The Journal of Laryngology & Otology (2006), ***120***, *289–297.*

doi:10.1017/S0022215106000594
Printed in the United Kingdom
First published online 10 March 2006

Main Article

Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses

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Abstract

Introduction: Small cell neuroendocrine carcinoma (SNEC) of the sinonasal tract is a rare disease.

Objective: Report a descriptive study of a relatively large cohort of SNEC of the nasal cavity and paranasal sinuses.

Method: The medical records of 21 patients presenting with nasal and paranasal SNEC to various French hospitals, from 1989 to 2003, were analysed to determine the clinical features and current treatment of the disease.

Results: Patient data were obtained from eight French hospitals. Twelve of the patients were male and nine were female, with a mean age at presentation of 55 years (range: 27 to 79 years). Patients' staging for nasal cavity malignancy was: T_1, four; T_2, three; T_3, one; T_4, 13; N_0, 18; N_2, three; M_0, 20; and M_1, one. None of the patients suffered from SNEC of the sinonasal tract with ectopic hormone production. Immunohistochemistry proved useful for diagnosis in 20 cases. Twelve cases were positive for cytokeratin, 14 for chromogranin, eight for neuron-specific enolase and 11 for neuron-specific synaptophysin. One patient had an adenocarcinoma and an inverted papilloma associated with neuroendocrine carcinoma. Patients underwent surgery (11 cases), radiotherapy (14 cases) and chemotherapy (12 cases). Recurrence occurred in 10 cases. Five patients had visceral metastases or cervical lymph node involvement. Nine of the patients died within four years of onset of the disease.

Conclusion: Small cell neuroendocrine carcinoma of the sinonasal tract is an uncommon neoplasm with aggressive clinical behaviour. Recurrence is frequent and the prognosis is poor. However, the current treatment of these neuroendocrine neoplasms varies widely.

Key words: Carcinoma, Small Cell; Carcinoma, Neuroendocrine; Nasal Cavity; Paranasal Sinuses

Introduction

Small cell neuroendocrine carcinoma (SNEC) was first described in the nineteenth century in the context of lung cancer. Head and neck SNECs have been reported only since 1965.[1,2] However, an understanding of the pathology of this disease has been difficult to obtain due to its rarity and the complexity of the histological diagnosis. We have therefore collected data on the clinical characteristics and the treatment of nasal and paranasal SNEC from several French hospitals. The purpose of the current study was to report a descriptive study of a relatively large cohort of a rare tumour.

Patients and methods

This retrospective study reviewed nasal and paranasal SNEC, analysing the medical records of patients presenting with the disease in several French hospitals. Each center established histological diagnosis of these SNEC. Slides were not reviewed. The study covered the clinical presentation, laboratory results, medical imagery, localization and extent of the tumour (according to the recommendations of the American Joint Committee on Cancer for staging tumours of the nasal cavity and the ethmoid sinus),[3] the associated endocrine syndrome, histological diagnosis, treatment, and the course of the disease.

Results

Eight French hospitals participated in the study (the University Hospitals of Caen, Nancy, Nantes, Rouen, Lyon and Montpellier and the Comprehensive Cancer Centres of Caen and Nancy). The study

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Accepted for publication: 29 September 2005.

spanned a 14-year period, from 1989 to 2003, during which 21 patients presented with nasal and paranasal SNEC.

The mean age at presentation was 55 years (range: 27 to 79 years). A tumoral syndrome, with nasal obstruction and epistaxis, was present in 18 cases (86 per cent). Pain was experienced in the maxillary sinus (T_4 N_0 M_0) and the sphenoidal sinus (T_1 N_0 M_0). In three cases, the tumour was revealed by the presence of a node.

All patients had undergone computed tomography (CT) or magnetic resonance image (MRI) scanning. In most cases, primary tumour localization was difficult because of the considerable spread of the disease at the time of discovery. The sex distribution, tumour staging, presence of nodes and metastasis for the patients studied are shown in Table I. None of the patients presented with paraneoplastic endocrine syndrome.

