified as a predictive factor for improved outcome.[7,8] While no statistical conclusions can be drawn from our series, we observed the best treatment outcome for patients treated by

multimodality therapy. It is important to carefully weigh the impact of treatment on the remaining quality of life, especially in patients of old age and/or with a prognostically unfavorable histological subtype, like SmCC.

Recurrence & Prognosis

The recurrence rate of SCND in general is high and lies above 50% in most series.[1,3,4] Correspondingly, in our study population, five of the ten patients in which disease control was initially achieved developed a recurrence. Despite of this high proportion, patients with local or loco-regional recurrence survived for a median of 80 months after salvage treatment. Unlike SNEC and SNUC, SmCC are known to have an exceptionally high propensity for distant metastasis with a 5-year distant metastasis free survival of only 25%, underlining the importance of (adjuvant) chemotherapy in this group of patients.[1]

The 5-year OS for SNUC and SNEC varies widely between series. Early accounts reported a poor response to therapy and abysmal prognosis, while later studies, incorporating multi-modality therapy, have shown more encouraging results.[1,3,4,9] From these later series, the 5-year OS for SNEC and SNUC can be estimated to lie somewhere between 60 and 70%. The 5-year OS in this series lies slightly below these figures, with 60% for SNEC and 44% for SNUC, likely due to the lack of (adjuvant) chemotherapy and the choice for single modality treatment in a proportion of patients. This can be explained by the long inclusion interval of 30 years. The 5-year OS for SmCC lies below 30%.[1,6] In our study, only one patient with a SmCC was treated with curative intent. Unfortunately, no chemotherapy was applied in this case either and the patient died within 5 months of diagnosis.

Conclusion

Combining the sparse evidence from our personal experience and the information in the literature, we feel that an aggressive multi-modality approach incorporating (neoadjuvant) chemoradiotherapy, radical surgery and elective treatment of the neck is the best treatment strategy for SCND. While SNEC and SNUC appear to have a similar clinical behavior, SmCC are clearly more aggressive. Their high propensity for distant metastasis and poor prognosis warrants systemic therapy with careful consideration of the impact of treatment on the remaining quality of life.

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CHAPTER IV

Carcinoid Tumor of the Middle Ear

A Case Report With Review of the Literature

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Abstract

Carcinoid tumors of the middle ear (CTME) are extremely rare. There is an ongoing debate in the literature about the distinction between CTME and middle ear adenoma (MEA). We report a case of CTME and discuss the literature with special emphasis on the differentiation between CTME and MEA.

Introduction

Carcinoid tumors are neoplasms that, depending on the site, are believed to originate from cells of the neuroendocrine system or pluripotent stem cells.[1] They are most frequently found in the gastrointestinal tract and the lung, where they account for 59 and 27 percent of all neuroendocrine tumors respectively.[2] In the head and neck area they are most often located in the larynx.[3] One particularly unlikely site for these neoplasms to arise is the middle ear, with an estimated share of less than one percent of all neuroendocrine tumors.[3] Its existence at this location is debated, with some authors preferring to classify these tumors as middle ear adenoma (MEA) with neuroendocrine differentiation.[4] MEA are considered benign neoplasms, while carcinoid tumors are known to be able to undergo malignant transformation, necessitating a more radical surgical approach.[5] It is therefore important that clinicians are aware of these rare and confusingly similar tumors. We report a case of a carcinoid tumor of the middle ear (CTME) and discuss the distinction between these neoplasms and MEA.

Report of a Case

A 29 year old man presented with a one year history of a pounding sensation and tinnitus of the right ear, recently accompanied by progressive hearing loss. Otoscopy revealed a sphere shaped swelling protruding through the tympanic membrane. A 30dB conductive hearing loss was measured for all frequencies with normal sensorineural threshold. A CT-scan (Figure 1) showed a mass in the posterosuperior part of the right middle ear, completely veiling the epitympanum and mastoid with impaction of the ossicles. Magnetic resonance imaging (Figure 2) demonstrated a soft tissue mass in the right middle ear and a fluid collection located in the mastoid. Explorative tympanotomy was performed. A fibrous tumor was found to fill the entire middle ear. A biopsy was taken for frozen section intra-operatively, which revealed the lesion to be a “carcinoid/adenoma with neuroendocrine features”. The surgery was extended to a modified radical mastoidectomy. The revised pathology report described an unencapsulated tumor, covered by an uninvolved surface of squamous epithelium. The growth pattern was cribriform with monotonous cells with round nuclei, finely stippled chromatin, and a low N/C ratio. There was no necrosis. The tumor cells were uniformly positive for chromogranin and synaptophysin. The mitotic activity was less than 1/10 HPF. The amount of Ki-67 positive cells was less than 2%. (Figure 3). The patient is alive, without evidence of disease, 10 years after surgery.

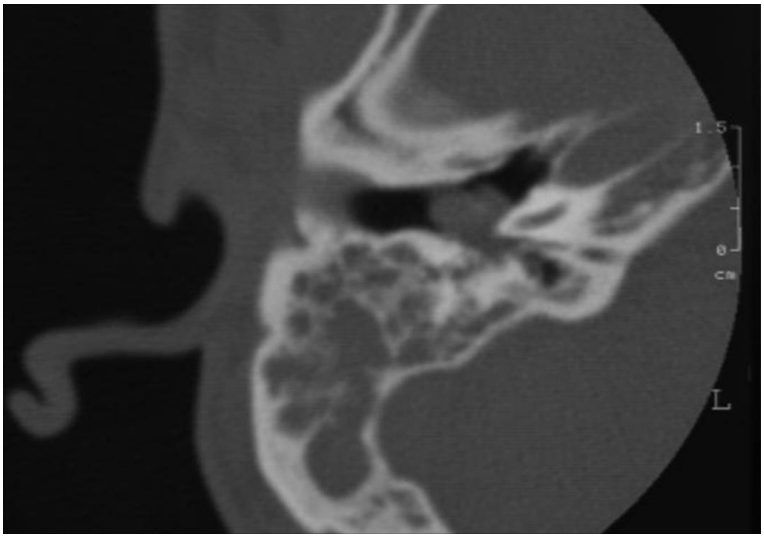

FIGURE 1
Axial CT scan of the right temporal bone demonstrates veiling of the epitympanum and the mastoid.

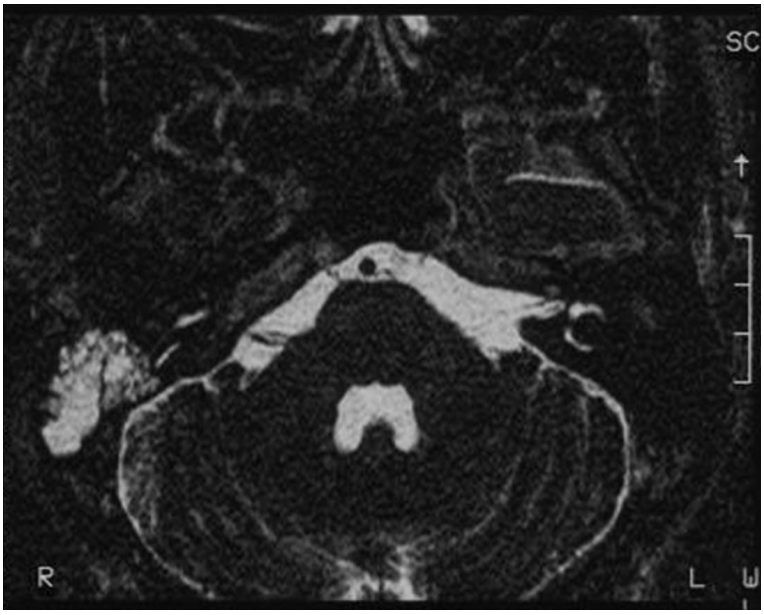

FIGURE 2
T2 weighted axial magnetic resonance image of the head shows a mass in the right middle ear with fluid collection in the mastoid.

Discussion

The first published case of a carcinoid tumor of the middle ear was reported in 1980 by Murphy et al.[6] Prior to this report, these tumors were usually classified as adenomas. More recently, this designation has become subject of debate, with several authors claiming that it is impossible to distinguish CTME from MEA.[4,7,8] We present a short overview of the disease entities and the arguments in this debate.

CTME and MEA are rare tumors. Males are slightly more often effected than females with a reported ratio of 1.4:1.[9] The average age at presentation is similar for both tumor types and is located around the 4th decade.[4,7,9] Both neoplasms share the same clinical features.[4,7,9] Patients commonly present with hearing loss, aural fullness, tinnitus, otorrhea and more rarely otalgia. Otoscopy reveals a mass in the middle ear in the majority of cases. Bone erosion or invasion is rare, although involvement of the facial nerve has been described.[9,10] Systemic symptoms of carcinoid tumors, like flushing, diarrhea and abdominal cramps have also been reported.[11,12]

Several studies have pointed out that it is impossible to distinguish CTME and MEA on the basis of their light microscopical or immunohistochemical features.[4,8] CTME commonly display glandular features and MEA often stain positive for neuroendocrine markers, suggesting that CTME and MEA are indeed the same tumor entity with different degrees of glandular and neuroendocrine differentiation.

The preferred treatment modality is the same for both tumor types and consists of surgery. Adjuvant radiotherapy is considered unnecessary and may even adversely affect the prognosis by inducing malignant transformation.[13] There is no data on the sensitivity of these tumors for chemotherapy.

It may be tempting, due to the benign nature of MEA and CTME, to perform conservative surgery in order to achieve better postoperative hearing results. However, malignant transformation has been described for CTME[1] and recurrences, although uncommon, do occur.[4,9] Therefore, at least (modified) radical mastoidectomy appears to be necessary in order to achieve complete tumor ablation. With adequate treatment the prognosis of these neoplasms is excellent. Recurrence of the primary tumor occurred in approximately 20 percent of published cases[4,9] but was virtually inexistent when the ossicular chain was

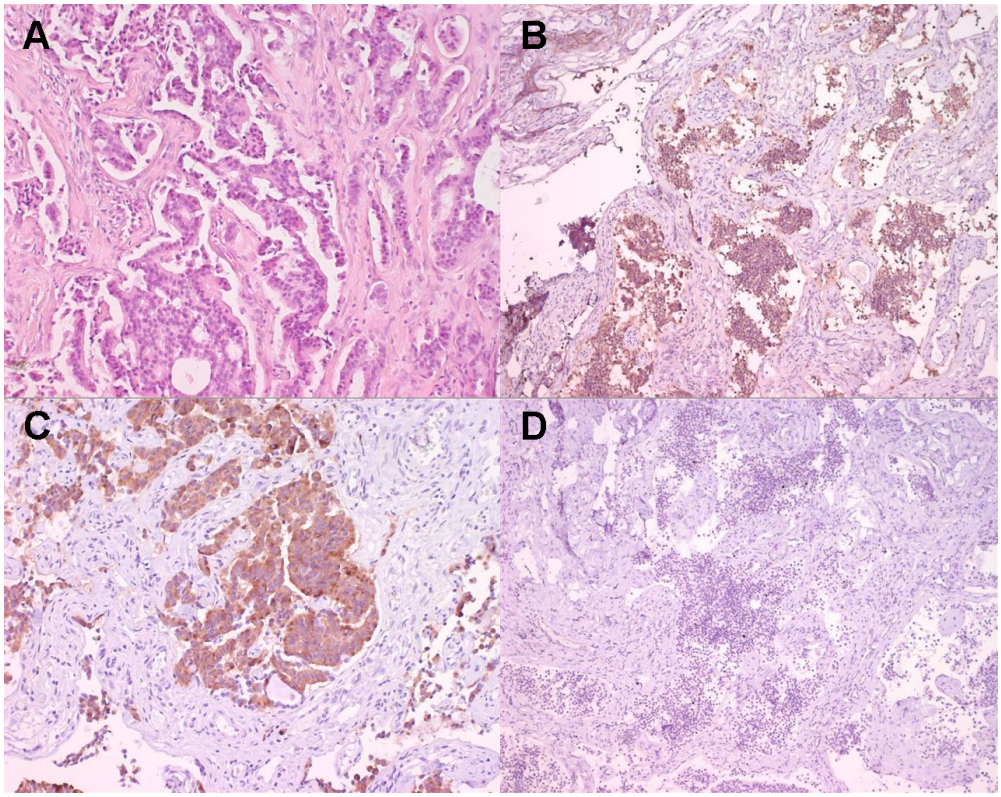

FIGURE 3

A. Hematoxylin-eosin staining revealed an unencapsulated tumor, covered by an uninvolved surface of squamous epithelium (20X). B. The chromogranin immunostaining was positive (20X). C. Tumor cells were also positive for synaptophysin (20X). D. Less than 2 % of the tumor cells were positive for Ki-67 (10X).

removed on initial surgery.[4] In a review by Ferlito et al., five cases of metastatic CTME are described[5], contradicting the generally held believe that these tumors are of an exclusively benign nature. In the same article, a parallel is drawn between CTME and neuroendocrine tumors of the lung, which before being recognized as low-grade malignancies were also grouped with adenomas. The time to recurrence varies widely with recurrent disease occurring up to 33 years after treatment.[9] To this date, there is no report of distant metastasis associated with CTME.

Concluding, it seems clear that CTME and MEA are not the same tumor entity, as their behavior is not uniformly benign, with CTME possessing low-grade malignant features.

However, presently, it is not possible to make a histological distinction between these tumors prior to observing this malignant behavior. Therefore, CTME and MEA warrant a similar aggressive therapeutic approach: complete surgical removal by (modified) radical mastoidectomy. Radiotherapy should be discouraged. Long term follow-up is advised as these neoplasms tend to recur many years after treatment. Our case demonstrates one of these rare tumors. This young adult was diagnosed with a CTME and successfully treated by modified radical mastoidectomy; the patient is alive and without evidence of recurrent disease for more than 10 years. As the literature shows that it is currently not possible to differentiate between CTME and MEA, the choice for radical mastoidectomy was a reliable decision.

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PART II

Review of the Literature

CHAPTER V

Clinical Recommendations on the Treatment of Neuroendocrine Carcinoma of the Larynx

A Meta-Analysis of 436 Reported Cases

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Abstract

Introduction Current recommendations on the treatment of neuroendocrine carcinoma of the larynx (NCL) are based on anecdotal evidence. With this meta-analysis we aim to provide clinicians with more substantiated guidelines in order to improve the treatment outcome of patients affected.

Material and Methods A structured literature search for all research concerning NCL was performed against the MEDLINE and EMBASE databases. Available data was normalized, pooled and statistically analyzed.

