Clinical Characteristics and Prognosis of Small Cell Carcinoma in the Nasopharynx: A Population-Based Study

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Abstract

Background: Nasopharyngeal small cell carcinoma (SmCC) is a rare histological type of nasopharyngeal cancer, and its prognosis remains poor. This study aimed to determine the clinical characteristics and survival prognostic factors of nasopharyngeal SmCC.

Methods: Detailed clinicopathologic and therapeutic characteristics of a patient diagnosed with nasopharyngeal SmCC were determined. Nasopharyngeal SmCC cases reported previously were reviewed and summarized. Furthermore, a retrospective analysis was performed on data from the Surveillance, Epidemiology, and End Results (SEER) Program database. Kaplan–Meier analysis was conducted to compare survival within groups. Univariate and multivariate analyses were performed to investigate prognostic factors.

Results: A nasopharyngeal SmCC patient treated with chemoradiotherapy who achieved 46 months long-term survival was reported. In reviewing 16 reported cases with epidemiologic and therapeutic details, we found most of nasopharyngeal SmCC patients were diagnosed with advanced grades and received chemoradiotherapy. In total, 13,993 cases of nasopharyngeal cancer were extracted from the SEER database, from which 57 nasopharyngeal SmCC cases were eventually screened out. The mean age of the patients was 55.70 years, and 64.9% of these cases were either grade III or IV; the median overall survival (OS) was 18 months. Statistically significant differences were observed in the OS values of groups categorized by age (P = .025) or radiotherapy (P = .037). Age (<70 years) and radiotherapy were identified as independent survival and prognostic factors.

Conclusion: Patients with nasopharyngeal SmCC are usually diagnosed with advanced grades and have poor prognoses; nevertheless, they can benefit from radiotherapy with prolonged overall survival.

Keywords

nasopharyngeal small cell carcinoma, prognostic factors, SEER database, radiotherapy, clinical characteristics

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Introduction

In 2018, 129,079 new cases of nasopharyngeal carcinoma (NPC) were reported globally; more than 70% of these cases occurred in East and Southeast Asia. In recent years, most NPC patients have exhibited substantially reduced mortality and prolonged survival times, owing to the sensitivity of NPC to chemoradiotherapy. Nevertheless, the prognosis of nasopharyngeal small cell carcinoma (SmCC), which is a relatively rare type of nasopharyngeal cancer, remains poor. A population-based analysis of the National Cancer Database revealed that only 3% of all head and neck cancer patients were diagnosed as having SmCC, among which 10% were nasopharyngeal in origin. Moreover, nasopharyngeal SmCC has been reported to have the worst prognosis of all SmCCs of the head and neck.

According to previous studies, the age of patients with SmCC varies from 5 to 80 years, and most nasopharyngeal SmCC cases have been found to be incredibly lethal, with poor survival outcomes; it has been demonstrated that patients are mainly in advanced stages when diagnosed with SmCC, and that they are prone to metastasis. To date, there are no standard therapeutic schemes or guidelines for nasopharyngeal SmCC, and this condition is so rare that to date it has not been listed in the World Health Organization (WHO) classification of nasopharyngeal cancer. Furthermore, its diagnosis and treatment are challenging. Current strategies for the therapeutic treatment of nasopharyngeal SmCC comprise chemotherapy and/or radiotherapy; surgery can also serve as a therapeutic modality for early stage nasopharyngeal SmCC. Unfortunately, there are few available studies in this regard. Various therapies, including surgery, radiotherapy, chemotherapy, immune therapy, and combined therapies, have been studied for SmCCs of the head and neck.

However, to date, there has been no large-scale population-based analysis of the specific clinical characteristics and survival prognostic factors of nasopharyngeal SmCC. Accordingly, in this study, we aimed to determine the clinical characteristics and survival prognostic factors of nasopharyngeal SmCC by studying the case of a patient with nasopharyngeal small cell neuroendocrine cancer who presented at the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China. According to the search results of medical records, this was the only case of nasopharyngeal SmCC in our hospital in the recent 10 years. Detailed information on his radiological and pathological images and results, course of treatment, and follow-up were collected and analyzed.