The histological diagnosis of SNEC (Table II) was performed by optical microscopy using hematoxylin-Eosin-Safran (HES)-stained sections in all cases, and additionally by electron microscopy in two cases. Immunohistochemical analysis helped confirm the diagnosis in 20 cases. Several tumour antigens were identified: cytokeratin (12 cases), chromogranin (14 cases), neuron-specific enolase (eight cases) and synaptophysin enolase (12 cases). One SNEC was associated with an inverted papilloma and another with an adenocarcinoma.

The treatment of nasal and paranasal SNEC varied widely, with patients receiving a combination of surgery (nine excisions through a medial maxillectomy approach, one craniofacial resection, one endonasal procedure and two modified radical neck dissections), radiotherapy and chemotherapy (Table I).

Ten patients suffered recurrence of the disease. Eight of the recurrences occurred within the first two years, four were locoregional and one was locoregional with lymph node involvement. Four patients had metastases: bone metastases in two cases, liver metastases in one case, and liver and cerebral metastases in one case.

At the end of the study, nine of the 21 patients had died within six months to four years of presentation, and only one patient survived for more than 10 years.

Discussion

Classification

The classification of neuroendocrine tumours is particularly difficult, as noted by several authors.[4–6] Carcinoid tumours are commonly considered to be well differentiated neuroendocrine carcinomas, whereas atypical carcinoid tumours are regarded as moderately differentiated neuroendocrine carcinomas and SNECs are classified as poorly differentiated neuroendocrine carcinomas.

Small cell neuroendocrine carcinomas are mainly located in the lungs and account for 20 per cent of all lung carcinomas.[7] These tumours are characterized by rapid local invasion, metastasis and a median survival time for untreated patients of only two to three months. Extrapulmonary SNEC represents 4 per cent of all SNECs.[1] Less than 250 cases of head and neck SNEC have been published so far,[6] including 48 cases of SNEC in the nasal and paranasal cavities. Over a 40-year period, most reports have described very few such cases. Thus, eight reports discuss only one case;[2,6,8–13] three deal with two cases;[14–16] two describe four cases;[17,18] and one presents six cases.[19] Only one study covers 20 such cases.[20]

Aetiopathogenesis

It has been suggested that the location of SNEC in the nasal and paranasal cavity is explained by the existence of accessory salivary glands.[14]

Histological diagnosis

Macroscopic examination shows a whitish, friable and haemorrhagic tumour. Optical microscopy using HES-stained sections reveals sheets, cords or ribbons of small cells with little cytoplasm (Figure 1). The nuclei are large and pleomorphic, varying in appearance from the densely hyperchromatic to that of a punctate chromatin distribution. Mitotic figures are common. Scattered areas of necrosis may be observed and the typical crush artefact of neoplastic cells is often visible (Figure 1). The infiltrative nature of the tumour is evidenced by lymph-vascular spaces and perineural invasion.

However, HES staining may not be sufficient for the diagnosis of SNEC,[6,21–23] and other methods may prove useful. Grimelius' argentic staining reveals the cytoplasmic neurosecretory granulation characteristic of the neuroendocrine nature of the carcinoma; this coloration is positive in 80 per cent of cases.[24] Immunocytochemistry involves a carcinoma marker containing cytokeratine, and neuroendocrine differentiation is based on markers containing chromogranin (Figure 2), synaptophysin and neuron-specific enolase. Antibodies against protein convertase have also been used as endocrine cell markers.[25] Electron microscopy shows 50–200 nm neurosecretory granulations in the cytoplasm (Figure 3).[6] It also reveals intermediate filaments (tonofilaments) and cell-to-cell adhesive junctions (desmosomes). The absence of sustentacular cells suggests neuroendocrine carcinoma rather than esthesioneuroblastoma.[26]

Most authors agree on the usefulness of immunocytochemistry and electron microscopy in the diagnosis of SNEC.[6,26]

Population

Reports of cases of nasal and paranasal SNEC include 28 males and 20 females, with a mean age of about 50 years. No particular risk factor for this tumour appears to have been identified.[20,27]

Clinical signs

The clinical signs of SNEC are non-specific. The most frequent are the rhinological syndrome (nasal

https://doi.org/10.1017/S0022215106000594 Published online by Cambridge University Press