Results 436 cases of NCL were extracted from 182 studies, of which 23 typical carcinoid (TC), 163 atypical carcinoid (AC), 183 small cell neuroendocrine carcinoma (SCNC), 29 large cell neuroendocrine carcinoma (LCNC) and 38 unspecified carcinoid tumors. 5-Year disease-specific survival (DSS) was 100% for TC, 53% for AC, 19% for SCNC, 15% for LCNC ($p < .001$). Patients with an AC treated with surgery had better DSS than those treated with radiotherapy (60% versus 54%, $p = .035$). Post-operative radiotherapy did not result in better DSS in AC. Patients with an AC, not undergoing surgical treatment of the neck developed isolated regional recurrence in 30% of cases ($p = .001$). Radio-chemotherapy yielded the best DSS for SCNC compared to other modalities (31% versus 13%, $p = .001$).

Conclusion TC can be treated by local excision alone. AC do not appear to respond well to radiotherapy and are best managed through radical surgical excision in combination with elective neck dissection. Patients with a SCNC or LCNC appear to benefit most from chemoradiotherapy.

Introduction

Neuroendocrine carcinoma of the larynx (NCL) are a rare group of tumors believed to originate from pluripotent stem cells.[1] Four histological subtypes are distinguished based on differentiation grade and cell size.[2,3] Well- and moderately differentiated NCL are referred to as typical carcinoid and atypical carcinoid, respectively. Poorly-differentiated NCL are divided in small and large cell neuroendocrine carcinoma. This distinction has therapeutic implications as the clinical behavior and response to treatment differs greatly between subtypes.[4,5] A proper delineation of these differences has been hampered by the relatively small number of patients affected.

The literature on NCL is fragmented over numerous case reports and series of small sample size[3,6-186], often with contradicting results, making it difficult to decide on an appropriate treatment strategy. Consequently, physicians facing these tumors often resort to treatment paradigms developed for better known neoplasms (e.g. squamous cell carcinoma). However, in order to achieve optimal treatment outcome, a very different approach is required for NCL.

This study aims to better describe the clinical behavior of NCL with regard to patient characteristics, treatment outcome and prognosis by combining all available data on NCL in the literature. In particular, we want to provide physicians with guidelines for the optimal treatment of their patients.

Material and Methods

A structured literature search for all clinical research concerning NCL was performed against the MEDLINE and EMBASE databases. Keywords included neuroendocrine carcinoma, carcinoid, small cell (neuroendocrine) carcinoma, oatcell (carcinoma), head and neck, laryngeal and larynx. Applicable articles were reviewed for references to additional research. Full text copies were retrieved for all studies published in English. Where available, English abstracts of articles published in other languages were included. Data on age, gender, duration of symptoms, tobacco use, tumor location, tumor stage on presentation, treatment, recurrence, recurrence location, disease-specific survival (DSS), overall survival, local control, regional control and distant metastasis free survival were extracted, normalized and pooled in a single dataset. Duplicate cases were identified and

TABLE 1 Neuroendocrine Carcinoma of the Larynx - Patient & Treatment Characteristics

	CNOS	TC	AC	SCNC	LCNC
Age (Median, Range)	61 (36 - 82)	62 (43 - 72)	63 (20 - 83)	59 (23 - 91)	60 (31 - 81)
Male Gender (N, %)	25 (71.4)	12 (54.5)	112 (70.9)	127 (81.4)	19 (70.4)
Duration of Symptoms (Median, Range)	12 (1 - 132)	9 (1 - 120)	4 (1 - 180)	3 (1 - 24)	4 (1 -72)
History of Tobacco Use	8 (80.0)	11 (73.3)	92 (78.6)	98 (94.2)	19 (90.5)
Tumor Location (N, %)					
Supraglottic	28 (82.4)	21 (95.5)	125 (93.3)	84 (57.9)	22 (81.5)
Glottic	1 (2.9)	0 (0)	6 (4.5)	13 (9.0)	1 (3.7)
Subglottic	0 (0.0)	1 (4.5)	3 (1.8)	23 (15.9)	2 (7.4)
Multiple	5 (14.7)	0 (0)	0 (0.0)	25 (17.2)	2 (7.4)
Tumor Stage (N, %)					
Stage I	5 (22.7)	10 (83.3)	72 (55.0)	11 (9.6)	3 (13.0)
Stage II	1 (4.5)	1 (8.3)	13 (9.9)	15 (13.2)	2 (8.7)
Stage III	3 (13.6)	1 (8.3)	7 (5.3)	12 (10.5)	2 (8.7)
Stage IV	13 (59.1)	0 (0)	39 (29.8)	76 (66.7)	16 (69.6)
Treatment (N, %)					
Surgery	24 (70.6)	16 (76.2)	91 (58.0)	22 (14.0)	12 (42.9)
Radiotherapy	1 (2.9)	13 (14.3)	11 (7.0)	19 (12.1)	6 (21.4)
Chemotherapy	0 (0.0)	0 (0)	1 (0.6)	9 (5.7)	0 (0.0)
Surgery & Radiotherapy	7 (20.6)	2 (9.5)	44 (28.0)	25 (15.9)	3 (10.7)
Surgery & Chemotherapy	1 (2.9)	0 (0)	2 (1.3)	7 (4.5)	1 (3.6)
Radiotherapy & Chemotherapy	0 (0.0)	0 (0)	4 (2.5)	54 (34.4)	4 (14.3)
Surgery & Radiotherapy & Chemotherapy	0 (0.0)	0 (0)	3 (1.9)	14 (8.9)	2 (7.1)
Pallitation	1 (2.9)	0 (0)	1 (0.6)	7 (4.5)	0 (0.0)

CNOS, Carcinoid tumor Not Otherwise Specified; TC, Typical Carcinoid; AC, Atypical Carcinoid; SCNC, Small Cell Neuroendocrine Carcinoma; LCNC, Large Cell Neuroendocrine Carcinoma

removed. In order to be able to evaluate the impact of time on the proper classification of subtypes and treatment outcome, cases were divided in two groups: those reported before and after 1996, 5 years after the formal separation of subtypes by the WHO.[2] Statistical analysis was performed using IBM SPSS Statistics 20 for Microsoft Windows. Continuous variables were compared using the Student's *t*-test. Categorical data was analyzed using the

exact chi-square test. Survival estimates were calculated using the Kaplan-Meier method and compared using the log-rank test. Alpha was set at 0.05. Reported confidence intervals are for 95% probability.

Results

After filtering the initial search results on title and abstract, 361 articles remained. Of these, 182 contained clinical data. Full-text articles were available for all 153 studies in English. The 29 papers written in other languages provided English abstracts, yielding a total of 436 cases of NCL available for analysis. Of these, 23 concerned typical carcinoid tumors, 163 atypical carcinoid tumors, 183 small cell neuroendocrine carcinoma, 29 large cell neuroendocrine carcinoma and 38 unspecified carcinoid tumors.

TABLE 2 Neuroendocrine Carcinoma of the Larynx - Recurrence & Survival Data

	CNOS	TC	AC	SCNC	LCNC
Recurrence (N, %)	14 (51.9)	7 (35.0)	80 (62.5)	65 (58.0)	17 (81)
Recurrence Location (N, %)					
Local	2 (15.4)	2 (33.3)	13 (18.1)	3 (4.7)	0 (0.0)
Locoregional	4 (30.8)	2 (33.3)	7 (9.7)	8 (12.5)	3 (17.6)
Distant	2 (15.4)	0 (0)	28 (38.9)	37 (57.8)	4 (23.5)
Local & Locoregional	0 (0.0)	0 (0)	2 (2.8)	0 (0.0)	2 (11.8)
Local & Distant	3 (23.1)	0 (0)	10 (13.9)	6 (9.4)	2 (11.8)
Locoregional & Distant	2 (15.4)	2 (33.3)	8 (11.1)	9 (14.1)	6 (35.3)
Local & Locoregional & Distant	0 (0.0)	0 (0)	4 (5.6)	1 (1.6)	0 (0.0)
Median Survival (months, SE)					
5-Year Disease-specific Survival	56.4 (12.4)	83.3 (15.2)	57.7 (4.7)	19.3 (5.5)	15.3 (9.0)
5-Year Overall Survival	40.2 (11.2)	81.7 (12.3)	51.5 (4.6)	14.8 (4.7)	14.4 (8.5)
5-Year Local Control	81.3 (8.5)	81.7 (12.3)	82.9 (4.7)	91.6 (3.4)	88.2 (7.8)
5-Year Locoregional Control	63.5 (14.4)	60.0 (20.1)	91.2 (3.7)	84.0 (4.0)	20.9 (12.7)
5-Year Distant Metastatis Free Survival	66.5 (11.8)	83.3 (15.2)	71.7 (5.2)	46.5 (7.5)	28.5 (11.9)

CNOS, Carcinoid tumor Not Otherwise Specified; TC, Typical Carcinoid; AC, Atypical Carcinoid; SCNC, Small Cell Neuroendocrine Carcinoma; LCNC, Large Cell Neuroendocrine Carcinoma

Patient & Treatment Characteristics

Patient and treatment characteristics are presented in Table 1. The median age on presentation lay around the 6th decade of life. There was a male preponderance of 3:1 for all subtypes except typical carcinoid tumors, for which no gender predilection was observed. The median duration of symptoms varied between 3 and 12 months. The majority of patients had a history of tobacco use (73.3 - 94.2%). The tumor was most often located in the supraglottis (57.9 - 95.5%). Patients with a poorly differentiated subtype (small or large cell neuroendocrine carcinoma) more often presented with advanced disease (66.7% and 69.6% respectively) compared to the other subtypes (0.0% for typical carcinoid tumors, 29.8% for atypical carcinoid tumors, $p < .001$). Patients with a typical carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma or unspecified carcinoid tumor were most often treated with surgery (42.9% - 76.2%), while there was a preference for radio-chemotherapy in those with a small cell neuroendocrine carcinoma (34.4%).

Composite Tumors & Paraneoplastic Syndromes

A small percentage of cases presented as a composite tumor (n = 22, 5.0%) with features of both NCL and squamous cell carcinoma on histological examination. The vast majority of these patients had a small cell neuroendocrine carcinoma (n = 20, 90.9%).[27,40,42,50,55,69,96,99,131,146,154,172,182] The other two cases concerned an atypical[174] and an unspecified carcinoid tumor.[62] In an even smaller number of cases, ectopic hormone

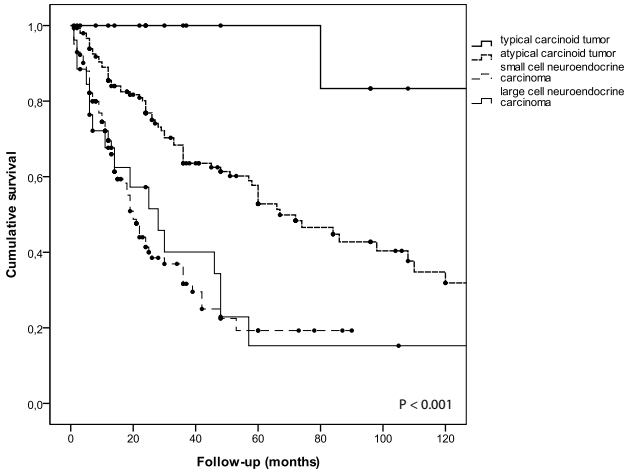

FIGURE 1
Kaplan-Meier plots of 5 and 10-year disease-specific survival for neuroendocrine carcinoma of the larynx per tumor subtype.

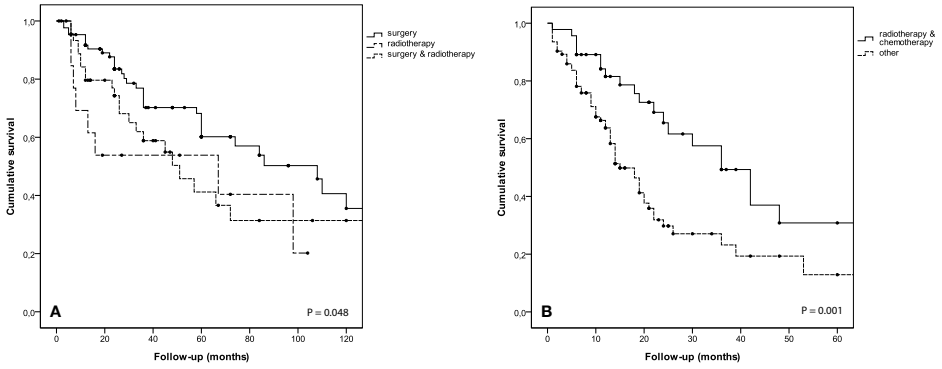

FIGURE 2
Kaplan-Meier plots of disease-specific survival for atypical carcinoid tumors (A) and small cell neuroendocrine carcinoma (B) per choice of treatment

production was described (n = 14, 3.2%). This concerned the production of calcitonin[86,98,116,114,126,83], serotonin[48,86,109,91], ADH[23,108,79], ACTH[47], somatostatin[83] and CEA[83]. Only one study reported clinical signs of the carcinoid syndrome.[109]

Recurrence

Recurrence and survival data are presented in Table 2. The recurrence rate ranged from 35.0% for typical carcinoid tumors to 81.0% for large cell neuroendocrine carcinoma. Patients with an atypical carcinoid tumor or poorly differentiated subtype more often developed distant metastasis compared to those with a typical carcinoid tumor (42.0 - 57.1% versus 11.1%, $p = .016$). The 5-year local control ranged from 81.7 - 91.6%. The 5-year regional control was 60.0% for typical carcinoid tumors, 91.2% for atypical carcinoid tumors, 84.0% for small cell neuroendocrine carcinoma and 34.6% for large cell neuroendocrine carcinoma. There was a significant difference in 5-year distant metastasis free survival with 83.3% for typical carcinoid tumors, 67.2% for atypical carcinoid tumors, 46.5% for small cell neuroendocrine carcinoma and 34.7% for large cell neuroendocrine carcinoma ($p = .001$). Patients with an atypical carcinoid tumor, not undergoing surgical treatment of the neck, developed regional recurrence without local recurrence in 29.8% of cases versus 0% for patients undergoing neck dissection ($p < .001$). For the other subtypes, not enough data was available to estimate the influence of (elective) treatment of the neck.