Immunohistochemistry was performed as described in previous studies. Tissue specimens were fixed, sectioned, and stained according to standard procedures. Hematoxylin and eosin (H&E) staining was performed on tumor tissue samples, followed by immunohistochemical staining with Ki67 rabbit monoclonal antibody (1:400, #9027, Cell Signaling Technology, Boston, the United States), CD56 mouse monoclonal antibody (1:800, #3576, Cell Signaling Technology, Boston, the United States), pan-keratin mouse monoclonal antibody (1:200, #67306, Cell Signaling Technology, Boston, the United States), synaptophysin (SYN) rabbit monoclonal antibody (1:200, #36406, Cell Signaling Technology, Boston, the United States), and an EBER detecting kit (ISH-7001, ZSGB-BIO, Beijing, China).

Methods

Case Presentation

A patient was diagnosed with primary nasopharyngeal small cell neuroendocrine carcinoma at the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China. According to the search results of medical records, this was the only case of nasopharyngeal SmCC in our hospital in the recent 10 years. Data concerning SmCC cases were obtained from the SEER database, which provides detailed patient outcomes and covers approximately 27.8% of the population of the United States of America (USA). In accordance with the primary site code C11.1-C11.9 and the International Classification of Disease, Oncology, third revision (ICD-O-3) code 8041/3, 60 cases were screened from 1975 to 2015; the primary site of each case was the nasopharynx, and the histology type was SmCC. Three cases with an overall survival (OS) of less than 1 month were excluded in the survival analysis session, considering that they might be in poor performance status or the time frame is too short for the treatment to be effective. The variables analyzed included age (for further analysis, patients were divided into 2 groups [age <70 or ≥70 years]) according to previous studies, sex, race, year of diagnosis, grade, histology, metastasis, surgery, radiotherapy, chemotherapy, and survival time.

Literature Review

An updated review of nasopharyngeal small cell cancer (SmCC) plus original report through October 2021 was conducted by searching PubMed for articles in any languages as well as their references, with the terms “SmCC,” “small cell cancer,” and “nasopharyngeal cancer.” And then, the epidemiologic features, therapeutic strategies, and survival status of reported cases including the present case were gathered and summarized.

Patient Selection From the SEER Database

Data concerning SmCC cases were obtained from the SEER database, which provides detailed patient outcomes and covers approximately 27.8% of the population of the United States of America (USA). In accordance with the primary site code C11.1-C11.9 and the International Classification of Disease, Oncology, third revision (ICD-O-3) code 8041/3, 60 cases were screened from 1975 to 2015; the primary site of each case was the nasopharynx, and the histology type was SmCC. Three cases with an overall survival (OS) of less than 1 month were excluded in the survival analysis session, considering that they might be in poor performance status or the time frame is too short for the treatment to be effective. The variables analyzed included age (for further analysis, patients were divided into 2 groups [age <70 or ≥70 years]) according to previous studies, sex, race, year of diagnosis, grade, histology, metastasis, surgery, radiotherapy, chemotherapy, and survival time.
Figure 1. (A) Hematoxylin and eosin (H&E) staining of the nasopharyngeal tumor specimen under ×100 magnification. (B) Hematoxylin and eosin (H&E) staining of the nasopharyngeal tumor specimen under ×200 magnification. The tumor mass is immunopositive for (C) CD56, (D) creatine kinase (CK), (E) Ki67, and (F) synaptophysin (SYN; ×200 magnification); it is immunonegative for (F) chromogranin A (CgA), (G) EBER, (H) p40, and (I) p63.
nasopharyngeal neoplasm was performed. The mass in the nasopharynx, following which a biopsy of the endoscopic examination indicated the presence of a malignant bleeding and a headache that had lasted for 4 days. A nasal Sun Yat-sen University, Zhuhai, China, complaining of nasal

Statistical Analysis

The clinical characteristics of patients with SmCC were examined and summarized in a table. The Kaplan–Meier estimator was used to describe the distribution of survival time. The reverse Kaplan–Meier methods were applied to estimate the median follow-up time. The log-rank test was used to compare survival between different strata. The OS was defined as the period of time from the date of diagnosis to the date of either death or the end of follow-up. Univariate and multivariate Cox regression analyses were performed to analyze the variables associated with OS. We checked the validation of proportional assumptions of the cox models as previously described, and there were no significant violations. Variables with P-value <.1 in univariate analysis were included for multivariate analysis. The corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. A two-tailed P < .05 was considered to represent statistical significance. All statistical analyses were performed using the “survival” R package (v. 3.6.3) and IBM SPSS 26.0 software (IBM Corporation, Chicago, IL, USA).