TABLE I

TNM CLASSIFICATION AND CURRENT TREATMENT OF NASAL AND PARANASAL SNEC

Patient number	Sex	Age (years)	Tumour stage[3]	Associated lesion	Head and neck imagery	Treatment	Course of disease	Last reported status (time since diagnosis)
1	M	64	T_1 N_0 M_0	–	CT MRI	S (tl)	R° at 10 years then R (60 Gy)	A (14 years)
2	M	51	T_1 N_0 M_0	–	CT MRI	S (sl) R C (fotemustin, Endoxan, Vepeside)		A (3 months)
3	F	65	T_1 N_{2a} M_0	–	CT	S of T + N (tl) R (30 Gy on T + 30 Gy on N) C (cisplatin + fluorouracil)	R° (N + metastasis)	D (8 months)
4	M	79	T_{4a} N_0 M_0	–	CT MRI	R (70 Gy on T)	–	D, oesophageal cancer (3 years)
5	F	47	T_{4b} N_0 M_0	–	CT	C (cisplatin + Vepeside) R running	–	A, treatment running (3 months)
6	F	59	T_2 N_0 M_0	–	CT	C (Adriblastin, Vepeside, Endoxan) R (60 Gy on T)	–	A (8 months)
7	M	60	T_{4b} N_0 M_1	–	CT	C (cisplatin, Vepeside)	Liver + cerebral metastasis at 9 months	D (1 year)
8	M	44	T_{4b} N_0 M_0	–	CT MRI	C (cisplatin, Adriblastin, Vepeside, Endoxan) R (70 Gy on T)	Loco-regional R° at 18 months	D (20 months)
9	M	54	T_2 N_0 M_0	–	CT	S R (55 Gy on T) C (cisplatin, Adriamycin, bleomycin)	Loco-regional + N R°	D (1 year)

Continued

TABLE I *Continued*

Patient number	Sex	Age (years)	Tumour stage[3]	Associated lesion	Head and neck imagery	Treatment	Course of disease	Last reported status (time since diagnosis)
10	F	47	T_{4b} N_0 M_0	–	CT MRI	S (sl) R (60 Gy on T, 60 Gy on N) C (cisplatin, Vepeside)	Loco-regional R°	D (4 years)
11	M	27	T_2 N_0 M_0	–	CT MRI	S (sl) C (Endoxan, Adriamycin)	Loco-regional R° at 1 year then R	D (18 months)
12	M	57	T_{4a} N_0 M_0	Inverted papilloma	CT MRI	S (il)	R° (N + bone metastasis)	D (6 months)
13	F	67	T_1 N_0 M_0	–	MRI	S (il) R (60 Gy on T)	–	A (4 years)
14	F	50	T_3 N_0 M_0	–	CT	S (sl)	–	A (3 years) then DO
15	F	63	T_{4b} N_{2c} M_0	–	CT MRI	C (cisplatin, Vepeside)	–	D (5 months)
16	M	51	T_{4a} N_0 M_0	Adenocar cinoma	CT MRI	C (cisplatin, Vepeside) then CRC (78 Gy on T + 50 Gy on N)	Continuous disease	A (1 year)
17	M	36	T_{4b} N_0 M_0	–	CT MRI	C (cisplatin, Vepeside) then CRC (70 Gy on T + 50 Gy on N)	–	A (1 year)
18	M	66	T_{4b} N_0 M_0	–	CT	R (76 Gy on T + 50 Gy on N)	–	A (1 year) then DO
19	M	53	T_{4a} N_{2a} M_0	–	CT MRI	S of T + N (sl) R (70 Gy on T + 50 Gy on N)	Bone metastasis at 6 months	A with continuous disease (6 months) DO at 2 years
20	F	54	T_{4b} N_0 M_0	–	CT MRI	S R (70 Gy on T)	Liver metastasis at 1.5 years	A (2 years)
21	F	72	T_{4b} N_0 M_0	–	CT MRI	R	–	A, treatment running (1 month)

TNM = tumour–node–metastasis; SNEC = small cell neuroendocrine carcinoma; M = male; F = female; CT = computed tomography scan; MRI = magnetic resonance imaging; S = surgery; sl = sane limits; tl = tangent limits; il = invaded limits; ni = no information; R = radiotherapy; C = chemotherapy; CRC = concomitant radio-chemotherapy; R° = recurrence; A = alive; D = dead; DO = dropped out