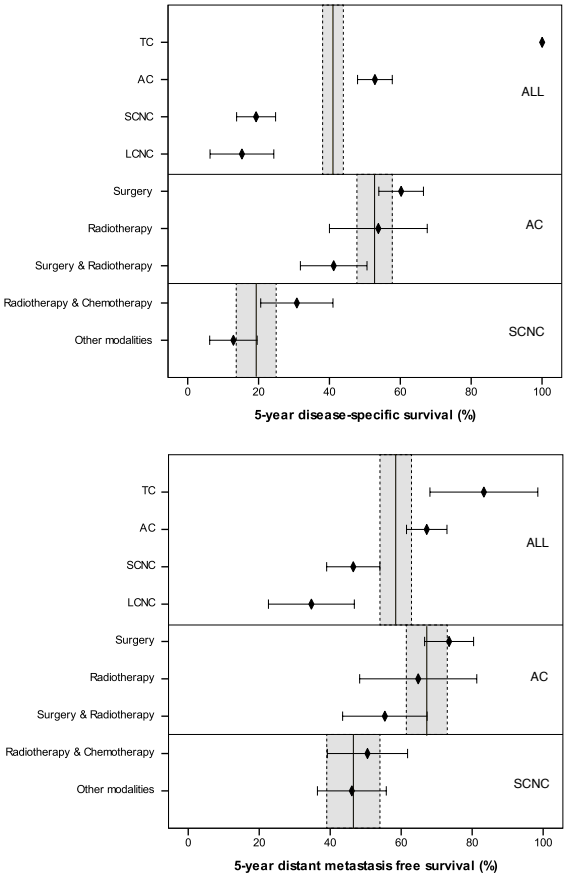

FIGURE 3
Overview of 5-year disease-specific survival (DSS) and metastasis free survival with 95% confidence interval for neuroendocrine carcinoma of the larynx, ordered by subtype and initial treatment. The grey bar represents the 95% confidence interval of the 5-year DSS of the group. TC, Typical Carcinoid tumors; AC, Atypical Carcinoid tumors; SCNC, Small Cell Neuroendocrine Carcinoma; LCNC, Large Cell Neuroendocrine Carcinoma.

Survival

Treatment outcome was strongly dependent on histological subtype (Figure 1), with a 5-year DSS of 100% for typical carcinoid tumors versus 52.8% for atypical carcinoid tumors, 19.3% for small cell neuroendocrine carcinoma and 15.3% for large cell neuroendocrine carcinoma ($p < .001$). Extending the follow-up period to 10 years revealed a further decrease in the DSS for patients with an atypical carcinoid tumor to 31.9%. No significant changes in the DSS were observed for the other subtypes. Patients with an atypical carcinoid tumor that presented with stage IV disease had significantly worse 5-year DSS compared to those with stage I to III (9.3% versus 66.7 - 72.9%, $p < .001$). Tumor stage on presentation was also a strong predictor of 5-year DSS in small cell neuroendocrine carcinoma (8.5% for stage IV versus 25.9 - 45.8% for stage I - III, $p = .002$).

Patients with an atypical carcinoid tumors treated with surgery had better 5-year DSS compared to those treated with radiotherapy (60.2% versus 53.8%, p = .035). Post-operative radiotherapy did not result in better DSS in atypical carcinoid tumors (Figure 2a). This remained to be the case after correcting for tumor stage on presentation. Radio-chemotherapy yielded the best 5-year DSS for small cell neuroendocrine carcinoma compared to other modalities (30.8% versus 12.9%, p = .001, Figure 2b). No reliable estimate could be calculated for the relationship between tumor stage on presentation or choice of treatment and DSS for typical carcinoid tumors and large cell neuroendocrine carcinoma, as numbers were too small. A graphical overview of the 5-year DSS and distant metastasis free survival ordered by subtype and treatment is presented in Figure 3.

Trends Over Time

Comparing cases reported before and after 1996 revealed no significant differences in patient or treatment characteristics except for the tumor stage on presentation in the atypical carcinoid group, which was lower for patients treated before 1996 (p < .001). No changes were observed in DSS for atypical carcinoid tumors and small cell neuroendocrine

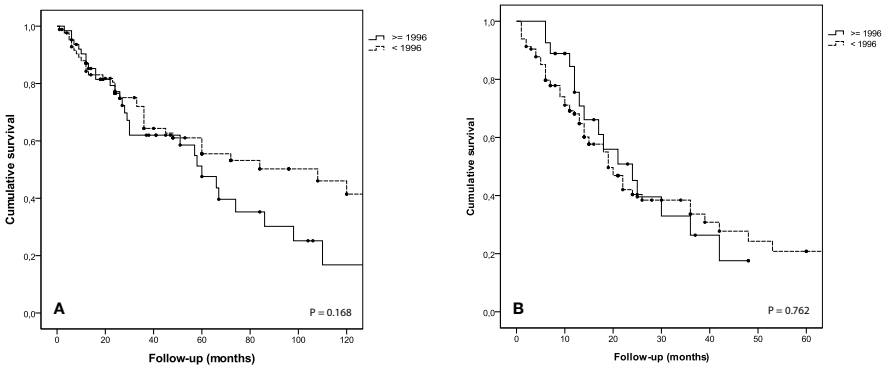

FIGURE 4

Kaplan-Meier plots of disease-specific survival for atypical carcinoid tumors (A) and small cell neuroendocrine carcinoma (B) per publication date.

carcinoma (Figure 4). This remained to be the case after correcting for tumor stage on presentation.

Discussion

General

The first case of a NCL was reported by Goldman et al. in 1969 whom described the tumor as a 'carcinoid' in reference to its similarity to carcinoid tumors of the appendix and small intestine.[6] Approximately three years later Olofsson et al. reported the first case of a small cell neuroendocrine carcinoma of the larynx[8], followed by Duvall et al. who, in 1983, were the first to use the adjective 'atypical' in order to differentiate between well and moderately differentiated carcinoid tumors.[39] The resulting three subtypes were formalized in the 1991 WHO classification[2], which, despite the inception of other classification systems, remains the standard today. However, most authors agree that large cell neuroendocrine carcinoma, currently a subset of atypical carcinoid tumors, is best regarded as a separate entity since its clinical behavior is markedly more aggressive.[3] Due to the lack of data on these tumors, various therapeutic strategies have been employed over the years, the results of which were reported in numerous small series and case reports. Although these studies resulted in a better understanding of the clinical behavior of NCL, no improvement in treatment outcome could be detected in our analysis. This comes as no surprise as treatment selection has remained heterogeneous. By combining all available data in the literature, this meta-analysis provides the most comprehensive body of evidence upon which to base treatment selection.

Typical Carcinoid

Typical carcinoid tumors are the least prevalent subtype of NCL. They present almost exclusively as stage I supraglottic tumors. According to our analysis, their well-differentiated nature translates to the most favorable clinical course among NCL. However, earlier studies, among which two meta-analyses on carcinoids by Soga, reported a 5-year survival rate of only 48.7% for typical carcinoid tumors.[187,188,189] This discrepancy is very likely due to the inclusion of cases of atypical carcinoid tumors as typical carcinoid tumors. Not all reports in the literature provide sufficient data to be confident of the histological nature of the tumor. Therefore, in our study we chose to include a group called "unspecified

carcinoid tumors" which includes data from reports with insufficient or contradicting data concerning histology. The 5-year survival rate in this group is estimated to be 40.2%.

Inclusion of cases from this group in the typical carcinoid group would readily explain the difference in survival found in the study by Soga and that of ours. Therefore, we think that, if an accurate histological diagnosis of typical carcinoid tumor is made by an experienced head and neck pathologist, surgical excision, either through partial laryngectomy or CO2 laser resection, is the preferred treatment.

Atypical Carcinoid

Atypical carcinoid tumors represent the largest group of NCL. As with typical carcinoid tumors, there is a strong preference for a supraglottic tumor location. However, the stage on presentation is more diverse with nearly 30% of patients presenting with advanced disease due to early distant metastasis. The recommended treatment for atypical carcinoid tumors is radical surgical resection. Patients not undergoing surgical treatment of the neck developed regional recurrence in the absence of a second primary tumor in 29.8% of cases versus 0% of patients undergoing neck dissection ($p < .001$). Therefore, elective treatment of the neck is indicated and should only be restricted to bilateral dissection of levels IIA and III if the tumor does not extend beyond the supraglottis.[5] The radio-sensitivity of atypical carcinoid tumors is questionable. Patients treated with primary radiotherapy had a lower DSS compared to those treated with surgery (53.8% versus 60.2%, $p = .035$), while patients receiving post-operative radiotherapy fared even worse (41.2%, $p = .050$). Correcting for tumor stage on presentation revealed similar results. Therefore, contrary to the most recent guidelines[5], radiotherapy appears to have no role in the treatment of atypical carcinoid tumors. Despite adequate treatment most patients will develop a recurrence (62.5%), many of them with distant metastasis (69.4%). It is important to note that recurrences can occur after the conventional 5-year follow-up period. Therefore, it is advisable to extend this period to 10 years.

Small Cell Neuroendocrine Carcinoma

Although considered much rarer than atypical carcinoid tumors, most cases returned by our search involved small cell neuroendocrine carcinoma. Small cell neuroendocrine carcinoma have a more varied origin in comparison to the other subtypes. However, most tumors still arise from the supraglottis (57.9%). The majority of patients (66.7%) present with stage IV

disease due to early distant metastasis. The preferred treatment is similar to that of small cell neuroendocrine carcinoma of the lung and consists of a combination of radio- and chemotherapy. While this approach yielded the best results in our analysis, outcome remained poor with a 5-year DSS of just 30.8% versus 12.9% for the other modalities ($p = .001$).

Large Cell Neuroendocrine Carcinoma

It is hard to estimate the true incidence of large cell neuroendocrine carcinoma because the WHO classification does not make a distinction between atypical carcinoid tumors and large cell neuroendocrine carcinoma. However, from our data we can deduce that large cell neuroendocrine carcinoma are much more aggressive, closely resembling the clinical behavior of small cell neuroendocrine carcinoma, albeit with a stronger predilection for the supraglottis (81.5%). Distant metastasis occurs early, causing most patients to present with advanced disease (69.6%). Unfortunately numbers are too small to make any statements in regard to the efficacy of different treatment modalities. Based on the current data, we consider a systemic approach, similar to that of small cell neuroendocrine carcinoma, warranted in treating these patients.

Composite Tumors & Paraneoplastic Syndromes

A small percentage of cases reported the presence of both a neuroendocrine and a squamous cell carcinoma in the same patient. These cases mainly concerned small cell neuroendocrine carcinoma. As small cell neuroendocrine carcinoma are considered more aggressive than squamous cell carcinoma, these patients are best treated as small cell neuroendocrine carcinoma. However, in patients with an atypical carcinoid tumor combined with a squamous cell carcinoma, adding radiotherapy to the treatment regimen warrants consideration.

As evidenced by a small number of reports, NCL have the potential to produce several different hormones. However, almost none of the patients concerned developed a true paraneoplastic syndrome (e.g. the classic carcinoid syndrome with flushing and diarrea). Therefore, the role of routine evaluation of hormone levels in patients with NCL remains questionable.

Trends Over Time

The 1991 WHO classification of NCL coincided with the advancement of immunohistochemistry in routine diagnostic processing, allowing for a more accurate separation of subtypes and consequently, the potential for better treatment selection and outcome. In order to allow for sufficient follow-up we added 60 months to this date, separating cases reported before and after 1996. Surprisingly, we were not able to detect a significant difference in any of the variables included in our research other than tumor stage on presentation. The latter can be explained by the inclusion of a large study on T1 tumors in the pre-1996 group.[72] However, correcting for tumor stage on presentation did not explain the lack of improvement in treatment outcome one would expect considering the advancements made in histopathology, radiotherapy, and available data on NCL over time. Instead, the choice of treatment was uniformly heterogeneous in both groups, stressing the importance of clear guidelines in treating these neoplasms.

Limitations

Obviously, the retrospective nature of this study limits our ability to make definitive statements with regard to the clinical behavior of NCL. Cases were reported by various institutions over a protracted timeline and involved the use of different diagnostic and therapeutic modalities. Although the consistency of our results between different time periods somewhat negates these limitations, a more consistent approach to studying these tumors is required. As prospective data is nearly impossible to acquire, a multi-center retrospective study with a consistent protocol is the next best step in expanding our knowledge of these rare neoplasms.

Conclusion

NCL represent a pluriform group of tumors with characteristics differing from squamous cell carcinoma. It is important that physicians are aware of these differences and the need to deviate from the standard therapeutic approach they have grown accustomed to in their daily routine with squamous cell carcinoma. The high propensity for recurrence and variable response to radiotherapy require a treatment strategy that takes tumor subtype into consideration and is less concerned with the T stage on presentation. Typical carcinoid tumors represent the more benign end of the spectrum and can be treated by local excision alone. Atypical carcinoid tumors do not appear to respond well to radiotherapy and are best managed through radical surgical excision in combination with bilateral neck dissection.

Patients with a small cell neuroendocrine carcinoma or large cell neuroendocrine carcinoma appear to benefit most from a combination of radio- and chemotherapy, although survival remains poor. For patients with an atypical carcinoid tumor, it is advisable to extend the follow-up period to 10 years as late recurrences are common. A multi-center retrospective study with a consistent protocol is in order to further our understanding of these rare neoplasms.

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CHAPTER VI

Meta-Analysis of 701 Published Cases of Sinonasal Neuroendocrine Carcinoma

The Importance of Differentiation Grade in Determining Treatment Strategy

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Abstract

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

Material and Methods 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.

Results 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%, $p < .001$). In SNUC, radiotherapy was a beneficial supplement to surgery (5-year DSS 54.7% versus 15.7%, $p = .027$), while radiotherapy as monotherapy performed poorly (5-year DSS 17.9%). Chemotherapy did not appear to contribute to survival.

Discussion Based on our findings, we can conclude that the most important predictors of survival in SNC are differentiation grade and associated choice of treatment strategy. 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 variant.

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 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 (CI) 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.

TABLE 1 Patient Characteristics of Sinonasal Neuroendocrine Carcinoma

	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)	**.023**
Gender (male, %)	378 (64.6)	70 (56.9)	239 (68.7)	69 (60.5)	**.038**
Tumor Stage (%)					
Stage I	25 (5.0)	8 (10.4)	8 (2.5)	9 (9.2)	**.002**
Stage II	38 (7.6)	15 (19.5)	10 (3.1)	13 (13.3)	**< .001**
Stage III	61 (12.2)	10 (13.0)	45 (13.8)	6 (6.1)	.125
Stage IV	375 (75.0)	44 (57.1)	262 (80.6)	69 (70.4)	**< .001**
Stage IVA	116 (23.3)	16 (20.8)	67 (20.7)	33 (33.7)	**.025**
Stage IVB	147 (29.5)	22 (28.6)	104 (32.2)	21 (21.4)	.116
Stage IVC	22 (4.4)	2 (2.6)	17 (5.2)	3 (3.1)	.480
Treatment (%)					
Surgery	56 (10.3)	22 (24.4)	15 (4.3)	19 (17.4)	**< .001**
Radiotherapy	52 (9.5)	4 (4.4)	43 (12.4)	5 (4.6)	**.011**
Chemotherapy	12 (2.2)	0 (0.0)	7 (2.0)	5 (4.6)	.080
Surgery & Radiotherapy	88 (16.1)	22 (24.4)	54 (15.6)	12 (11.0)	**.033**
Surgery & Chemotherapy	12 (2.2)	3 (3.3)	2 (0.6)	7 (6.4)	**.006**
Surgery & Radiotherapy & Chemotherapy	150 (27.5)	16 (17.8)	110 (31.7)	24 (22.0)	**.015**
Radiotherapy & Chemotherapy	138 (25.3)	21 (23.3)	85 (24.5)	32 (29.4)	.546
Palliative care	38 (7.0)	2 (2.2)	31 (8.9)	5 (4.6)	**.044**
Median Disease-specific Survival	36 (27 - 45)	174 (69 - 279)	28 (23 - 33)	22 (6 - 38)	**< .001**
Median Overall Survival	32 (25 - 39)	120 (55 - 185)	25 (21 - 29)	22 (14 - 30)	**< .001**

SNEC, well or moderately differentiated Sinonasal Neuroendocrine Carcinoma; SNUC, Sinonasal Undifferentiated Carcinoma; SmCC, Sinonasal small Cell Carcinoma. Survival in months.