Results

Case Presentation of a Nasopharyngeal SmCC Patient Exhibiting Complete Remission

On January 8, 2018, a 44-year-old male patient visited the head and neck surgery clinic of the Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China, complaining of nasal bleeding and a headache that had lasted for 4 days. A nasal endoscopic examination indicated the presence of a malignant mass in the nasopharynx, following which a biopsy of the nasopharyngeal neoplasm was performed. The final pathological diagnosis was nasopharyngeal small cell neuroendocrine cancer. Microscopic analysis revealed clusters of small cells (Figure 1 A and B), which were found to be immunopositive for CD56, creatine kinase (CK), Ki67, and SYN (Figure 1 (C)-(F)) and immunonegative for CgA, p63, p40, and EBER (Figure 1 (G)-(J)).

The patient was then admitted to the Cancer Center of the Fifth Affiliated Hospital of Sun Yat-sen University for further diagnosis and treatment. Magnetic resonance imaging (MRI) confirmed the presence of a tumor mass, which was primarily located in the left side of the nasopharynx. It had invaded the sphenoid bone and the ethmoid, with retropharyngeal lymph node metastases occurring on both sides. A chest X-ray, abdominal ultrasound, and emission computed tomography bone scan all confirmed that there were no distal metastases. Thus, the tumor was staged as T4N2M0, IVA. The Eastern Cooperative Oncology Group performance status (ECOG-PS) of this patient was 0. Subsequently, the patient received intensity modulated radiotherapy for a total dose of 66 Gy with 33 fractions. They received concurrent chemotherapy, comprising 1 course of cisplatin followed by 2 courses of cisplatin (40 mg, day 1–3) and etoposide (150 mg, day 1–3). The patient completed radiotherapy and chemotherapy in June, 2018, following which they received a regular follow-up. MRI images of the tumor before and after therapy are shown in Figure 2 (A) and (B), respectively. The response was assessed as complete remission. As of the last follow-up date (23 November, 2021), the patient remains in complete remission, indicating that his OS is 46 months.

Literature Review of Reported Cases of Nasopharyngeal SmCC Patients

A review of the literature identified 16 pertinent cases of nasopharyngeal SmCC (Table 1); with the case reported here being the 17th case. The age of patients diagnosed in these cases ranged from 5 to 80 years, with the most affected age range being 40–60 years. There was a relatively equal sex distribution of 9:8 (male vs female). A large proportion of these patients (12 cases out of 17 cases) received chemoradiotherapy, with their total radiation doses ranging from 59.4 to 70 Gy; cisplatin-etoposide was the most commonly scheduled chemotherapy regime. The longest overall survival time of those reported patients was 4 years, and some patients died before the treatment could be initiated.