TABLE II

HISTOLOGICAL DIAGNOSIS OF NASAL AND PARANASAL SNEC

Patient number	OM	EM	IC	K	C	NSE	ESA	Other
1	Yes	No	Yes	−	+	+	−	
2	Yes	Yes	Yes	−	−	+	NI	Vimentin+
3	Yes	No	Yes	+	+	+	NI	CLA−
4	Yes	NI	Yes	NI	+	NI	+	CLA−
5	Yes	NI	Yes	NI	+	NI	NI	NI
6	Yes	No	Yes	+	−	−	NI	NI
7	Yes	No	Yes	+	+	NI	NI	NI
8	Yes	No	Yes	NI	−	−	NI	NI
9	Yes	No	Yes	−	+	+	−	NI
10	Yes	Yes	Yes	NI	+	NI	+	NI
11	Yes	NI	NI	NI	NI	NI	NI	NI
12	Yes	No	Yes	+	+	+	+	NI
13	Yes	No	Yes	+	+	+	+	NI
14	Yes	No	Yes	+	−	+	+	NI
15	Yes	No	Yes	+	NI	NI	+	CD 56+ LMP+
16	Yes	No	Yes	NI	+	NI	+	NI
17	Yes	No	Yes	+	NI	NI	+	CD 56+
18	Yes	No	Yes	+	+	NI	+	CD 56+
19	Yes	No	Yes	+	+	+	+	NI
20	Yes	No	Yes	+	+	NI	+	NI
21	Yes	No	Yes	+	+	NI	+	NI

SNEC = small cell neuroendocrine carcinoma; OM = optical microscopy with HES (hematoxylin-Eosin-Safran); EM = electron microscopy; IC = immunocytochemistry; K = keratin; C = chromogranin; NSE = neuron-specific enolase; ESA = enolase synaptophysin; NI = no information

obstruction, rhinorrhoea and epistaxis)[6,11,20] and ophthalmic signs (exophthalmos, visual acuity trouble and limitation of eye mobility).[11,20]

Less frequently, other signs suggesting loco-regional invasion have been reported such as local pain or anosmia.[20] Metastatic cervical nodes have also been described.[20]

Anatomical imaging

Anatomical imaging can reveal signs of malignancy, such as the existence of a lytic process. Magnetic resonance imaging with T1, T2 and gadolinium injections improves differentiation between inflammatory reaction, tumour and liquid retention; MRI also identifies the anatomical relationship between the tumour and the meninges.[27] Nasal and paranasal CT or MRI scans of the sinuses are more useful than conventional radiography.

Staging classification for nasal cavity malignancy

The initial localization of the tumour is rarely precise, usually because of its late discovery. To date, no staging system has been generally adopted for carcinomas of the nasal cavity. For neuroendocrine tumours of the sinonasal tract, the Kadish classification[28] is often used.[3,20,27] This staging allows differentiation between the several groups of tumour: group A (tumours limited to the nasal cavity), group B (tumours localized in the nasal

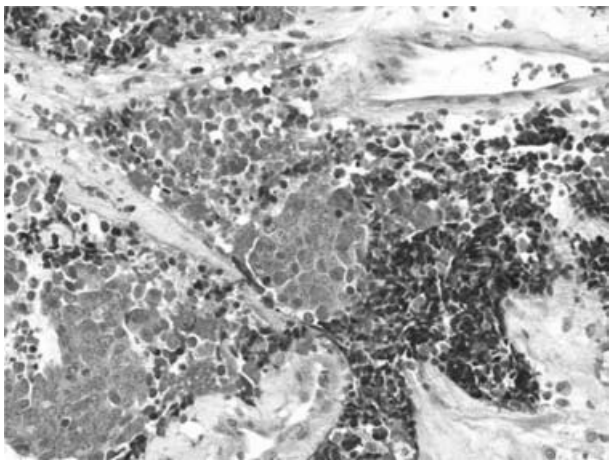

FIG. 1

Neuro-endocrine carcinoma composed of small cells, with marked crush artefact.