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% ($p < .001$). 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, $p < .001$). SNUC were more often treated with radiotherapy as monotherapy compared to SNEC and SmCC (12.4% versus 4.4% and 4.6% respectively, $p = .011$), while SNEC were more frequently treated with surgery combined with radiotherapy (24.4% versus 15.6% for SNUC and 11.0% for SmCC, $p = .033$). SNUC was rarely managed with a combination of surgery and chemotherapy (0.6% versus 3.3% for SNEC and 6.4% for SmCC, $p = .006$), 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, $p = .015$).

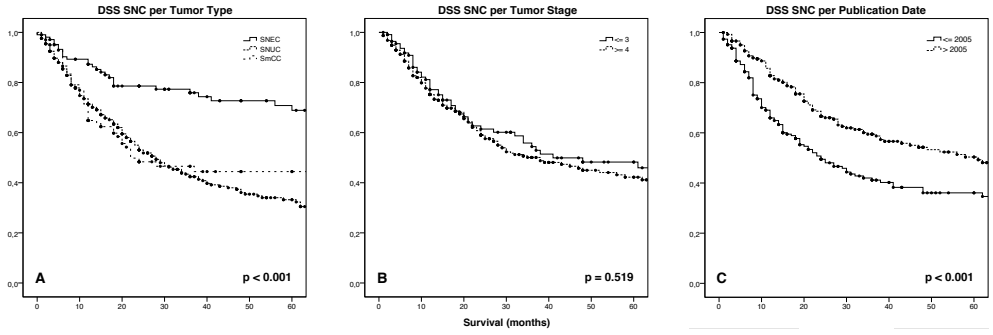

FIGURE 1 Disease-specific survival (DSS) of sinonasal neuroendocrine carcinoma (SNC) per tumor type, stage and publication date. SNEC, well or moderately differentiated Sinonasal Neuroendocrine Carcinoma; SNUC, Sinonasal Undifferentiated Carcinoma; SmCC, Sinonasal small Cell Carcinoma.

TABLE 2 Univariate Analysis of Factors Influencing the Disease-Specific Survival of Sinonasal Neuroendocrine Carcinoma

	OR (95% CI)	P-value
Age	1.009 (1.001 - 1.017)	**.019**
Gender (male as reference)	0.874 (0.660 - 1.159)	.351
Tumor Type		
SNEC	1 (reference)	
SNUC	2.601 (1.783 - 3.794)	**< .001**
SmCC	2.410 (1.539 - 3.774)	**< .001**
Tumor Stage		
Stage I	1 (reference)	
Stage II	2.152 (0.781 - 5.930)	.139
Stage III	3.672 (1.425 - 9.460)	**.007**
Stage IV	3.663 (1.462 - 9.180)	**.006**
Stage IVA	2.210 (0.871 - 5.607)	.095
Stage IVB	3.050 (1.224 - 7.597)	**.017**
Stage IVC	7.612 (2.695 - 21.499)	**< .001**
Treatment (decoupled)		
Surgery	0.521 (0.400 - 0.677)	**.000**
Radiotherapy	0.898 (0.631 - 1.279)	.898
Chemotherapy	1.243 (0.944 - 1.636)	.121
Treatment		
Surgery	1 (reference)	
Radiotherapy	2.261 (1.329 - 3.847)	**.003**
Chemotherapy	6.182 (2.803 - 13.633)	**< .001**
Surgery & Radiotherapy	0.779 (0.444 - 1.366)	.383
Surgery & Chemotherapy	1.810 (0.801 - 4.090)	.154
Surgery & Radiotherapy & Chemotherapy	1.052 (0.638 - 1.735)	.905
Radiotherapy & Chemotherapy	1.712 (1.050 - 2.791)	**.031**
Palliative care	15.769 (7.408 - 33.567)	**< .001**

OR, Odds Ratio; CI, Confidence Interval; SNEC, well or moderately differentiated Sinonasal Neuroendocrine Carcinoma; SNUC, Sinonasal Undifferentiated Carcinoma; SmCC, Sinonasal small Cell Carcinoma.

TABLE 3 Multivariate Analysis of Factors* Influencing the Disease-Specific Survival of Sinonasal Neuroendocrine Carcinoma Treated with Curative Intent per Tumor Type

	OR (95% CI)	P-value
Well or Moderately Differentiated Sinonasal Neuroendocrine Carcinoma		
Surgery	1 (reference)	
Radiotherapy	-	-
Chemotherapy	-	-
Surgery & Radiotherapy	4.604 (0.514 - 41.212)	.172
Surgery & Chemotherapy	6.950 (0.355 - 135.961)	.201
Surgery & Radiotherapy & Chemotherapy	4.804 (0.370 - 62.430)	.230
Radiotherapy & Chemotherapy	11.464 (1.125 - 116.796)	**.039**
Sinonasal Undifferentiated Carcinoma		
Surgery	1 (reference)	
Radiotherapy	0.643 (0.254 - 1.632)	.353
Chemotherapy	1.644 (0.443 - 6.105)	.458
Surgery & Radiotherapy	0.337 (0.125 - 0.908)	**.032**
Surgery & Chemotherapy	3.164 (0.359 - 27.890)	.300
Surgery & Radiotherapy & Chemotherapy	0.368 (0.147 - 0.921)	**.033**
Radiotherapy & Chemotherapy	0.471 (0.185 - 1.200)	.115
Sinonasal Small Cell Carcinoma		
Surgery	1 (reference)	
Radiotherapy	3.669 (0.677 - 19.900)	.132
Chemotherapy	6.964 (1.104 - 43.930)	**.039**
Surgery & Radiotherapy	0.529 (0.123 - 2.278)	.393
Surgery & Chemotherapy	1.057 (0.239 - 4.669)	.942
Surgery & Radiotherapy & Chemotherapy	0.811 (0.234 - 2.806)	.741
Radiotherapy & Chemotherapy	1.078 (0.370 - 3.146)	.890

OR, Odds Ratio; CI, Confidence Interval. Reported odds ratios for patient dying of disease.
* 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.

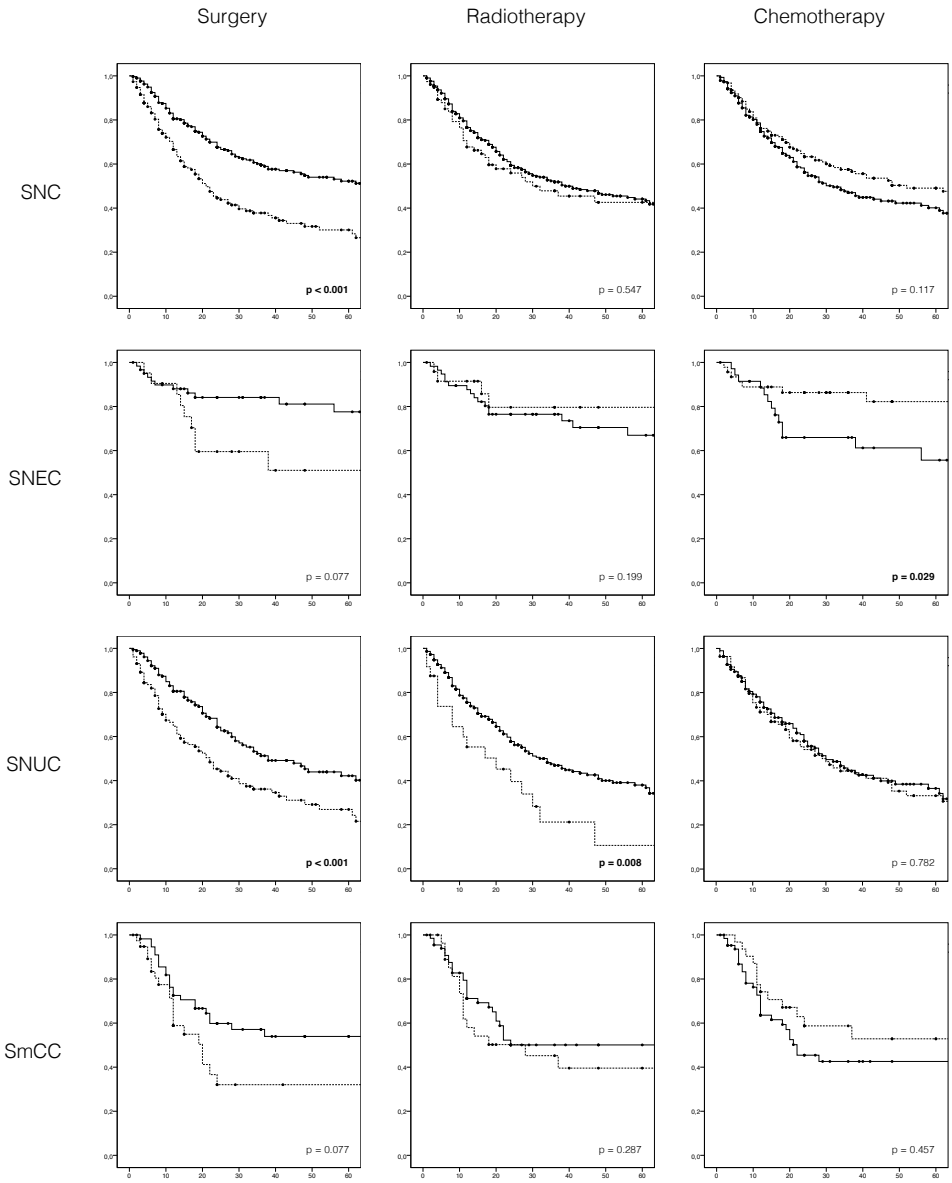

FIGURE 2

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.

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). Figure 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 ($p < .001$). There was no significant difference between the 5-year DSS of SNUC and SmCC ($p = .792$). Comparable results were produced by the univariate analysis presented in Table 2. Overall, tumor stage did not significantly affect survival as shown in Figure Ib. 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, $p = .095$).

Figure 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 ($p < .001$).

While there was a trend favoring surgery in SNEC, no significant difference could be observed ($p = .077$). Radiotherapy did not yield better results in these patients ($p = .199$), while the application of chemotherapy was associated with a significantly unfavorable outcome (5-year DSS of 55.7% versus 82.2%, $p = .029$).

Both surgery and radiotherapy were associated with significantly better outcome in patients with SNUC (5-year DSS of 42.2% versus 26.9%, $p < .001$, and 38.0% versus 10.6%, $p = .008$, respectively). The application of chemotherapy did not improve survival in these patients (5-year DSS of 36.6% versus 33.3%, $p = .782$).

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%, $p = .077$), 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, $p = .287$ and 42.6% for

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; SmCC, Sinonasal small Cell Carcinoma.

patients treated with chemotherapy versus 52.9% for those without, $p = .287$ 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 surgery had a significantly higher change of dying of disease (OR 11.464, CI 1.125 - 116.796, $p = .039$). 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, $p = .032$ and OR 0.368, CI 0.147 - 0.921, $p = .033$ 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 combination of surgery and radiotherapy (5-year DSS of 54.7% and 71.3% respectively).

Trends Over Time

As shown in Figure 1c, cases reported after 2006 show improved outcome compared to those reported before this date (5-year DSS of 50.4% versus 36.1%, $p < .001$). This trend was present for all tumor types, although only SNUC remained significant after sub-analysis ($p = .001$). 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 stage. 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 a 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 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.

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

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, Figure 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, due to semantic deficiencies in the literature, no strong recommendations can be made in this regard. 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.

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PART III

Human Papillomavirus Infection in Neuroendocrine Carcinoma of the Larynx

CHAPTER VII

Is Human Papillomavirus Involved in Laryngeal Neuroendocrine Carcinoma?

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Abstract

Introduction The purpose of this study was to detect human papillomavirus (HPV) infection in laryngeal neuroendocrine carcinoma (LNEC) and to explore the possible relationship between HPV induced malignant transformation and prognosis in LNEC.

Material and Methods Ten cases of LNEC from a tertiary referral hospital were retrospectively analyzed. Clinical data were subtracted from patients' files. Pretreatment biopsy material was tested for the presence of HPV6, 11, 16 and 18 using a PCR-based detection method. Immunohistochemical staining was performed for Ki-67, $p16^{INK4A}$ and p53 expression.

Results All cases were negative for the low-risk HPV types HPV6 and HPV11 that are associated with laryngeal papillomatosis. High-risk HPV was detected in 2 cases; an atypical carcinoid was positive for HPV16 and a large cell neuroendocrine carcinoma for HPV18. Both HPV-positive tumors had a high Ki-67 labeling index. Two of the 4 cases with a good response to therapy were hrHPV-positive (both HPV DNA positive) compared to none of the 5 poor responders.

Conclusion Our findings show that HPV may play a role in the pathogenesis of LNEC. The relationship between HPV, improved prognosis and good response to therapy for squamous cell carcinoma of the head and neck may also be true for a subset of LNEC.

Introduction

Human papillomavirus (HPV) is well known for its involvement in the carcinogenesis of cervical cancer with an estimated prevalence of almost 100% and mainly concerns high-risk HPV types (hrHPV) including HPV 16, 18, 31, 33, 45.[1] HrHPV has also been implicated in oropharyngeal[2,3] and laryngeal cancer.[4] The presence of hrHPV in head and neck squamous cell carcinoma (HNSCC) was reported to be associated with a good response to radiotherapy.[5,6] For oropharyngeal cancer in particular, a strong correlation has been established between the response to therapy and the presence of hrHPV in tumor tissue.[7] This association has led to an increased interest in the relationship between HPV and other tumors of the head and neck region.