Clinical Characteristics of Nasopharyngeal SmCC Patients in the SEER Database

The clinical characteristics of 60 nasopharyngeal SmCC cases extracted from the SEER database are described in Table 2. The patient selection flow chart was shown in Figure 3. The mean age of patients with nasopharyngeal SmCC was 56.70 years; 78.3% of the patients were aged <70 years, whereas 21.7% were ≥70 years old. Among the 60 cases, 20 (33.3%) were females and 40 (66.7%) were males, and the sex ratio (male: female) was 2:1. The majority of the patients were white (81.7%), and 80.0% of the cases were diagnosed during 1995–2015. Most of nasopharyngeal SmCC cases had
| Case | Study                      | Year of Report | Gender | Age (years)  | Stage                  | Treatments                                                                 | Responses and outcomes                                                                 | Survival status |
|------|----------------------------|----------------|--------|--------------|------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------|
| 1    | Galera-Ruiz et al.         | 2001           | Female | 48           | Not available          | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 59.4 Gy)             | PD; DOD 4 months after completion of treatment                                      | Dead            |
| 2    | Lin et al.                 | 2008           | Female | 53           | T4N0M0/IV              | Chemoradiotherapy (cisplatin-VP-16 + radiotherapy 50 Gy)                   | CR, followed by PD (lymph node and lung metastasis) after 6 months, DOD at 38 months | Dead            |
| 3    | Mohebbi et al.             | 2008           | Female | 74           | Not available          | Complete resection followed by chemotherapy                                | CR; NED at 18 months                                                                  | Alive           |
| 4    | Deviprasad et al.          | 2008           | Male   | 40           | Not available          | Surgery                                                                      | Local recurrence at 6 months; DOD at 11 months                                       | Dead            |
| 5    | Hatoum et al.              | 2009           | Female | 66           | T4N1M0/IV              | Chemoradiotherapy (Cytoxan-vincristine-lomustine-methotrexate + radiotherapy, radiation dose: unknown) | Local recurrence; DOD at 15.2 months                                                  | Dead            |
| 6    | Hatoum et al.              | 2009           | Male   | 80           | T4N2M0/IV              | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 70 Gy)               | CR; NED at 5.4 months                                                                | Alive           |
| 7    | Lee et al.                 | 2011           | Male   | 41           | T1N1M0/II              | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 70 Gy)               | CR; NED at 9 months                                                                  | Alive           |
| 8    | Subha et al.               | 2011           | Male   | 51           | Not available          | Radiotherapy                                                               | CR; local recurrence and liver metastasis; DOD at 2 months                          | Dead            |
| 9    | Shunyu et al.              | 2012           | Male   | 52           | Not available          | Chemoradiotherapy                                                           | Not available                                                                         | Alive           |
| 10   | Nandi et al.               | 2012           | Male   | 5            | T4N3M0/IV              | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 63 Gy)               | PR; brain metastasis at 3 months; AWD at 17 months on palliative treatment         | Alive           |
| 11   | Azevedo et al.             | 2017           | Female | 43           | Not available          | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 70 Gy)               | Persistent disease; AWD at 10 months                                                  | Alive           |
| 12   | Takahashi et al.           | 2014           | Male   | 54           | T3N3M0/IV              | Chemoradiotherapy (radiotherapy 60 Gy)                                      | CR; brain and spinal cord metastasis treated with palliative radiotherapy; DOD at 32 months | Dead            |
| 13   | Azevedo et al.             | 2017           | Male   | 54           | T2N0M0/II              | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 70 Gy)               | CR; NED at 4 years                                                                   | Alive           |
| 14   | Bellahammou et al.         | 2017           | Female | 46           | Unknown/IV             | Chemotherapy (etoposide-cisplatin-biphosphonate)                           | DOD 4 months after diagnosis                                                        | Dead            |

(continued)
Table 1. (continued)

| Case | Study | Year of Report | Gender | Age (years) | Stage | Treatments | Responses and outcomes | Survival status |
|------|-------|---------------|--------|-------------|-------|------------|-----------------------|----------------|
| 15   | Bhardwaj et al. | 2018 | Female | 30 | Not available | Two biopsies | DOD before treatment initiation | Dead |
| 16   | Mesolella et al. | 2020 | Female | 59 | Not available | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 70 Gy) | CR: 2 years in follow | Alive |
| 17   | Present case | 2021 | Male | 44 | T4N2M0/IV | Chemoradiotherapy (cisplatin-etoposide + radiotherapy 66 Gy) | CR: 45 months in follow | Alive |

Abbreviations: AWD, alive with disease; CR, complete response; DOD, dead of disease; NED, no evidence of disease; PD, progressive disease; PR, partial response.

1. Galera-Ruiz, H., Villar-Rodriguez, J. L., Sanchez-Calzado, J. A., Martin-Mora, J. & Ruiz-Carmona, E. (2001) Sinonasal neuroendocrine carcinoma presenting as a nasopharyngeal mass, Otolaryngology–head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery. 124, 475-6.

2. Lin, C. H., Chiang, T. P., Shum, W. Y., Hsu, C. H., Tsai, Y. C., Tsao, T. Y. & Su, C. C. (2009) Primary small cell neuroendocrine carcinoma of the nasal cavity after successful curative therapy of nasopharyngeal carcinoma: a case report, The Kaohsiung journal of medical sciences. 25, 145-50.

3. Mohhebbi, A. R., Daneshi, A. & Emami, A. R. (2008) Nasopharyngeal neuroendocrine carcinoma: a case report, Ear, nose, & throat journal. 87, E14.

4. Deviprasad, S., Rajeshwari, A., Tahir, M., Adarsha, T. V. & Gangadharara, S. (2008) Small-cell neuroendocrine carcinoma originating from the lateral nasopharyngeal wall, Ear, nose, & throat journal. 87, E1-3.

5. Hatoum, G. F., Patton, B., Takita, C., Abdel-Wahab, M., LaFave, K., Weed, D. & Reis, I. M. (2009) Small cell carcinoma of the head and neck: the university of Miami experience, International journal of radiation oncology, biology, physics. 74, 477-81.