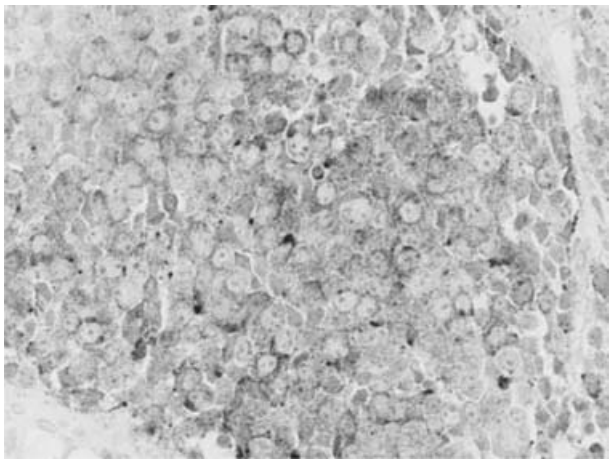

FIG. 2

Tumour cells expressing chromogranin.

https://doi.org/10.1017/S0022215106000594 Published online by Cambridge University Press

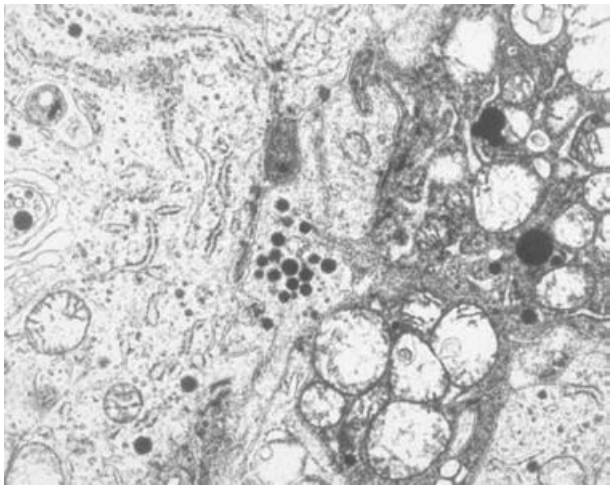

FIG. 3
Ultrastructure (electron microscopy): cytoplasmic dense core granules.

cavity and paranasal sinuses) and group C (tumours extending beyond the nasal cavity and paranasal sinuses). Only two stage-A SNECs have been reported so far.[19,20] However, the Kadish classification is not considered to be reliable enough. In particular, it fails to take into account several factors such as cerebral invasion, lymph node involvement, visceral metastases and the associated endocrine syndrome. Although tumour–node–metastasis staging is not perfect for SNECs, it seems more accurate than the Kadish classification and may prove to be a better tool for the prediction of mean survival times.

Associated tumours

Only one case of an association between SNEC and adenocarcinoma of the nasal cavity has been reported.[20] In our study, we found one case of SNEC associated with an inverted papilloma and another associated with a nasal adenocarcinoma.

Associated endocrine syndrome

The association between the paraneoplastic endocrine syndrome and SNEC is well documented. The most frequent endocrine syndrome, an abnormal secretion of antidiuretic hormone, is found in 10 per cent of pulmonary SNECs.[29] Other paraneoplastic hormones have been described, such as corticotrophin, calcitonin, parathormone, glucagons and somatotrophin-releasing hormone.[7,30]

The paraneoplastic endocrine syndrome appears rarely in head and neck cancers. More than 75 per cent of cases concern epidermoid carcinoma.[31] Only 20 cases of endocrine syndrome associated with head and neck SNECs have been reported.[6] The tumour location was the larynx in 12 cases,[6,32–34] the tonsil in one case,[6] the parotid in two cases,[6,35] and the nasal and paranasal cavities in five cases.[6,13,17] The hormones implicated were antidiuretic hormone, corticotrophin, calcitonin, serotonin and parathormone. Four cases presented simultaneous secretion of two or three of these hormones.[6] Only half of the patients had symptoms of paraneoplastic secretion.[6]

Paraneoplastic endocrine secretion is usually detected during the diagnosis of SNEC but it may appear at various stages of the course of the disease.[6]