A classical site in the head and neck area affected by HPV is the larynx. Most cases with laryngeal papillomatosis are associated with low-risk HPV (lrHPV) types HPV6 and HPV11. In a recent review[4], it is concluded that the role of hrHPV infection in laryngeal squamous cell carcinoma (LSCC) is not yet well established, with several larger studies reporting heterogeneous results. The reported presence of hrHPV in LSCC tumor tissue varied between 7.4% and 58.8%. No reliable data are available concerning the prevalence of HPV in normal laryngeal tissue, but estimates run as high as 19%.[4]

Although rare, laryngeal neuroendocrine carcinoma (LNEC) are the second most common group of cancers of the larynx, after LSCC. These neoplasms form a rare group of tumors with divergent clinical behavior and prognosis.[8,9] Little is known about the association of HPV with LNEC. A relationship between HPV and neuroendocrine carcinoma of the cervix has already been established.[10,11] Presently, there is only one case report that tested the tumor tissue of a patient with a LNEC for HPV, with negative result.[12]

The goal of this study was to evaluate the possible involvement of hrHPV and lrHPV in LNEC. Since hrHPV encodes for the oncogenic E6 and E7 proteins inactivating p53 and pRB respectively, resulting in increased proliferation of tumor cells[1], we also performed immunohistochemistry for Ki67, p53 and p16. For this purpose, we selected all LNEC cases treated in our Institute between 1988 and 2010.

Material and Methods

The Dutch nationwide digital database of histo- and cytopathology (PALGA) was queried for LNEC diagnosed at the Department of Pathology of the University Medical Center Groningen (UMCG) between 1988 and 2010. All pathology reports were revised by an experienced head and neck pathologist.

Corresponding clinical data concerning age, gender, smoking history, tumor stage, treatment, disease-free survival, recurrence, salvage treatment, and overall and disease-specific survival were collected from the medical charts and electronic patient dossiers of the Department of Otolaryngology, Head and Neck Surgery of the same institution. Age at onset corresponds with the patients' age in years at the time of the histopathological diagnosis. Disease-free survival was defined as the time in months from the last day of treatment to the first follow-up date where symptoms of recurrence were apparent. Survival times were calculated in months by subtracting the last day of treatment from the last follow-up date. The study was approved by the Institutional Review Board of the UMCG. Patients gave written informed consent prior to biopsies taken.

Sample Collection Procedure, DNA Isolation and HPV Detection and Typing

A 4 µm section was obtained from each paraffin block and stained with hematoxylin and eosin to confirm the presence of tumor tissue in the primary tumor. Primary tumors with < 70% tumor cells were macrodissected to enrich for tumor cells. DNA was extracted from consecutive formalin-fixed paraffin embedded tissue sections as reported previously.[13] Three 10 µm tissue sections were transferred to eppendorf tubes. DNA was extracted by overnight incubation at 56°C in 250µl buffer containing SDS-proteinase K (600µg/ml), heated to 100°C for 5 minutes to inactivated proteinase K and centrifuged at room temperature at 13,000rpm. The aqueous solution was transferred into a new eppendorf tube and directly used for PCR analysis or stored at -20°C. The concentration of DNA was determined using the Nanodrop.

For the detection of high risk HPV, 100ng genomic DNA extracted from the paraffin embedded tissue was analyzed by PCR using HPV16 and HPV18 specific primers as described previously.[14] For the detection of the presence of the low-risk HPV6 and HPV11, genomic DNA was analyzed using specific HPV6-PCR-primers (HPV 6.1:

5'TAGTGGGCCTATGGCTCGTC and HPV 6.2: 5' TCCATTAGCCTCCACGGGTG) and HPV11-specific primers (HPV 11.1: 5'GGAATACATGCGCCATGTGG and HPV 11.2: 5'CGAGCAGACGTCCGTCCTCG) as described previously.[15] On all HPV-negative cases, a general primer-mediated PCR using the HPV consensus primer set GP5+/6+ with subsequent nucleotide sequence analysis was used as described previously.[14]

As a control for the analytical specificity and sensitivity of each hrHPV-PCR, a serial dilution of DNA extracted from CaSki (ATCC; CRL1550; 500 integrated HPV16 copies), HeLa (ATCC; CCL2; 20–50 integrated HPV 18 copies), SiHa (ATCC; HTB35; 1 - 2 integrated HPV16 copies), CC10B (HPV45-positive cell line) and CC11 (HPV67 positive cell line)[16], and HPV-negative cell lines were included in each experiment. DNA - extracted from HPV6- and HPV11-positive laryngeal papillomas that were previous identified - was used for the analytical specificity of the HPV6 and HPV11 PCR.

All standard precautions were taken to avoid contamination of amplification products using separate laboratories for pre- and post-PCR handling. To avoid cross-contamination, a new microtome blade was used each time a new case was sectioned. For quality control, genomic DNA was amplified in a multiplex PCR containing a control gene primer set resulting in products of 100, 200, 300, 400 and 600bp according to the BIOMED-2 protocol.[17] Only DNA samples with PCR products of 300bp and larger were used for the detection of HPV. All samples were tested on DNA extracted from two independent slides (duplicates).

Immunohistochemistry

Paraffin-embedded formalin-fixed sections (4µm) were deparaffinized and antigen retrieval was performed by overnight incubation at 80°C in 0.1M Tris/HCl buffer pH = 9.0 for Ki67, or heating in a microwave oven for 15 minutes in 10mM Tris/1mM EDTA buffer pH = 9.0 for p53. After blocking endogenous peroxidase with 0.3% hydrogen peroxide, sections were stained for one hour at room temperature with an antibody against Ki67 (mouse monoclonal antibody, clone MIB-1, 1:350, DakoCytomation), or p53 (mouse monoclonal, clone DO-7, 1:1000, DakoCytomation) diluted in phosphate buffered saline (PBS) containing 1% bovine serum albumin (BSA). The secondary (rabbit anti-mouse peroxidase) and tertiary (goat anti-rabbit peroxidase) antibodies for Ki67, or Envision (DAKO) for p53 were precipitated using 3.3 diaminobenzidine tetrachloride as a substrate, and slides were

counterstained using hematoxylin. For p16INK4A immunohistochemistry, the CINtecTM Histology kit (MTM Laboratories AG, Germany) was used. Scoring of the immunohistochemical stainings was performed as previously described.[18] For both Ki67 and p53, the percentage of positive nuclear tumor cells was counted. A cut-off above 70% was considered positive for p53 and Ki-67. p16INK4a protein expression was scored as positive if there was a strong and diffuse nuclear and cytoplasmic staining was present in greater than 70% of the malignant cells as described previously.[19]

Results

Clinical Data

A total of 10 cases of LNEC were retrieved from the pathology-database. Formalin-fixed, paraffin-embedded, pretreatment biopsy material was available for all 10 cases. The clinical characteristics and immunohistochemical features of these cases are summarized in Table 1.

There were seven male and three female patients. The median age at the time of diagnosis was 68 years (range, 51 - 81). The histological classification of the tumors was atypical carcinoid (AC) in five and large cell neuroendocrine carcinoma (LCNEC) in three. Of the two remaining patients, one presented with a typical carcinoid (TC) and the other with a small cell neuroendocrine carcinoma (SCNEC). The tumor stage on presentation was stage I, II, III and IVa in respectively three, three, one and three cases; the TNM classification of each case is shown in Table 1.

Four patients underwent surgery, four received radiotherapy, one was treated with a combination of chemo- & radiotherapy and another with surgery followed by postoperative radiotherapy. Surgery varied from laryngeal preservation techniques using transoral CO2 laser surgery (2 cases) to total laryngectomy (TLE) (3 cases). Resection margins were free of tumor cells in all patients who underwent TLE (3 cases). In the 2 laser-resection specimens radicality could not be evaluated. The patients who received radiotherapy were treated with a median total dose of 64Gy (range, 37.5 - 70). One patient received concomitant chemotherapy with palliative intention, consisting of a combination of etoposide and carboplatin. Seven of the ten patients developed loco-regional recurrence. Four patients developed distant metastasis, of which three cutaneous. Mean time to recurrence was 35 months (95% CI, 9-60).

TABLE I Clinical Characteristics, HPV Status and Immunohistochemical Features of Ten Cases of Neuroendocrine Carcinoma of the Larynx.

Case	Age/ Sex	Histol. Subtype	TNM	Treatment[a]	Recurrence	Salvage[a]	HPV 16	HPV 18	HP GP5+/6+	p16	Ki-67	p53 Expression	Follow-up/ Status
1	69/M	AC	T1N0M0	TLE	Regional, distant	MRND	-	-	-	-	1%	-	74/DOD
2	57/M	SCNEC	T2N2cM0	CRX (Etoposide, Carboplatin) (37.5 Gy)	Distant	Palliative chemotherapy (Carboplatin/ Paclitaxel)	-	-	-	-	70%	1%	11/DOD
3	57/F	TC	T1N0M0	Rx (70Gy)	-	-	-	-	-	-	1%	-	96/NED
4	51/F	AC	T2N0M0	TLE	Regional	RND	-	Positive	Positive	-	90%	-	215/NED
5	81/M	LCNEC	T4aN2bM0	Rx (70Gy)	Regional	TLE, MRND	-	-	-	-	10%	-	48/AWD
6	75/F	AC	T2N0M0	MLS+CO_2-laser resection	Regional, distant	TLE	-	-	-	-	10%	1%	26/AWD
7	73/M	LCNEC	T2N0M0	Rx (70Gy)	Regional, distant	TLE, Chemotherapy (Etoposide)	-	-	-	-	1%	-	30/DOD
8	67/M	AC	T3N0M0	Rx (70 Gy)	Regional	TLE	-	-	-	-	10%	< 1%	27/NED
9	75/M	AC	T1N0M0	MLS+CO_2-laser resection	-	-	-	-	-	Positive	20%	30%	19/DOOC
10	53/M	LCNEC	T3N2bM0	TLE, MRND, Radiotherapy (60Gy)	-	-	Positive	-	Positive	-	70%	-	105/NED

AC, Atypical Carcinoid; SCNEC, Small Cell Neuroendocrine Carcinoma; TC, Typical Carcinoid; LCNEC, Large Cell Neuroendocrine Carcinoma; TLE, Total Laryngectomy; CRX, Chemoradiation; Rx, Radiotherapy; MLS, microlaryngosurgery; MRND, Modified Radical Neck Dissection; RND, Radical Neck Dissection; DOD, Dead Of Disease; NED, No Evidence of Disease; AWD, Alive With Disease; DOOC, Dead Of Other Cause. Follow-up in months.

Salvage therapy was performed in all but one case (6/7). This patient had a second primary pulmonary tumor at that time which was deemed irresectable and the patient abstained from further treatment. Four patients were laryngectomized (one in combination with a neck dissection and another one with postoperative chemotherapy) and two patients with only lymph node metastasis underwent neck dissection. Resection margins were free of tumor in all of the patients who underwent salvage surgery. The patient with a TC developed loco-regional recurrence. There was no relationship between tumor stage or choice of initial treatment and recurrence.

Two patients died of their disease after a median follow-up of 52 months (range, 30 - 74). One patient died of unrelated pulmonary malignancy. The seven censored patients were followed for a median time of 48 months (range, 26 - 215). At the last follow-up, four were without evidence of disease and three were alive with disease. Mean overall survival and disease-specific survival time was 140 months (95% CI, 74 - 205) and 155 months (95% CI, 88 - 222) respectively. Tumor type, stage, location and or initial treatment were not significantly related to either overall or disease-specific survival.

HPV Typing and Immunohistochemistry

Of the ten LNEC, 2 cases were positive for hrHPV (HPV16 and HPV18, respectively). All other cases were negative for both the hrHPV-consensus GP5+/6+-PCR as well as the specific HPV16 and HPV18 PCR. None of the 10 LNEC was positive for the lrHPV types HPV6 or HPV11.

Immunohistochemical staining for p16INK4A was positive in only one (hrHPV-negative) case. The HPV16 and HPV18 positive samples both showed over-expression of Ki67 versus only 1 out of 8 of the HPV-negative cases. High p53 expression was not found in any of the cases.

Prognosis of HPV Positive LNEC

The HPV16 positive tumor was interpreted as a LCNEC, staged T3N2bM0 and treated with surgery and radiotherapy. The patient is alive and without evidence of disease 105 months after therapy. The HPV18 positive sample was interpreted as an AC, staged T2N0M0. The patient was treated with a TLE. Nine months after surgery the tumor recurred. A RND was performed and the patient is alive and without evidence of disease 215 months after salvage

surgery. Interestingly, 2 of the 4 cases, which live without evidence of disease were hrHPV-positive compared to none of the 5 patients who died of their disease or are alive with disease. The patient with the p16INK4A positive AC presented with an early stage glottic tumor and was successfully treated by endolaryngeal CO2-laser resection. This patient died of a second primary non-small cell lung cancer 19 months after surgery without evidence of recurrence of the LNEC.

Discussion

Laryngeal Neuroendocrine Carcinoma

The WHO classification divides LNEC in typical and atypical carcinoid tumors (TC, AC, respectively), and small cell neuroendocrine carcinoma (SCNEC).[8] Several authors consider large cell neuroendocrine carcinoma (LCNEC) a separate category.[20] Significant progress has been made in determining an appropriate treatment strategy for the different histological tumor subtypes. A prognostic marker that allows for better pre-treatment assessment of response to therapy and clinical outcome could further improve on these efforts. Despite the small number of cases, the results from this study imply that the involvement of hrHPV in LNEC might be associated with a better response to therapy and prognosis in these tumors.

Human Papillomavirus Detection

HPV consists of a family of over 120 viruses.[21] Not all of these viruses have the same oncologic potential. About a dozen viruses have been designated as 'high-risk' including the most common HPV16 and HPV18. The reported association between HPV and oropharyngeal cancer is also based largely on these two high-risk viruses.[22,23] There is large variance in the reported prevalence of HPV in head and neck carcinoma. This might be caused by the different sensitivity and specificity of respective analytical methods used for detecting HPV. PCR-based detection probably overestimated the percentage of positive patients, as very few viral particles are needed in order to produce a positive test result.[23] Thus, PCR-positivity might represent transient not-clinically-relevant low copy HPV load. In our study we used a PCR-based HPV-detection assay including serial dilution series of HPV-positive cell lines to determine high copy load. Two patients tested positive for hrHPV (HPV16 and HPV18). To evaluate the possible attributive effect of HPV16 to the malignant transformation of the laryngeal mucosa, biologically active viral infections have been

associated with up-regulated protein p16INK4A expression through inactivation of pRB by HPV16-E7.[24] However, both hrHPV-positive LNEC cases were p16-negative. A possible explanation for the lack of p16INK4A expression in the HPV16-positive LNEC is that hrHPV virus infection may have played a role in the carcinogenesis in an earlier stage, but the virus was inactive at the time of sampling. In agreement with this assumption, loss of the CDKNA2 gene encoding p16 is found in precursor fields (reviewed by Leemans).[25] On the other hand, despite the high association between HPV16-positivity and p16INK4A expression in tonsillar carcinomas[19], in various studies a disagreement was observed in the detection of HPV DNA and p16INK4A.[26,27] These observations suggest that p16INK4A can not serve as a reliable surrogate marker in HNSCC and might support our findings that our HPV-positive samples are p16INK4A-negative. The prevalence of tumors in our study that appear to be associated with HPV (2 out of 10) is in line with the estimated worldwide prevalence of HPV-induced HNSCC.[28]

P53 Expression

The possibility of HPV induced malignant transformation was further explored by p53 expression. Mutation in p53 plays an important role in tobacco and alcohol related cancers.[29] It results in protein over-expression of p53, accumulation of genetic damage, and eventually, uncontrolled cell proliferation. While p53 expression can also be elevated in HPV induced cancer, this is thought to be a physiological response to increased cell proliferation.[22] The retained expression of wild-type p53 is thought to be one of the reasons why HPV induced cancers have a relatively good prognosis. It is hypothesized that the intact p53-mediated apoptotic response to chemo- or radiotherapy induced stress is responsible for this mechanism.[5] No p53 over-expression was found for the HPV positive samples in this our suggesting that an alcohol or tobacco related cause for these cancers is less likely.