6. Lee, L. Y., Chang, K. P., Hsu, C. L., Chen, T. C. & Kuo, T. T. (2011) Small-cell neuroendocrine carcinoma of the nasopharynx: report of a rare case lacking association with Epstein-Barr virus, Int J Surg Pathol. 19, 199-202.

7. Subha, S. (2011) Neuroendocrine carcinoma of the nasopharynx: a case report, Med Health Sci J. 9, 101-103.

8. Shunyu, N., Lynah, Z., Goyal, Z. A., Raphal, Y. (2012) Small-cell neuroendocrine carcinoma of the nasopharynx, Clin Rhinol. 5, 130-131.

9. Nandi, M., Arun, I., Bhattacharya, A., Sen, S., Ray, S. & Mallick, I. (2014) Reporting of a primary sinonasal neuroendocrine small cell carcinoma in the pediatric age group, Head Neck Oncol. 6, 5.

10. Aguiar, A., Jacome, M., Azavedo, I., Monteiro, E., Castro, V. (2015) Small-cell neuroendocrine carcinoma originating from the nasopharynx: report of a rare case, Rep Radiother Oncol. 2, e3814.

11. Takahashi, S., Miyashita, T., Hoshikawa, H., Haba, R., Togami, T. & Shibata, T. (2015) Accelerated hyperfractionated radiotherapy for small cell carcinoma of the nasopharynx, Head & neck. 37, E63-5.

12. Azavedo, D., Rios, E., Vendeira, L., Sarmento, C. (2017) Small cell neuroendocrine carcinoma of the nasopharynx: a rare case report, Autopsy & case reports. 7, 31-35.

13. Bellahammou, K., Lakhdissi, A., Akkar, O., Kouhen, F., Rais, F., Drahroui, S., M’rabet, H., Errini, H. (2017) Small-cell neuroendocrine carcinoma of nasopharynx: a case report, Int J Surg Med. 3, 132-135.

14. Bhardwaj, N., Kakkar, A., Irugu, D. V. K. (2018) Small Cell Neuroendocrine Carcinoma: A Rare Nasopharyngeal Malignancy with Aggressive Clinical Course, Indian journal of otolaryngology and head and neck surgery: official publication of the Association of Otolaryngologists of India. 70, 454-458.

15. Mesolella, M., Alissos, S., Varricchio, S., Russo, D., Pignatelli, S., Buono, S. & Motta, G. (2020) Small-Cell Carcinoma of Nasopharynx: A Case Report of Unusual Localization, Ear, nose, & throat journal. 145 561 320 973 780.
advanced grades, with 63.3% of patients being in grade III (11 cases) or IV (27 cases). In half of the cases, the tumor, nodes, and metastases (TNM) stage were unknown. Three cases developed metastases, of which 2 were bone metastases; the metastatic site of the third was not recorded. These nasopharyngeal SmCC patients received radiation therapy (73.3%) and chemotherapy (73.3%) more frequently than surgery (26.7%); they mostly received combined therapies.

**Survival Analysis of Different Clinical Features**

The median OS of patients (n = 57) was 18 months (95% CI = 13.00–35.00 months; Figure 4) and the median follow-up time was 138 months. Survival analysis showed that the OS values of patients who were <70 years old (P = .019), male (P = .022), grade III (P = .048), and received radiotherapy (P = .029), were significantly better than those patients who were ≥70 years old, female, grade IV, and were in the “no/unknown radiotherapy” group (Figure 5(A), (C), (E), and (J)). No statistically significant differences were observed upon categorizing the groups by race, year of diagnosis, T stage, N stage, surgery, and chemotherapy (Figure 5(B), (D), (F), (G), (H), and (i)). Using the “Survival” R package, the one-, three-, and 5-year survival rates of all patients were determined to be 62.6, 33.9, and 29.6%, respectively. The one-, three-, and 5-year survival rates of patients who received therapies featuring radiation and chemotherapy were 62.9, 62.5, and 56.3%, respectively.

**Prognostic Factors of Nasopharyngeal SmCC**

As shown in Table 3, the univariate analysis revealed that variables such as the year of diagnosis, T stage, N stage, surgery, and chemotherapy were not significantly associated with OS, while race and grade may have been related (P < .1). Age, sex, and radiotherapy showed significant associations with OS, which indicated that patients who were <70 years old (P = .025), male (P = .028), and received radiotherapy (P = .037) had better survival outcomes. Subsequently, multivariate analysis revealed that age (P = .029, HR = 2.56, and 95% CI = 1.10–5.94) was independent prognostic factor and radiation (P = .028, HR = .66, and 95% CI = .46–.95) was predictive factor. However, grade IV (P = .074, HR = .78, and 95% CI = .58–1.02) and the absence of chemotherapy (P = .068, HR = .44, 95%, and CI = .19–1.06) might contribute to unfavorable survival outcomes.