We found no cases of endocrine secretion in our study. This may be explained by the low incidence of endocrine secretion in the SNEC localizations concerned, and the difficulty in identifying this secretion due to the absence of symptoms and the lack of variation of the secretion over time. However, the detection of paraneoplastic endocrine secretion could contribute to the diagnosis of SNEC and to improvement of patients' quality of life and could even increase the survival rate through early detection of the disease.[6]

Treatment

Three therapeutic methods are currently used: surgery, radiotherapy and chemotherapy, usually with cisplatin and etoposide. Different associations have been described in the 48 cases published: one case without treatment; seven with surgery alone; two with radiotherapy alone; one with chemotherapy alone; 18 with surgery followed by radiotherapy; two with surgery associated with chemotherapy; eight with chemotherapy associated with radiotherapy; and six with all three methods. Three reports of SNEC gave no information on treatment.

The treatment of SNECs has varied considerably over time. Thus, in the 1980s, surgery followed by radiotherapy was favoured by the authors of the largest study[20] and has also been recommended more recently.[18] In the late 1990s, the association of chemotherapy and radiotherapy, with or without surgery, produced encouraging results at 14 months and 45 months for neuroblastoma and SNECs of the nasal and paranasal cavities.[36,37]

Lymph node treatment with dissection and/or radiotherapy does not seem justified in the absence of a palpable node. Cerebral radiotherapy has been reported in only one case of a nasal cavity tumour extending to the maxillary sinus and orbit.[14]

Taking into account the information available in the literature,[36,37] for neuroendocrine carcinoma with good results, it could be interesting to suggest the same strategy for the treatment of SNECs of the sinonasal tract. The protocol was proposed in the 35th Congress of the French Cervico-Facial Carcinological Society (November 2003) and is presented in Figure 4.

Course of the disease and prognostic factors

Recurrences of SNEC or metastases have been reported to occur after three years in 70 per cent of patients, i.e. 14 of the 20 patients, with multiple recurrences in more than half of the cases.[20] However, in our study, 80 per cent of patients, i.e. 17 of the 21 patients, suffered relapses or metastases within the first two years. Recurrence or