Ki-67 Expression

Further information on tumor proliferation was obtained through measurement of the expression of Ki-67. The fraction of Ki-67-positive tumor cells (the Ki-67 labeling index) is often correlated with the clinical course of the disease.[30] HPV induced cancers are known to be associated with high levels of Ki-67.[31] Indeed, both HPV positive samples in our series had a high Ki-67 labeling index, whereas this was only true for one out of the eight HPV-negative cases.

HPV Status and Prognosis

Due to the small sample size, no firm conclusions can be drawn regarding the relationship between HPV positivity and treatment outcome. However, it is remarkable that the two hrHPV DNA positive cases had the longest survival in this series. Both patients were without evidence of disease 105 and 215 months after initial treatment, despite having bad prognostic subtypes. Despite the fact that the patient with the p16INK4A positive sample died of another malignancy without evidence of recurrence of the LNEC, p16INK4A positivity was also associated with a better treatment response of the LNEC. In this study four patients remain alive with no evidence of disease; one with a TC, two with an AC, and one with a LNEC. TC are known to have a good prognosis, but the other three patients survived despite of unfavorable tumor subtypes. Remarkably, two of these three patients were HPV positive. This finding is in line with previous observations in HPV-positive head and neck cancer.[5-7,32,33] However, in laryngeal cancer in particular, these favorable prognostic features of HPV-positive tumors have not been detected so far.[34,35] No strong conclusions can be drawn from our series due to the small sample size and differences pertaining to tumor stage on presentation and applied treatment modality. Both HPV-positive patients were primarily treated with aggressive surgery, while other LNEC patients were subjected to various other treatment modalities including minimally invasive endoscopic surgery, radiotherapy and chemo-radiotherapy. The exact mechanism behind the better response rate of HPV positive head and neck tumors to (chemo)radiotherapy is still unknown. However, genetic differences, like p53 mutation or EGFR expression level, between HPV negative and positive tumors have been proposed.[36,37]

Conclusions

We describe the detection of hrHPV in laryngeal neuroendocrine carcinoma (LNEC) for the first time. Two out of ten tissue samples of LNEC tested positive for hrHPV. These tumors had a high Ki-67 labeling index and very good prognosis. Despite the small number of cases, the results suggest that the involvement of hrHPV in LNEC might be associated with a better response to therapy and prognosis for these tumors. The detection of hrHPV might act as a potential marker in determining individual optimal treatment strategy. An independent larger series of LNEC is needed to confirm our findings.The authors have no conflict of interest to declare

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CHAPTER VIII

General Discussion

Neuroendocrine carcinoma of the head and neck (NCHN) are rare neoplasms with clinical characteristics different from squamous cell carcinoma (SCC).[1] A proper delineation of these differences and consequent treatment adjustments are of great importance, as previous studies have shown improved survival in patients treated with adapted treatment protocols.[2-9] Currently, our understanding of these tumors is hampered by their confusing nomenclature and fragmented literature.[10] As new data is hard to come by, we set out to combine all existing data, both from our own experience and from previous studies, in order to be able to make statistical inferences and provide clinicians with guidelines to improve treatment selection and patient outcome. In addition, we studied the role of human papillomavirus (HPV) infection in the carcinogenesis of NCHN as a possible prognostic factor. Our results, as presented in this thesis, reveal the potential for improving treatment outcome in patients with NCHN through adapting treatment selection to differentiation grade and tumor location.

Tumor Subtypes

NCHN suffer from a confusing nomenclature, with legacy terminology and competing classification schemes being used across studies. Taking a reductive view, four subtypes can be delineated based on differentiation grade (well, moderate and poor) and cell size (small, and intermediate to large).[11] Furthermore, a small percentage of patients present with a composite tumor, most often a combination of a SSC and a poorly differentiated small cell neuroendocrine carcinoma.

Clinical Presentation

Patient with NCHN present with similar symptoms as those with SCC of the same location (Chapter II and III). While NCHN have the potential for ectopic hormone production as evidenced by a number of reports, few patients develop a paraneoplastic syndrome. Therefore, routine evaluation of hormone levels appears to be of limited value in the diagnostic work-up of these patients.

Tumor Location

In the larynx the tumor is most often located in the supraglottis (57.9 - 95.5%, depending on subtype), correlating with a high propensity for loco-regional metastases (Chapter V).

Unfortunately, it was not possible to reliably infer the original tumor location in patients with a neuroendocrine carcinoma of the sinonasal tract (NCS) due to the advanced stage on presentation.

Tumor Stage on Presentation

The tumor stage on presentation for neuroendocrine carcinoma of the larynx (NCL) was highly dependent on subtype. Patients with a well differentiated tumor presented with stage I disease in 83.3% of cases, while those with a poorly differentiated subtype presented with stage IV disease in 66.7 - 69.6% of cases (Chapter V). In NCS, this difference was less pronounced, with patients presenting with stage IV disease in 57.1% versus 70.4 - 80.6% in patients with well and poorly differentiated subtypes respectively (Chapter VI). This can be attributed to patient and doctor delay, caused by a lack of disconcerting symptoms and the close anatomical proximity of the tumor to adjacent structures.

Treatment and Prognosis

Regardless of location, differentiation grade is the most important predictor of survival in NCHN with a 5-year disease-specific survival (DSS) of 70.2 - 100% for patients with a well-differentiated tumor, compared to 15.3 - 46.1% for those with a poorly differentiated subtype (Chapter V and VI). After differentiation grade, treatment selection is the second most important factor determining prognosis. Response to treatment is dependent on both tumor location and tumor subtype. Due to the lack of larger series it was not possible to infer these dependencies in earlier studies. This lead to a multitude of treatment strategies being employed with variable outcomes. In Chapter V and VI we showed that by combining all available cases in the literature we are able to make statistical inferences that allow us to better understand the relationship between tumor location, subtype, and treatment outcome. In the following paragraphs our findings will be discussed per tumor subtype and location.

Neuroendocrine Carcinoma of the Larynx

Well Differentiated Neuroendocrine Carcinoma of the Larynx

Most patients with a well-differentiated NCL were treated by surgical excision alone (76.2%), with the remainder treated with radiotherapy or a combination of surgery and

radiotherapy. This yielded excellent results with a 5-year DSS of 100%. There was no difference in survival between patients treated with surgery, radiotherapy or a combination thereof.

Moderately Differentiated Neuroendocrine Carcinoma of the Larynx

The best treatment outcome for moderately differentiated carcinoma of the larynx was seen in patients treated with surgery as monotherapy, with a 5-year DSS of 60.2%. Patients treated with radiotherapy or a combination of surgery and radiotherapy fared worse, with a 5-year DSS of 53.8% and 41.2% respectively. Surprisingly, correcting for tumor stage on presentation revealed similar results. Patients not undergoing (elective) treatment of the neck presented with a loco-regional recurrence in 29.8% of cases versus 0% of those who did. Therefore, we advise to treat these patients with radical surgical excision combined with bilateral neck dissection. Despite adequate treatment, most patients will develop a recurrence (62.5%), often with distant metastases (69.4%). It is important to note that late recurrences are common, necessitating prolonged follow-up.

Poorly Differentiated Neuroendocrine Carcinoma of the Larynx

Poorly differentiated NCL are best treated with a combination of radiotherapy and chemotherapy. This treatment strategy yielded the best results for patients with a poorly differentiated small cell (neuroendocrine) carcinoma (PDSCNC) of the larynx, with a 5-year DSS of 30.8% versus 12.9% for patients treated by other (combinations of) treatment modalities. While there is insufficient data on patients with a poorly differentiated large cell neuroendocrine carcinoma of the larynx to compare the outcome of different treatment protocols, their clinical similarity to PDSCNC warrants a similar treatment strategy.

Recurrence in Neuroendocrine Carcinoma of the Larynx

In addition to the review of our institutional experience as reported on in Chapter II we also performed a case control study (see supplementary analyses, page 29), matching patients with a NCL and SCC of the larynx (SCCL) on age, primary tumor location and tumor stage on presentation. The most striking difference we found was the relatively high propensity for recurrence in the NCL group, with 80% of patients developing recurrent disease versus only 23% in the SCCL group. No relationship could be found between tumor stage and the development of recurrent disease, with most recurrences occurring in patients with stage II disease. A similar high rate of recurrence was found in the meta-analysis in Chapter V.

Despite their high recurrence rate, no statistically significant difference in overall or disease-specific survival was found between the NCL and SCCL group, suggesting that patients with a NCL that develop recurrent disease can survive relatively long with adequate salvage therapy.

Neuroendocrine Carcinoma of the Sinonasal Tract (NCS)

Well and Moderately Differentiated Neuroendocrine Carcinoma of the Sinosasal Tract

Unfortunately, almost no studies make a distinction between well and moderately differentiated sinonasal neuroendocrine carcinoma (WMDSNC). Therefore, we are not able to discuss these entities separately. From the results in Chapter VI we can conclude that the application of surgery is the strongest positive predictor of survival in WMDSNC. The 5-year DSS ranged from 66.7 to 83.3% in treatment protocols in which surgery was employed, while patients treated with a combination of radio- and chemotherapy performed poorly, with a 5-year DSS of 39.2%. It is unclear if patients with a moderately differentiated neuroendocrine carcinoma benefit from the addition of postoperative radiotherapy. However, as resection margins cannot be evaluated properly, postoperative radiotherapy remains warranted in these patients.

Poorly Differentiated Carcinoma of the Sinonasal Tract

Both small and intermediate to large cell subtypes of poorly differentiated sinonasal neuroendocrine carcinoma appear to benefit most from the combination of surgery and radiotherapy. For the intermediate to large cell subtype in particular, strong evidence for this treatment strategy is presented in Chapter VI, with a significant odds ratio of 0.337 for dying of disease after multimodality treatment compared to surgery as monotherapy in the multivariate analysis. However, prognosis in this group remains poor, with a 5-year DSS of 15.7 - 17.9% for patients treated with mono therapy and 40.2 - 54.7% for those treated with multimodality therapy. While not significant, the lowest odds ratios for the small cell poorly differentiated subtype were observed for treatment strategies employing a combination of surgery and radiotherapy. The 5-year DSS for this strategy ranged from 57.6 to 71.3%. The application of chemotherapy yielded no improvement in survival.

Neuroendocrine Carcinoma of the Middle Ear

During the review of our institutional experience we encountered one case of neuroendocrine carcinoma of the middle ear (NCME) as described in Chapter IV. The middle ear is an extremely unlikely site for these neoplasms to arise, with an estimated share of less than one percent of all neuroendocrine tumors.[12] Its existence at this location is debated, with some authors preferring to classify these tumors as middle ear adenoma with neuroendocrine differentiation.[13]

The preferred treatment modality is the same for both tumor types and consists of surgery. Adjuvant radiotherapy is considered unnecessary and may even adversely affect the prognosis by inducing malignant transformation[14] There is no data on the sensitivity of these tumors for chemotherapy.

With adequate treatment, the prognosis of these neoplasms is excellent. Recurrence of the primary tumor occurred in approximately 20 percent of published cases[13,15] but was almost inexistent when the ossicular chain was removed on initial surgery.[13] In a review by Ferlito et al., five cases of metastatic NCME are described[16], contradicting the generally held belief that these tumors are of an exclusively benign nature. In the same article, a parallel is drawn between NCME and neuroendocrine tumors of the lung, which before being recognized as low-grade malignancies were also grouped with adenomas. The time to recurrence varies widely with recurrent disease occurring up to 33 years after treatment, a common feature of neuroendocrine carcinoma.[15] To this date, there is no report of distant metastasis associated with NCME.

Trends over Time

In Chapter V and VI, we separated cases based on publication date into two groups in order to evaluate the effect of improvement in diagnostic and therapeutic modalities and treatment selection over time. Surprisingly, for NCL no difference in treatment outcome was observed. This could be explained by the heterogenous treatment selection in both groups, stressing the importance for clear treatment guidelines. Instead, for NCS, a shift towards multimodality therapy and the abandonment of radiotherapy as monotherapy resulted in an improvement in DSS, showing the potential benefit of custom treatment strategies for NCHN.

Limitations

The studies described in Chapter V and VI suffer from obvious limitations as the data was collected from different institutions over a protracted timeline, leading to inevitable variation in diagnostic and therapeutic modalities between cases and missing data. Therefore, even after combining all the data available, we cannot make definitive statements with regard to the clinical behavior of NCHN and care should be taken with interpreting the results.

Human Papillomavirus Infection in NCL

In Chapter VII we evaluated HPV infection as a potential prognostic marker in NCL. While no strong conclusions could be drawn due to the small sample size, our findings are of interest as both patients in which a causative role for HPV in the carcinogenesis was implied by their immunohistochemical profile had excellent survival, with a disease free follow-up period of 105 and 215 months, despite having an unfavorable prognostic subtype (atypical carcinoid and large cell poorly differentiated neuroendocrine carcinoma respectively). Larger series will have to further elucidate these findings and their implications for treatment selection.

Conclusions

This thesis provides a near complete overview of all data concerning NCHN, including our own experience. It offers an essential understanding of their clinical behavior, prognosis and response to therapy. From the results presented in the preceding chapters, we can conclude that NCHN form a pluriform group of tumors with differing characteristics depending on differentiation grade and tumor location. By far the most important step towards deciding on an appropriate treatment strategy is obtaining an accurate histopathological diagnosis from an experienced head and neck pathologist, with an emphasis on differentiation grade. Well differentiated NCHN can be treated by surgery alone, regardless of tumor location. Moderately differentiated NCL are best treated by surgical resection and elective bilateral neck dissection. No benefit could be demonstrated for postoperative radiotherapy in this group. Instead, due to the lack of adequate resection margins, moderately differentiated NCS are best treated by surgical resection, followed by postoperative radiotherapy. Poorly differentiated NCL are best treated with a combination

of radiotherapy and chemotherapy, while their sinonasal counterparts benefit most from surgical resection followed by postoperative radiotherapy. No additional benefit from chemotherapy could be demonstrated for NCS. Table 1 presents an overview of treatment recommendations per differentiation type and tumor location. Additionally, Chapter V shows the potential for HPV as a future prognostic marker in NCHN.