**Discussion**

This study presents the first large-scale population-based study revealing the clinical features and prognostic factors of nasopharyngeal SmCC. The clinical characteristics, survival outcomes, and prognostic factors of nasopharyngeal SmCC were analyzed. Here, nasopharyngeal SmCC was found to be an aggressive carcinoma with poor one- (62.6%), three- (33.9%), and 5-year (29.6%) OS rates. Furthermore, the tumor pathological grade was found to be important for prognosis, with 64.9% of nasopharyngeal SmCC patients being in grade III or IV (poorly differentiated or undifferentiated); this might have contributed to their poor prognosis. The mean age of patients with nasopharyngeal SmCC was 55.70 years. Patients aged under 70 years showed better

**Table 2. Clinical characteristics of nasopharyngeal small cell carcinoma.**

| variable       | Frequency | Percent (%) |
|----------------|-----------|-------------|
| Age            |           |             |
| <70 years      | 47        | 78.3        |
| ≥70 years      | 13        | 21.7        |
| Sex            |           |             |
| Male           | 40        | 66.7        |
| Female         | 20        | 33.3        |
| Race           |           |             |
| White          | 49        | 81.7        |
| Black          | 5         | 8.3         |
| Other          | 6         | 10.0        |
| Year of diagnosis |       |             |
| 1975–1994     | 12        | 20.0        |
| 1995–2015     | 48        | 80.0        |
| Stage          |           |             |
| Grade I/II     | 1         | 1.7         |
| Grade III      | 11        | 18.3        |
| Grade IV       | 27        | 45.0        |
| Unknown        | 21        | 35.0        |
| T              |           |             |
| T1             | 8         | 13.3        |
| T2             | 7         | 11.7        |
| T3             | 8         | 13.3        |
| T4             | 5         | 8.3         |
| Unknown        | 32        | 53.3        |
| N              |           |             |
| N0             | 9         | 15.0        |
| N1             | 9         | 15.0        |
| N2             | 7         | 11.7        |
| N3             | 2         | 3.3         |
| Unknown        | 33        | 55.0        |
| M              |           |             |
| M0             | 24        | 40.0        |
| M1             | 3         | 5.0         |
| Unknown        | 33        | 55.0        |
| Surgery        |           |             |
| Yes            | 16        | 26.7        |
| No or unknown  | 44        | 73.3        |
| Radiotherapy   |           |             |
| Yes            | 44        | 73.3        |
| No or unknown  | 16        | 26.7        |
| Chemotherapy   |           |             |
| Yes            | 44        | 73.3        |
| No or unknown  | 16        | 26.7        |

*Other: American Indian/Alaska Native, Asian/Pacific Islander.*
survival outcomes than those aged over 70 years. The combination of radiotherapy and chemotherapy was the most common choice. Radiotherapy was revealed to be an independent prognostic factor for a longer OS; chemotherapy might also have been associated with a longer OS. Based on the findings presented in this study, nasopharyngeal SmCC should be listed as a distinct classification of nasopharyngeal cancer.

Kaplan–Meier survival analysis revealed different OS values within groups, but it was not possible to clearly identify patients who did not receive radiation therapy based on the SEER database. That is, those patients in the “no or unknown radiotherapy group” might have also received radiotherapy or other treatments. Nevertheless, radiotherapy, chemotherapy, and surgery were grouped together during multivariate analysis, which theoretically corrected for confounders among groups. This analysis revealed that a better OS was achieved in the radiotherapy group than in the “no or unknown radiotherapy group.” Furthermore, multivariate analysis revealed the statistical significance of radiotherapy, showing that it was still an independent predictor of OS. The P-value of chemotherapy was revealed to be <.1 through multivariate analysis, indicating that chemotherapy might also be an independent predictor. However, this needs to be further confirmed by larger clinical studies in the future.

