ORIGINAL ARTICLE

Challenges in the Treatment of Sinonasal Undifferentiated Carcinoma: A Ray of Hope

A N Norleza, MBBS, B S Gendeh, MS ORL HNS

Department of Otorhinolaryngology, Head & Neck Surgery, Faculty of Medicine, Hospital University Kebangsaan Malaysia, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur

Summary

We studied nine cases of SNUCs presented to the Department of Otorhinolaryngology, Hospital University Kebangsaan Malaysia from 1999 to 2003. There were 8 males and 1 female with ages ranging from 24 to 78 years (mean 46.5y). The racial distribution consisted of 5 Chinese (55.5%), 3 Malays (33.3%%) and 1 Indian (11.1%). Three patients were Kadish B (33.3%) and six were Kadish C (66.6%) by classification. In our series 2 years survival was 26.3% and median survival time was 14.2 months.

Key Words: Sinonasal undifferentiated carcinoma, Sinonasal tumors, Nasal tumors

Introduction

Sinonasal undifferentiated carcinoma (SNUC) is an aggressive neoplasm arising within the nasal cavity or paranasal sinuses. Advanced local disease at the time of diagnosis is not uncommon. Levine et al[2] reported involvement of the orbit in 6 patients and intracranial extension in 7 of 11 patients. Aggressive combined-modality treatment with surgery, radiation therapy, and chemotherapy have yielded an improved response, though the overall prognosis remains poor. The median survival ranges from 12.3 months to 40.5 months [1,2]. The optimal treatment is yet to be determined. It is important to recognize and differentiate this distinct tumor from other nasal tumors because of its aggressive behavior, since early intervention may result in a better outcome.

Materials and Methods

The data of nine cases of SNUCs seen in the Department of Otorhinolaryngology, Hospital University Kebangsaan Malaysia from 1999 to 2003 were analysed. Detailed clinical information, including the age, sex, symptoms, physical findings, localization and extension of tumors, status of the regional lymph nodes, evidence of distant metastasis, treatment modality and clinical status at last follow up were obtained from the hospital records. In all cases, nasal endoscopy, computed tomography and/or magnetic resonance imaging were performed to assess the tumour location and extent. The tumour staging was based on Kadish classification - Group A tumors limited to the nasal cavity, Group B tumors limited to the paranasal sinuses, Group C tumors extending beyond the paranasal sinuses[9]. Survival analysis was carried out using Kaplan-Meier method.

Results

Nine patients with adequate data of SNUC between 1999-2003 were included in the study. There were 8 males and 1 female with ages ranging from 24 to 78 years (mean 46.5y). The racial distribution consisted of 5 Chinese (55.5%), 3 Malays (33.3%%) and 1 Indian (11.1%). The mean duration of symptoms before

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Corresponding Author: Norleza A Norhan, Department of Otorhinolaryngology, Faculty of Medicine, Hospital Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, 56000 Cheras, Kuala Lumpur

diagnosis was 5.0 months. Five patients presented with epistaxis, four had diplopia or other ocular symptoms. Nasal blockage and headache were other frequent presenting symptoms. Three patients were Kadish B (33.3%) and six were Kadish C (66.6%) classification. The local extent of disease is shown in Fig 1. Two patients were initially treated for nasopharyngeal carcinoma with radiotherapy 2 and 13 years prior. Five patients received adjuvant radiotherapy but only two of them had chemotherapy.

The computed tomography and MRI features of sinonasal undifferentiated carcinoma were nonspecific in this series. The common findings were soft tissue mass within the nasal cavity and sinuses with bony destruction and invasion of adjacent structures, including the anterior cranial fossa, adjacent paranasal sinuses, and orbits. Obstruction of adjacent sinuses were commonly noted. The tumors were noncalcified and had variable contrast enhancement.

The neoplasms consists of medium-sized, polygonal cells with hyperchromatic nuclei and prominent nucleoli that form nests, wide trabeculae, ribbons and sheets. A high mitotic rate, tumor necrosis, and prominent vascular invasion were essential features. Immunohistochemical staining for cytokeratin was positive in all patients with positive epithelial membrane antigen (EMA) in three patients. Leucocyte common antigen (LCA) done in six patients and synaptophysin, chromogranin, S100, vimentin done in two patients were all negative.

The patients treatment and outcome were listed in Table I.

Maxillectomy

Three patients underwent partial or total maxillectomy. The first patient had no intracranial or orbital involvement and is alive without disease after 26 months post diagnosis. The second patient was initially misdiagnosed as recurrent nasopharyngeal carcinoma and treated with chemotherapy for 6 cycles with no response. He subsequently underwent maxillectomy with bilateral neck dissection but expired 12 months post diagnosis. The third patient had orbital exenteration followed by radiotherapy and died 15 months post diagnosis due to liver failure as a result of liver metastases.