In order to expand on the results presented in this thesis, a prospective multicenter clinical trial with consistent diagnostic and therapeutic protocols is necessary. Until such an endeavor is realized, the treatment guidelines as presented in this chapter can aid clinicians in making better decisions for their patients.

TABLE 1 Treatment Recommendations for Neuroendocrine Carcinoma of the Head and Neck

	Larynx	**Sinonasal Tract**
Well differentiated	Surgery	Surgery
Moderately differentiated	Surgery with (elective) bilateral neck dissection	Surgery & Radiotherapy
Poorly differentiated*	Radiotherapy & Chemotherapy	Surgery & Radiotherapy

* Both small and intermediate to large cell types

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Summary

Neuroendocrine carcinoma of the head and neck (NCHN) form a rare subgroup of head and neck cancer with clinical characteristics different from squamous cell carcinoma (SCC). NCHN most commonly involve the larynx and sinonasal tract. They can be subdivided based on differentiation grade into well, moderately and poorly differentiated neuroendocrine carcinoma (WDNC, MDNC and PDNC respectively). Additionally, the latter consists of a small and intermediate to large cell variant. Due to their rare nature and resulting lack of treatment guidelines, they are often approached using treatment protocols developed for SCC of the head and neck (SCCHN). This yields suboptimal treatment results as there are important differences in response to therapy between NCHN and SCCHN. The aim of this thesis was to elucidate these differences by reviewing our institutional experience and combining all available data in the literature. Furthermore, human papilloma virus (HPV) infection was studied as a possible prognostic marker in neuroendocrine carcinoma of the larynx (NCL).

Part I: Institutional Experience

Neuroendocrine Carcinoma of the Larynx

In Chapter II we reviewed our institutional experience with NCL. We retrieved all cases of NCL diagnosed and treated at the Department of Otolaryngology, Head and Neck surgery of the University Medical Center Groningen between 1988 and 2010, yielding a total of 11 cases available for analysis. These concerned one case of WDNC, six cases of MDNC and four cases of PDNC. The clinical presentation was similar to that of patients with SCC of the larynx and consisted of hoarseness, odynophagia, dysphagia and/or otalgia. The median age at the time of diagnosis was 67 years (range, 40 - 81). There was no mention of a paraneoplastic syndrome. Most patients presented with a supraglottic tumor (9/11). Tumor stage on presentation was variable. Primary treatment was split between surgery and radiotherapy, with two patients receiving multi-modality therapy. Due to the small sample size, no inferences could be made with regard to the efficacy of these treatment approaches; a common problem affecting studies on NCL. One patient presented with a WDNC and had excellent survival, with no evidence of disease after 96 months of follow-up. In contrast, most patients with a MDNC or PDNC had poor survival, irrespective of tumor stage on presentation. All but one of these patients developed a recurrence (9/10), five of which distant. Additionally, we compared our results with SCC of the larynx (SCCL) by matching each case of NCL with two cases of SCCL on age, tumor location and stage on

presentation. The most apparent finding was a significant difference in the rate of recurrence, with 80% of patients with a NCL developing recurrent disease versus only 23% in the LSCC group (p = .005), while no significant difference in survival was observed. Furthermore, while tumor stage on presentation was a strong predictor of survival in the SCCL group, no such relationship could be established for NCL.

Neuroendocrine Carcinoma of the Sinonasal Tract (NCS)

In Chapter III we reviewed our institutional experience with NCS in a similar way to NCL. Between 1980 and 2010 a total of 15 patients with NCS were treated at the Department of Otolaryngology, Head and Neck surgery of the University Medical Center Groningen. Eight patients presented with a poorly differentiated large cell neuroendocrine carcinoma (PDLCNC), five with a well or moderately differentiated neuroendocrine carcinoma (WMDNC) and two with a poorly differentiated small cell neuroendocrine carcinoma (PDSCNC). The median age at the time of diagnosis was 68 years (range 28 – 87). Again, no difference was found between the clinical presentation of patients with a NCS or SCC of the sinonasal tract, with patients presenting with (unilateral) nasal congestion, epistaxis and in some cases diplopia. No paraneoplastic syndromes were described. Nearly all patients presented with stage IV disease (12/15). Treatment consisted of surgery (2), radiotherapy (4), a combination of these modalities (6) and palliation (3). The estimated 5-year overall survival was 60% for WMDNC, 44% for PDLCNC and 0% for PDSCNC. While no statistical inferences could be calculated, patients treated with multimodality therapy appeared to perform better than those approached with single modality therapy. Five out of ten patients in whom disease control was initially achieved, developed a recurrence. Despite this high proportion, patients with a local or loco-regional recurrence survived for a median of 80 months after salvage treatment. These results were comparable to those presented in other series in the literature and point in the direction of multimodality therapy as a possible means of improving outcome in patients with a NCS. This hypothesis was further explored in Chapter VI.

Neuroendocrine Carcinoma of the Middle Ear

In Chapter IV we report a case of neuroendocrine carcinoma originating in the middle ear (NCME) of a 29 year old male, diagnosed and treated at the Department of Otolaryngology, Head and Neck surgery of the University Medical Centre Groningen. The patient presented with a one year history of a pounding sensation and tinnitus of the right ear, recently

accompanied by progressive hearing loss. On surgery, a fibrous tumor, attached to the tympanic membrane was found to fill the entire middle ear. A modified radical mastoidectomy was performed. The tumor was classified as a WDNC. The patient is alive and without evidence of disease 10 years after surgery. Upon reviewing the literature, it became clear that it is currently not possible to reliably differentiate between middle ear adenoma and NCME based on histopathological analysis. As the latter exhibits malignant features, both should be approached by radical surgical excision. Radiotherapy is discouraged and can even induce malignant transformation. As late recurrences are common, prolonged follow-up is in order.

Part II: Review of the Literature

Neuroendocrine Carcinoma of the Larynx

In Chapter V we report on our efforts to elucidate the clinical behavior and provide guidelines for the management of NCL by performing a structured literature search for all research concerning NCL against the MEDLINE and EMBASE databases. Available clinical data was extracted, normalized, and pooled in a single dataset. This resulted in a total of 436 cases of which 23 WDNC, 163 MDNC, 183 PDSCNC, 29 PDLCNC and 38 unspecified NCL. The 5-year disease-specific survival (DSS) was 100% for WDNC, 53% for MDNC and 15 - 19% for PDNC ($p < .001$), revealing an inverse correlation between differentiation grade and prognosis. Contrary to our findings in Chapter II, a clear relationship between tumor stage and prognosis was established for MDNC and PDNC. Various treatment strategies were employed, resulting in some unexpected results: patients with an MDNC treated with surgery had a better DSS than those treated with radiotherapy (60% versus 54%, $p = .035$), while postoperative radiotherapy did not result in improved survival. This remained the case after correcting for tumor stage on presentation. The combination of radiotherapy and chemotherapy yielded the best 5-year DSS for PDSCNC compared to other modalities (30,8% vs 12,9%, $p = .001$). No reliable estimates could be calculated for WDNC and PDLCNC due to the small sample size. However, WDNC had excellent survival regardless of choice of treatment, while PDLCNC generally behaved comparable to PDSCNC. Recurrence rate was high with 58 to 81%, with the exception of WDNC (35%). Patients with a MDNC, not undergoing surgical treatment of the neck, developed regional recurrence without local recurrence in 29,8% of cases versus 0% for patients undergoing neck dissection ($p < .001$). Based on these results, we were able to

provide the following guidelines for the management of NCL: patients with a WDNC can be treated with surgery alone. MDNC are best managed with radical surgical excision in combination with (elective) neck dissection. All PDNC should be treated alike, with a combination of radiotherapy and chemotherapy. Additionally, we advised to prolong the follow-up period of patients with a NCL from 5 to 10 years, as late recurrences are common.

Neuroendocrine Carcinoma of the Sinonasal Tract

In Chapter VI we combined all available data in the literature on NCS in order to evaluate the outcome of different treatment strategies. A literature search for all studies concerning NCS was performed against the MEDLINE and EMBASE databases. Available clinical data was normalized, and pooled in a single dataset. A total of 701 cases of NCS was available for analysis, comprising 127 WMDNC, 459 PDLCNC and 115 PDSCNC. Differentiation grade was the most important predictor of survival, with a 5-year DSS of 70,2% for WMDNC, 35,9% for PDLCNC and 46,1% for PDSCNC. Tumor stage on presentation was of limited value in predicting survival or response to treatment as most patients presented with advanced disease (stage IV in 75%). Overall, the application of surgery yielded significantly better results (5-year DSS 52,2% versus 30,1%, $p < .001$). In PDLCNC, radiotherapy was a beneficial supplement to surgery (5-year DSS 54,7% versus 15,7%, $p = 0.027$), while radiotherapy as monotherapy performed poorly in this group (5-year DSS 17,9%). Chemotherapy did not appear to improve survival. Based on these findings, we concluded that the most important predictors of survival in NCS are differentiation grade and associated treatment strategy. In contrast to other head and neck cancers, tumor staging appears of limited value in predicting survival in NCS. Surgery should be the cornerstone of treatment, supplemented by radiotherapy in moderately and poorly differentiated subtypes. Chemotherapy does not appear to improve survival.

Part III: Human Papillomavirus Infection as a Prognostic Marker

The purpose of Chapter VII was to detect HPV infection in NCL and to explore the possible relationship between HPV-induced malignant transformation and prognosis. For ten of the cases described from Chapter II, pretreatment biopsy material was available and tested for the presence of HPV 6, 11, 16, and 18 using a PCR-based detection method. Immunohistochemical staining was performed for Ki-67, p16 (INK4A), and p53

expression. All cases were negative for the low-risk HPV types HPV6 and HPV11, that are associated with laryngeal papillomatosis. High-risk HPV was detected in two cases; one sample from a MDNC was positive for HPV16 and another sample from a PDLCNC for HPV18. Both HPV-positive tumors had a high Ki-67 labeling index. Two of the four cases with a good response to therapy were hrHPV-positive (both HPV DNA positive) compared to none of the five poor responders. These findings suggest that HPV may play a role in the pathogenesis of NCL. Correspondingly, the relationship between HPV, improved prognosis and good response to (radio)therapy for SCCHN may also be true for a subset of NCL.

Overall Conclusions and Further Research

NCHN form a pluriform group of tumors with clinical characteristics distinct from HNSCC. By reviewing both our own experience and the literature, we were able to delineate their clinical characteristics and provide guidelines in order to improve treatment outcome of patients affected. Overall, differentiation grade is the most important factor determining prognosis and response to therapy. Therefore, the first step in the management of patients with an NCHN is acquiring an accurate histopathological diagnosis. Especially in NCS, clinicians should press the pathologist to differentiate between well and moderately differentiated NC, as these are commonly grouped together under the umbrella ‘sinonasal neuroendocrine carcinoma’, obfuscating important differences in clinical behavior. Furthermore, for the first time, we detected hr-HPV in NCL, alluding to a possible role for HPV as a biomarker for predicting prognosis and response to therapy in these patients.

Treatment Recommendations

WDNC are relatively benign neoplasms and can be managed by surgical excision alone, regardless of their location. MDNC of the larynx should be treated by radical surgical excision and elective bilateral neck dissection, while MDNC of the sinonasal tract are best approached with a combination of surgery and radiotherapy. PDNC of the larynx respond best to a combination of radio- and chemotherapy. In contrast, PDNC of the sinonasal tract do not appear to respond well to chemotherapy and are best treated with a combination of surgery and radiotherapy.

Additionally, it should be noted that NCHN show a strong preponderancy for (late) recurrence and therefore, we advise to extend the follow-up period of patients affected to at least ten years.

This thesis provides both an outline of the clinical behavior of NCHN and recommendations for deciding on a treatment strategy. However, due to its retrospective nature, care should be taken in interpreting our analyses. While a multi-centre prospective study could strengthen our conclusions, its execution is unlikely due to the rare nature of these tumors. Therefore, we encourage institutions to publish their experiences with these tumors as extensively as possible and add to the collective data already available.

Samenvatting

Neuro-endocriene carcinomen van het hoofd-hals gebied (NCHN) vormen een zeldzame subgroep van hoofd-hals kanker met klinische kenmerken die verschillen van die van plaveiselcelcarcinomen (SCC). NCHN komen het meest frequent voor in de larynx en de neusbijholten. Ze kunnen worden onderverdeeld op basis van differentiatiegraad in goed, matig en slecht gedifferentieerde neuro-endocriene carcinomen (respectievelijk WDNC, MDNC en PDNC). De laatstgenoemde groep wordt verder opgedeeld in een klein- en gemiddeld tot grootcelllige variant. Vanwege de lage incidentie en het daaruit voortvloeiende gebrek aan richtlijnen ten aanzien van de behandeling, wordt er vaak gebruik gemaakt van behandelprotocollen ontwikkeld voor SCC van het hoofd-hals gebied (SCCHN). Dit resulteert in suboptimale behandelresultaten, omdat er belangrijke verschillen bestaan in de respons op behandeling tussen NCHN en SCCHN. Het doel van dit proefschrift was om deze verschillen in kaart te brengen door onze eigen ervaring met deze tumoren te analyseren en te combineren met de beschikbare data in de literatuur. Daarnaast werd infectie met het humaan papillomavirus onderzocht als een mogelijke prognostische marker in neuro-endocriene carcinomen van de larynx (NCL).

Deel I: Eigen Ervaring

Neuro-Endocriene Carcinomen van de Larynx

In Hoofdstuk II analyseerden we onze eigen ervaring met NCL. Hiertoe werden de dossiers van alle casus van NCL, gediagnosticeerd en behandeld op de afdeling KNO-heelkunde, Hoofd-Hals Chirurgie van het Universitair Medisch Centrum Groningen, opgevraagd. Dit leverde in totaal 11 casus op in de periode van 1988 t/m 2010. In één casus was sprake van een WDNC, in zes casus van een MDNC en in de overige vier casus van een PDNC. De klinische presentatie was vergelijkbaar met die van patiënten met een SCC van de larynx en bestond uit heesheid, odynofagie, dysfagie en/of otalgie. De mediane leeftijd op het moment van diagnose was 67 jaar (range, 40 - 81). In geen van de casus was sprake van een paraneoplastisch syndroom. De meeste patiënten presenteerden zich met een supraglottische tumor (9/11). Het tumorstadium bij presentatie was variabel. De behandeling bestond uit chirurgie of radiotherapie. Twee patiënten werden behandeld met meerdere modaliteiten. Vanwege het kleine aantal casus konden geen conclusies worden getrokken ten aanzien van de effectiviteit van de verschillende behandelingen, een veelvoorkomend probleem bij studies naar NCL. Hoewel slechts één casus een WDNC betrof, kan wel worden opgemerkt dat deze patiënt een uitstekende overleving had, met

geen aanwijzingen voor ziekte na 96 maanden follow-up. Dit in tegenstelling tot patiënten met een MDNC of PDNC, welke, onafhankelijk van het tumor stadium bij presentatie, in de meeste gevallen een slechte overleving hadden. Op één casus na, ontwikkelden al deze patiënten een recidief (9/10), waarvan vijf met afstandsmetastasen. Aanvullend hebben we onze NCL casus vergeleken met patiënten met een SCC van de larynx (SCCL) door elke patiënt met een NCL te matchen met twee patiënten met een SCCL op basis van leeftijd, tumorlocatie en stadium. Hierbij was de meest opvallende bevinding dat er een significant verschil bestond in de frequentie van recidivering: 80% van de patiënten met een NCL ontwikkelde een recidief tegen slechts 23% in de LSCC groep (p = .005). Desondanks bestond er geen significant verschil in overleving tussen beide groepen. Verder viel op dat het tumorstadium bij presentatie een sterke voorspeller was voor de overleving van patiënten met een LSCC, terwijl een dergelijke relatie in de NCL groep niet kon worden vastgesteld.