Pertaining to treatment delivery, though most previous studies have focused on extrapulmonary SmCC cases where the patients underwent surgery, surgery is not usually recommended for nasopharyngeal SmCC patients. Here, no difference in survival was observed between the surgery and non-surgery groups. However, patients with nasopharyngeal SmCC were shown to have been mostly treated with radiation therapy combined with chemotherapy and had appreciable one- (62.9%), three- (62.5%), and 5-year (56.3%) OS rates. Similarly, most of the cases reported in the literature have received radiation therapy concurrent with chemotherapy, suggesting that chemoradiotherapy benefits SmCC patients, compared to chemotherapy or surgery alone. This
finding indicates that chemoradiotherapy might be a possible curative therapeutic choice for nasopharyngeal SmCC. The complete response and sustained survival observed in the case presented here also suggest the potential benefit of combination therapy for patients with nasopharyngeal SmCC. To abrogate the bias, however, larger number of patients need to be analyzed. Furthermore, stratification is generally recommended, but here, considering that more biases would be generated if stratification was performed, the previous results of multivariate analysis were retained. In summary, combined therapies, particularly the combination of radiation and chemotherapy, should be considered as the first-line choice of treatment for nasopharyngeal SmCC.

Undifferentiated nasopharyngeal carcinoma type (UNCT) is the most histological type of NPC; it has been verified as a distinct entity and has been demonstrated to exhibit radiosensitivity and chemosensitivity. However, because of its rarity, most treatment options for nasopharyngeal SmCC have instead been determined depending on experience. Furthermore, females with UNCT have exhibited better outcomes than males, which is contrary to the trend observed for SmCC. Thus, more clinical trials are needed to validate

![Figure 5. OS among groups divided by (A) age, (B) race, (C) sex, (D) year of diagnosis, (E) grade, (F) T stage, (G) N stage, (H) surgery, (I) chemotherapy, and (J) radiotherapy. Median OS is marked with horizontal and vertical dashed lines.](image-url)
treatment options for nasopharyngeal SmCC in the future. In addition, further efforts should focus on screening the molecular and genetic characteristics of nasopharyngeal SmCC. Studies are being conducted to further explore different approaches to treat extrapulmonary SmCCs, especially in the field of immunotherapy. Similarly, immunotherapy could also play an effective role in treating nasopharyngeal SmCC. To confirm the above-mentioned hypothesis, genetic and tumor microenvironment characteristics should be taken into consideration, which would help to reveal the landscape of tumor mutation burden, immune infiltration, and the distribution of immune checkpoint biomarkers of nasopharyngeal SmCC. This will permit the exploration of more specific schemes to make nasopharyngeal SmCC a potentially curable tumor.

This study has some limitations. First, authorization was not obtained to access detailed data regarding chemotherapeutic regimens, dosages of radiation therapy, and the specific time of surgery. Consequently, it was not possible to identify the suitable chemotherapy regimen or the most beneficial radiation dose and its fraction. Second, the population of nasopharyngeal SmCC cases was small because only a small proportion of American cancer patients have been recorded in the SEER database. Moreover, the information regarding the stages of each case was incomplete, and the metastasis status was unknown for more than half of the patients. Hence, some biases could have existed in the analysis of the prognostic roles of stages. In addition, the lack of ECOG-PS data from the SEER database may also contribute biases in our analysis. Furthermore, variations in genetic backgrounds may be one of the reasons for different therapeutic responses and outcomes in the nasopharyngeal SmCC patients studied here. Therefore, more nations and races, especially patients from areas where nasopharyngeal cancer is endemic, need to be included in future studies.

In conclusion, nasopharyngeal SmCC patients were found to have advanced grade cancers and poor prognoses. Treating nasopharyngeal SmCC remains challenging. This study revealed the clinical characteristics and prognosis factors of nasopharyngeal SmCC. It was found that nasopharyngeal SmCC patients can benefit from radiotherapy, which could contribute to decision-making regarding the clinical treatment of this condition. In view of the lethal nature of this cancer, more studies and clinical trials regarding nasopharyngeal SmCC should be performed in the future.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Table 3. Univariate and multivariate Cox analysis.