Craniofacial resection (CFR)

Two patients underwent CFR. The first patient was initially diagnosed as NPC and treated with radiotherapy. Two years later she presented with mass over the ethmoid region involving the orbit. Orbital exenteration with rectus abdominis flap was performed but recurrence involving the frontal lobe occurred 14 months later. The patient underwent tumour excision with rotational flap repair but died 27 months post diagnosis with evidence of rib metastases. The second patient had CFR complicated with CSF leak where lumbar drain was inserted. Intraoperatively margins were positive and received adjuvant radiotherapy. The patient subsequently died 12 months post diagnosis.

Microendoscopic technique

Two patients had combined microendoscopic debulking of tumour with neurosurgical cooperation. The first patient had endoscopic debulking of tumour with transglabellar approach and orbital exenteration. The patient had residual tumour with rib metastases and died 11 months after diagnosis. The second patient had LeFort 1 osteotomy with transphenoidal approach and endoscopic debulking of tumour. The patient received adjuvant chemoradiotherapy. At three months follow up MRI revealed residual tumour at the clival region.

Two patients with advanced intracranial involvement died before treatment was commenced. The 2 year survival for all nine patents was 26.3%. The Kaplan Meier survival curves with 95% confidence intervals for the 1999-2003 period is shown in Fig 2.

Discussion

SNUC was first described in 1986 by Frierson et al[1] as an aggressive neoplasm that was clinicopathologically distinct from other poorly differentiated malignancies of the nasal cavity and sinuses. Differential diagnosis of such tumors include esthesioneuroblastoma, neuroendocrine carcinoma (SNEC), rhabdomyosarcoma, lymphoepithelioma, lymphoma, melanoma and poorly differentiated adenoid cystic carcinoma. However, this tumors can be distinguish by correlating clinical, light microscopic and immunohistochemical features. SNUC commonly involve more anterior nasal cavity and ethmoids1. Microscopically it consist of small to medium sized polygonal cells which form nest, sheets and trabeculae[11]. The cells have high nucleus cytoplasmic ratios and numerous mitosis. Prominent angiolymphatic invasion, extensive necrosis, and absence of significant lymphoid population are often a distinguishing features. SNUC lack Homer Wright

Table I: Patients Diagnosed and Treated for SNUC at Hospital UKM 1999-2003

No	Age	Race	Intracranial	Orbital	Stage	XRT	Chemotherapy	Operation	Margins	Status	Metastasis	Survival
1	45	Chinese	No	No	B	Yes	None	Maxillectomy	Clear	NED	None	26
2	45	Chinese	No	Yes	B	None	Neoadjuvant	Maxillectomy	Close	DOD	None	12
3	48	Chinese	Yes	Yes	B	Yes	None	Maxillectomy	Clear	DOD	Liver	15
4	24	Malay	Yes	Yes	C	None	None	CFR	Clear	DOD	Ribs/Sternum	27
5	52	Chinese	Yes	No	C	Yes	None	CFR	Positive	DOD	None	12
6	24	Indian	Yes	Yes	C	Yes	Adjuvant	Endoscopic/ Transglabellar	Positive	DOD	Ribs/ Lymph Node	10
7	45	Malay	Yes	No	C	Yes	Adjuvant	Endoscopic/Le Fort 1	Positive	AWD	None	11
8	48	Chinese	Yes	Yes	C	None	None	None		DOD	None	3
9	78	Malay	Yes	Yes	C	None	None	None		DOD	Lymph Node	3

CFR - Craniofacial Resection AWD - Alive with Disease DOD - Died of Disease NED - No Evidence Disease