Neuro-Endocriene Carcinomen van de Neusbijholten (NCS)

In Hoofdstuk III analyseerden we onze eigen ervaring met NCS op een soortgelijke manier als met NCL. Tussen 1980 en 2010 werden in totaal 15 patiënten met een NCS behandeld op de afdeling KNO-heelkunde, Hoofd-Hals Chirurgie van het Universitair Medisch Centrum Groningen. Acht patiënten presenteerden zich met een slecht gedifferentieerd grootcellig neuro-endocrien carcinoom (PDLCNC), vijf met een goed of matig gedifferentieerd neuro-endocrien carcinoom (WMDNC) en twee met een slecht gedifferentieerd kleincellig neuro-endocrien carcinoom (PDSCNC). De mediane leeftijd op het moment van diagnose was 68 jaar (range 28 - 87). Wederom werd geen verschil gevonden tussen de klinische presentatie van patiënten met een NCS of een SCC van de neusbijholten. Patiënten presenteerden zich met (eenzijdig) neusverstopping, epistaxis en in sommige gevallen diplopie. In geen van de casus was sprake van een paraneoplastisch syndroom. Vrijwel alle patiënten presenteerden zich met tumor stadium IV (12/15). De behandeling bestond uit chirurgie (2), radiotherapie (4), een combinatie van deze modaliteiten (6) en palliatie (3). De geschatte 5-jaars overleving was 60% voor WMDNC, 44% voor PDLCNC en 0% voor PDSCNC. Hoewel het aantal casus te klein was voor statistische analyse, viel op dat patiënten die behandeld werden met een combinatie van modaliteiten het beter deden dan patiënten die behandeld werden met een enkele modaliteit. Vijf van de tien patiënten ontwikkelden een recidief. Ondanks dit hoge percentage was de mediane overleving na herhaalde behandeling 80 maanden. Deze resultaten waren

vergelijkbaar met die van andere series in de literatuur en wijzen in de richting van multimodale behandeling als een mogelijk middel om de overleving van patiënten met een NCS te verbeteren. Deze hypothese werd verder onderzocht in Hoofdstuk VI.

Neuro-Endocrien Carcinoom van het Middenoor

In Hoofdstuk IV beschrijven we een casus van een neuro-endocriene carcinoom originerend in het middenoor (NCME) van een 29-jarige man, gediagnosticeerd en behandeld op de afdeling KNO, Hoofd-Hals Chirurgie van het Universitair Medisch Centrum Groningen. De patiënt presenteerde zich met een sinds één jaar bestaande kloppende sensatie in het rechter oor, gepaard gaande met progressief gehoorverlies en tinnitus. Bij nadere analyse en chirurgische interventie bleek een fibreuze tumor, adherent aan het trommelvlies, het gehele middenoor op te vullen. Er werd een gemodificeerde radicale mastoïdectomie uitgevoerd. De tumor werd geclassificeerd als een WDNC. Tien jaar na deze operatie zijn er geen aanwijzingen voor residu of recidief ziekte. Op basis van de literatuur aangaande NCME werd duidelijk dat het momenteel niet mogelijk is om op betrouwbare wijze onderscheid te maken tussen een middenoor adenoom en een NCME op basis van histopathologische analyse. Aangezien de laatste kwaadaardige kenmerken vertoont, kunnen beiden het beste worden behandeld middels radicale chirurgische excisie. Behandeling middels radiotherapie wordt afgeraden en kan zelfs kwaadaardige transformatie induceren. Late recidieven komen vaak voor; derhalve is langdurige follow-up aangewezen.

Deel II: Literatuuronderzoek

Neuro-Endocriene Carcinomen van de Larynx

In Hoofdstuk V brengen we het klinische gedrag van NCL verder in kaart en geven we richtlijnen ten aanzien van de behandeling. Hiertoe werd een gestructureerd literatuuronderzoek, gebruik makend van de MEDLINE en EMBASE databases, uitgevoerd. Beschikbare klinische gegevens werden geëxtraheerd, genormaliseerd, en samengevoegd in één dataset. Dit resulteerde in een totaal van 436 casus, waarvan 23 WDNC, 163 MDNC, 183 PDSCNC, 29 PDLCNC en 38 niet-gespecificeerde NCL. De 5-jaars ziekte-specifieke overleving (DSS) was 100% voor WDNC, 53% voor MDNC en 15 - 19% voor PDNCL ($p < .001$), hetgeen een inverse correlatie tussen differentiatie graad en prognose laat zien. In tegenstelling tot onze bevindingen in Hoofdstuk II, was er sprake van een duidelijke relatie tussen tumorstadium bij presentatie en prognose voor MDNC en

PDNC. Verschillende behandelingsstrategieën werden toegepast, resulterend in een aantal verrassende resultaten: patiënten met een MDNC, die chirurgisch werden behandeld hadden een betere 5-jaar DSS dan patiënten behandeld met radiotherapie (60% vs 54%, $p = .035$), terwijl postoperatieve radiotherapie niet leidde tot een verbetering in overleving. Dit bleef het geval na correctie voor tumorstadium bij presentatie. De combinatie van radiotherapie en chemotherapie leverde de beste 5-jaar DSS voor PDSCNC in vergelijking met andere modaliteiten (30,8% versus 12,9%, $p = .001$). Er konden geen betrouwbare uitspraken worden gedaan over het effect van de verschillende behandelingen voor WDNC en PDLCNC vanwege het kleine aantal casus. Echter, patiënten met een WDNC hadden een uitstekende overleving, ongeacht de keuze van de behandeling, terwijl PDLCNC zich over het algemeen vergelijkbaar gedroegen als PDSCNC. Het recidiefpercentage was hoog met 58 tot 81%, met uitzondering van WDNC (35%). Patiënten met een MDNC, welke geen chirurgische behandeling van de nek ondergingen, ontwikkelden een regionaal recidief zonder lokaal recidief in 29,8% van de gevallen versus 0% van de patiënten die een halsklierdissectie ondergingen ($p < .001$). Gebaseerd op deze resultaten waren we in staat om de volgende richtlijnen voor de behandeling van NCL te formuleren: patiënten met een WDNC kunnen worden behandeld middels conservatieve chirurgie. Patiënten met een MDNC zijn het meest gebaat bij radicale chirurgische excisie in combinatie met bilaterale halsklierdissectie. PDSCNC en PDLCNC kunnen op gelijke wijze worden behandeld met een combinatie van radio- en chemotherapie. Daarnaast raden we aan om de follow-up periode van patiënten met een NCL te verlengen van 5 naar minimaal 10 jaar, omdat (late) recidieven veel voorkomen.

Neuro-Endocriene Carcinomen van de Neusbijholten

In Hoofdstuk VI trachten we om de uitkomst van verschillende behandeling-strategieën voor NCS te evalueren. Hiertoe werd een gestructureerd literatuuronderzoek uitgevoerd, gebruik makend van de MEDLINE en EMBASE databases. Beschikbare klinische gegevens werden geëxtraheerd, genormaliseerd en samengevoegd in één dataset. Een totaal van 701 casus van NCS was beschikbaar voor analyse, bestaande uit 127 WMDNC, 459 PDLCNC en 115 PDSCNC. Differentiatiegraad was de belangrijkste voorspeller voor overleving, met een 5-jaar DSS van 70,2% voor WMDNC, 35,9% voor PDLCNC en 46,1% voor PDSCNC. Tumor stadium bij presentatie bleek van beperkte waarde om de overleving en respons op behandeling te voorspellen, omdat de meeste patiënten zich presenteerden met gevorderde ziekte (stadium IV in 75%). In het algemeen leverde de toepassing van

chirurgie significant betere resultaten op (5-jaar DSS 52,2% versus 30,1%, $p < .001$). Radiotherapie was een waardevolle aanvulling op chirurgie voor patiënten met een PDLCNC (5-jaar DSS 54,7% versus 15,7%, $p = .027$), terwijl radiotherapie als monotherapie slecht presteerde in deze groep (5-jaar DSS 17,9%). Chemotherapie leverde voor geen van de groepen een verbetering op in overleving. Op basis van deze bevindingen concludeerden wij dat differentiatiegraad in combinatie met behandelstrategie, de belangrijkste voorspellers voor overleving zijn in NCS. In tegenstelling tot andere vormen van hoofd-halskanker, lijkt tumorstadium bij presentatie van beperkte waarde bij het voorspellen van de overleving. Chirurgie zou de basis moeten vormen van de behandeling, aangevuld met radiotherapie in matig of slecht gedifferentieerde neuro-endocriene carcinomen. De toepassing van chemotherapie lijkt geen verbetering van de overleving tot gevolg te hebben.

Deel III: Humaan Papillomavirus Infectie als Prognostische Marker

Het doel van Hoofdstuk VII was om humaan papillomavirus (HPV) infectie in NCL aan te tonen en de mogelijke relatie tussen HPV-geïnduceerde maligne transformatie en prognose te verkennen. Voor tien van de in Hoofdstuk II beschreven casus was biopsiemateriaal beschikbaar. Dit werd getest op de aanwezigheid van HPV 6, 11, 16 en 18 met behulp van een PCR-gebaseerde detectiemethode. Daarnaast werden immunohistochemische kleuringen uitgevoerd voor Ki-67, p16 (INK4A) en p53 expressie. Alle casus waren negatief voor de laag-risico HPV-typen HPV11 en HPV6, die worden geassocieerd met larynxpapillomatose. Hoog-risico HPV werd gedetecteerd in twee casus; één biopt van een MDNC was positief voor HPV16 en een ander biopt van een PDLCNC voor HPV18. Beide HPV-positieve tumoren hadden een hoge Ki-67 labeling index. Twee van de vier gevallen met een goede respons op de behandeling waren hrHPV-positief (beiden HPV-DNA positief) in vergelijking met geen enkele van de vijf slechte responders. Deze bevindingen tonen aan dat HPV een rol kan spelen in de pathogenese van NCL. Derhalve is het mogelijk dat de relatie tussen HPV en een gunstige prognose, zoals bekend in SCCHN, ook van toepassing is op een subset van NCL.

Algemene Conclusies en Verder Onderzoek

NCHN vormen een pluriforme groep tumoren met klinische kenmerken verschillend van HNSCC. Middels analyse van onze eigen ervaring en de literatuur bieden we in dit

proefschrift een overzicht van deze kenmerken en verschaffen we richtlijnen voor de behandeling van patiënten met een HCHN. In het algemeen kan gesteld worden dat de differentiatiegraad de belangrijkste factor is voor het voorspelen van de prognose en respons op therapie. Daarom is de eerste stap in de behandeling van patiënten met een NCHN het verkrijgen van een accurate histopathologische diagnose. Vooral in NCS moeten clinici er bij de patholoog op aandringen om onderscheid te maken tussen goed en matig gedifferentieerde neuro-endocriene carcinomen, omdat deze momenteel nog vaak onder de paraplu 'sinonasale neuro-endocriene carcinomen' worden geschaard, terwijl er grote verschillen bestaan in het klinische gedrag tussen deze tumoren. Verder hebben we voor het eerst de aanwezigheid van hr-HPV aangetoond in NCL, waarmee een mogelijke rol wordt gesuggereerd voor HPV als biomarker voor het voorspellen van de prognose en respons op therapie voor deze patiënten.

Richtlijnen voor Behandeling

WDNC zijn relatief goedaardige neoplasmen en kunnen worden behandeld middels chirurgische excisie, ongeacht hun locatie. MDNC van de larynx moeten worden behandeld middels radicale chirurgische excisie en electieve bilaterale halsklierdissectie, terwijl patiënten met een MDNC van de neusbijholten het meest gebaat zijn bij een combinatie van chirurgie en radiotherapie. PDNC van de larynx reageren het beste op een combinatie van radio- en chemotherapie. Daarentegen reageren PDNC van de neusbijholten niet goed op chemotherapie en kunnen het beste worden behandeld met een combinatie van chirurgie en radiotherapie.

Verder is het belangrijk dat clinici zich bewust zijn van de grote kans op een (laat) recidief. Het advies is dan ook patiënten met een NHNC minimaal tien jaar onder controle te houden.

Dit proefschrift verschaft een overzicht van het klinische gedrag van NCHN en aanbevelingen ten aanzien van de behandeling. Echter, gezien de retrospectieve aard van de studies is voorzichtigheid geboden bij de interpretatie van onze analyses. Hoewel een prospectief multi-center onderzoek onze conclusies zou kunnen versterken, is de uitvoering van een dergelijke studie in de praktijk onwaarschijnlijk vanwege de zeldzame aard van deze tumoren. Daarom moedigen we instellingen aan om hun ervaringen met HNNC te blijven publiceren.

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Curriculum Vitae

Tom-Paul van der Laan werd op 2 april 1985 geboren in Deventer, waar hij opgroeide bij zijn ouders en broertje. Na afronding van het VWO aan het Etty Hillesum Lyceum, startte hij in 2003 met de studie Geneeskunde aan de Rijksuniversiteit Groningen. Tijdens zijn coschappen in het Deventer Ziekenhuis raakte hij geïnteresseerd in de KNO-heelkunde, waarna hij is gestart met wetenschappelijk onderzoek naar neuro-endocriene tumoren van het hoofd-hals gebied onder begeleiding van dr G.B. Halmos. In afwachting van zijn keuze-coschap liep hij stage bij het Voice Center van het Massachusetts General Hospital in Boston onder begeleiding van dr. Zeitels. Na het behalen van zijn artsenexamen in 2012 startte hij met zijn promotietraject op de afdeling KNO-heelkunde van het Universitair Medisch Centrum Groningen onder leiding van prof. dr. B.F.A.M. van der Laan en dr. G.B. Halmos. Vanaf 2013 is hij in opleiding tot KNO-arts in het Universitair Medisch Centrum Groningen met als opleider prof. dr. B.F.A.M. van der Laan en in de Isala Klinieken te Zwolle onder dr. H.J. Rosingh.

Op 16 september 2017 trouwde hij met Anne den Heijer, met wie hij samenwoont in Groningen.