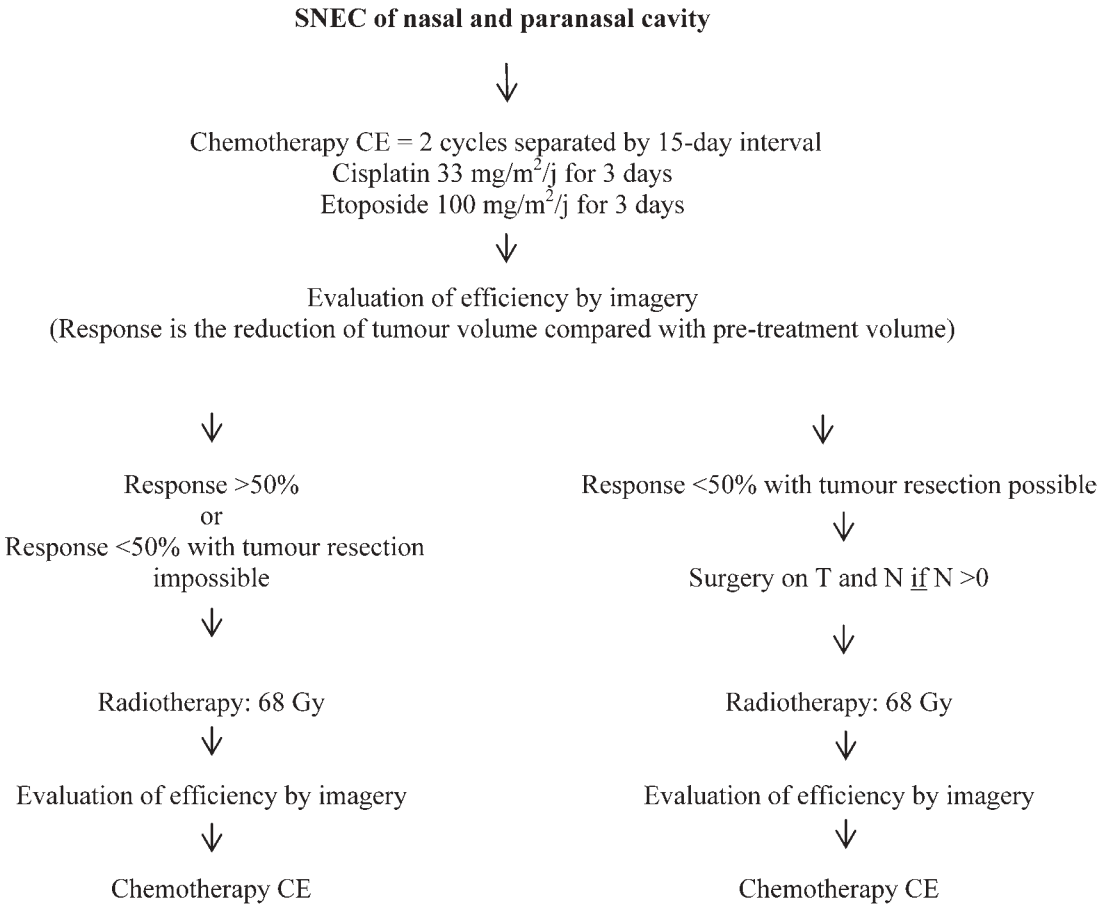

FIG. 4
Therapeutic protocol for nasal and paranasal cavities small cell neuroendocrine carcinoma (SNEC). Adapted with permission.[38–40] CE = Dr F. Flori [EDK desk editor].

death occurred on a mean timescale of 37 months,[19] with a risk of metastasis in 37 per cent of cases.[8,14,19]

The prognosis in cases of head and neck SNEC is very poor because of the high rate of metastases observed. Common metastatic locations are the brain, lungs, bones and skin.[6] Loco-regional invasion may also lead to death.[6]

Non-pulmonary SNECs are reported to be associated with a survival rate of up to 13 per cent at five years;[38] however, the survival rate is only about 13 months for head and neck SNECs.

The prognosis seems more favourable in the case of nasal and paranasal localizations, with 100 per cent of patients alive at five years, 88 per cent at seven years and 77 per cent at 10 years.[11] In our study, the median survival rate was between two and three years.[19]

Unfavourable prognostic factors, such as invasion of the lamina cribosa, have been discussed.[20] The ectopic hormone syndrome is a predictor of an increased mortality of pulmonary SNEC patients because of the higher risk of cerebral metastasis.[39] The endocrine syndrome also seems to worsen the prognosis in cases of head and neck SNEC. Thus, among the 20 patients reported, three dropped out, 15 died between six and 18 months, and only two survived, with no evidence of disease at seven and 18 months.[6,13,17] Among these 20 cases of head and neck SNEC, five involved the nasal and paranasal cavities. Four of the patients died of the disease, at six months, eight months, six years and 10 years, variously.[6,17] The last patient was alive with the disease at 16 months.[13] Other factors, such as size of the tumour and number of mitoses, show no correlation with recurrence, metastases or survival.[20]

Conclusion

Nasal and paranasal SNECs are aggressive tumours with a high rate of recurrence and a very poor short term prognosis. These tumours have low incidence and their diagnosis is difficult. Our study and our review of the literature does not, on its current form, provide evidence for a rational investigation and treatment protocol.

Acknowledgements

We are grateful to Mr K Malkani for his critical reading of the text, and we thank the following otolaryngologists and head and neck surgeons for giving us access to the medical records of their

patients: M Hitier and F Comoz, University Hospital (CHU) Caen; C Planes and C Simon, CHU Nancy; J P Rame, Centre François Baclesse, Caen; J C Pignat, Hôpital Croix Rousse, Lyon; and O Choussy, CHU Rouen.

- **Small cell neuroendocrine carcinoma (SNEC) of the sinonasal tract is a rare disease. This paper reviews the presentation, management and outcome of 21 patients with nasal SNEC in various French hospitals**
- **These tumours are aggressive in behaviour, with a poor prognosis. Both local and systemic metastasis is common**
- **An aggressive therapeutic approach, with combined chemotherapy, radiotherapy and surgery if possible, is advocated**

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Dr E Babin takes responsibility for the integrity of the content of the paper.
Competing interests: None declared