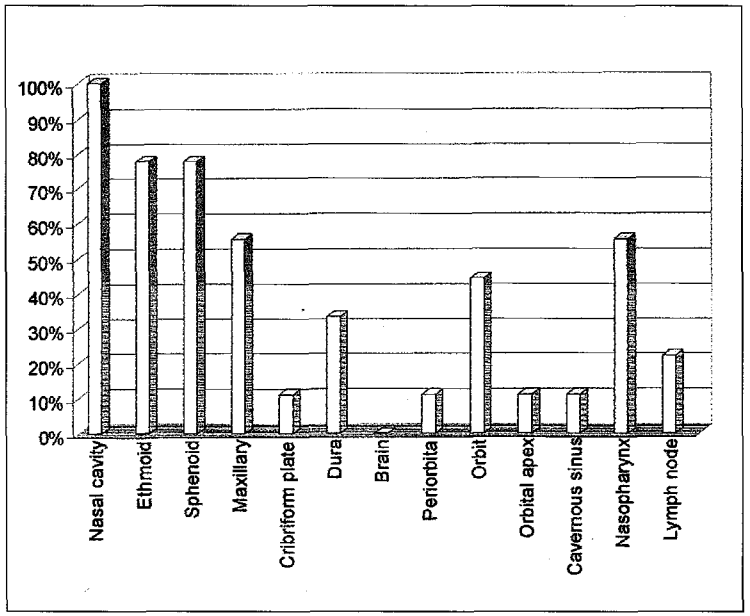

Fig. 1: Local extent of disease for patient with SNUC (1999-2003)

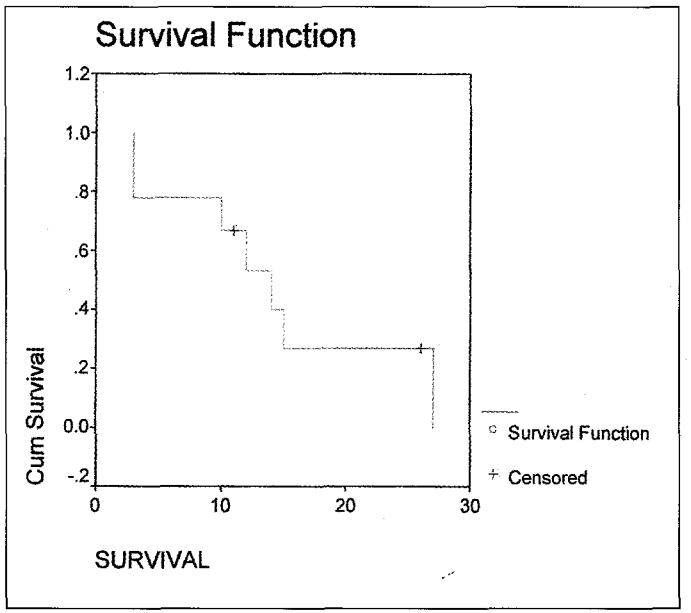

Fig. 2: Overall survival with 95% confidence intervals (1999-2003)

rosettes which often observed in esthesioneuroblastoma. Intercellular fibrils, argyrophilic granules and squamous or glandular differentiation are also absent[1]. Imunohistochemically all SNUCs are positive for cytokeratin or EMA and many stains for both epithelial markers. Approximately one half of the tumors are positive for NSE, most lack S100 immunoreactivity and all negative for vimentin[1,10,11].

The age at presentation of 45.5 years was similar to other studies at approximately 50 years (range, 20 to 77 years) [4,5,8]. The pathogenesis of SNUC remains unknown but it is reported to have an association with cigarette smoking? and ionising radiation. In a study reported by Jeng et al[6] five of 36 cases were long term survivors of NPC treated with radiotherapy at 6-26 years prior. The criteria for a diagnosis of radiation induced tumors includes documented history of irradiation, latency period longer than 5 years with histologically proven malignant tumor arising within the irradiation field and different histology of the new tumor if radiation therapy was administered for malignancy.

SNUC has a characteristics of rapid growth, propensity for invasion and destruction of local structures. In our series, despite the combined modality of treatment, most patients succumbed to the disease except one patient who had no orbital or intracranial involvement. Smith et al[4] reported six patients with SNUC who had been treated with surgical resection and postoperative radiotherapy. Only one of them died, and two had no evidence of disease. However, the mean follow-up was less than 12 months. The literature review reveals that patients treated with chemoradiotherapy may enjoy surprisingly long remissions[3]. Some authors recommended preoperative cyclophosphamide/ doxorubicin/vincristine chemotherapy and radiotherapy (50Gy) for patients without distant metastases and without extensive intracranial involvement[7]. In another study of 10 patients who underwent surgical resection, only 2 had no evidence of recurrences[3]. Analysis of patterns of failure reveals an approximately equal number of local, regional, and distant recurrences. Virtually all failures manifested within 2 years of surgery.

Our results revealed a 26.3% overall 2-year survival rate as compared to Miyamoto et al[5] 42% and Musy et al 47%[3]. The median survival time is 14.20 months.

We conclude that treatment of SNUC remain a challenge that requires multidisciplinary approach, including otolaryngology, neurosurgery, ophthalmology and oncology. Despite the generally guarded prognosis some patients were cured if diagnosed early and patients with locally advanced disease will enjoy prolongation of life with minimal treatment related morbidity with microendoscopic tumour resection followed by chemoradiotherapy only.

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