| Covariate                  | Univariate HR (95% CI) | P     | Multivariate HR (95% CI) | P     |
|----------------------------|------------------------|-------|--------------------------|-------|
| Age                        | 2.27 (.11–4.64)        | .025  | 2.56 (1.10–5.94)         | .029  |
| Sex                        | .50 (.27–.93)          | .028  | .61 (3.1–1.20)           | .153  |
| Race                       | .72 (.25–2.02)         | .528  | .64 (3.5–1.17)           | .148  |
| Year of diagnosis          | .31 (.10–1.04)         | .058  | -                        | -     |
| Grade                      | .97 (4.7–1.97)         | .921  | -                        | -     |
| T stage                    | .41 (.17–1.02)         | .055  | .78 (5.8–1.02)           | .074  |
| N stage                    | 1.56 (.60–4.00)        | .360  | -                        | -     |
| Surgery                    | .79 (.39–1.60)         | .509  | .79 (3.4–1.85)           | .591  |
| Radiation                  | .49 (2.5–96)           | .037  | .66 (4.6–95)             | .028  |
| Chemotherapy               | .85 (4.3–1.67)         | .632  | .44 (1.9–1.06)           | .068  |

*Other: American Indian/Alaska Native, Asian/Pacific Islander.
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Ethics Approval and Consent to Participate
The ethical approval (number: K306-1) for reporting individual cases or case series was obtained from our institution (the Affiliated hospital of Sun Yat-sen University, Zhuhai, China). Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Data Availability Statement
All data support the findings of this study are openly available in the SEER database after official registration and authorization.

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References
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jamal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin. 2018;68:394-424.
2. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet. 2019;3:644-68.
3. Bhardwaj N, Kakkar A, Iruku DVK. Small cell neuroendocrine carcinoma: A rare nasopharyngeal malignancy with aggressive clinical course. Indian J Otolaryngol. 2018;70:454-458.
4. Pointer KB, Ko HC, Brower JV, Witek ME, Kimple RJ, Lloyd RV, et al. Small cell carcinoma of the head and neck: An analysis of the National Cancer Database. Oral Oncol. 2017;69:92-98.
5. Bean MB, Liu Y, Jiang R, et al. Small cell and squamous cell carcinomas of the head and neck: Comparing incidence and survival trends based on surveillance, epidemiology, and end results (SEER) data. Oncol. 2019;24:1562-1569.
6. Azevedo D, Rios E, Vendeira L, Sarmento C. Small cell neuroendocrine carcinoma of the nasopharynx: a rare case report. Autopsy Case Rep. 2017;7:31-35.
7. Bellahammou K, Lakhdissi A, Akkar O, et al. Small-cell neuroendocrine carcinoma of nasopharynx: a rare case report. Int J Surg Med. 2017;3:132-135.
8. Deviprasad S, Rajeshwari A, Tahir M, Adarsha TV, Gangadhara S. Small-cell neuroendocrine carcinoma originating from the lateral nasopharyngeal wall. Ear Nose Throat J. 2008;87:E1-E3.
9. Galera-Ruiz H, Villar-Rodriguez JL, Sanchez-Calzado JA, Martin-Mora J, Ruiz-Carmona E. Sinonasal neuroendocrine carcinoma presenting as a nasopharyngeal mass. Otolaryngology–head and neck surgery. Official Journal of American Academy of Otolaryngology-Head and Neck Surgery. 2001;124:475-476.
10. Hatoum GF, Patton B, Takita C, et al. Small cell carcinoma of the head and neck: The university of Miami experience. Int J Radiat Oncol Biol Phys. 2009;74:477-481.
11. Lee LY, Chang KP, Hsu CL, Chen TC, Kuo TT. Small-cell neuroendocrine carcinoma of the nasopharynx: report of a rare case lacking association with Epstein-Barr virus. Int J Surg Pathol. 2011;19:199-202.
12. Lin CH, Chiang TP, Shum WY, et al. Primary small cell neuroendocrine carcinoma of the nasopharynx: report of a rare case lacking association with Epstein-Barr virus. Kaohsiung J Med Sci. 2009;25:145-150.
13. Mesolella M, Allosso S, Varricchio S, et al. Small-cell carcinoma of the nasopharynx: A case report. Ann Otol Rhinol Laryngol. 2017;7:31-35.
14. Mohebbi AR, Daneshi A, Emami AR. Nasopharyngeal neuroendocrine carcinoma: A case report. Ear Nose Throat J. 2008;87:E14.
15. Takahashi S, Miyashita T, Hoshikawa H, Haba R, Tomomi T, Shibata T. Accelerated hyperfractionated radiotherapy for small cell carcinoma of the nasopharynx. Head Neck. 2015;37:31-35.
16. Aguiar A, Jacome M, Azevedo I, Monteiro E, Castro V. Small-cell neuroendocrine carcinoma originating from the nasopharynx: Report of a rare case. Rep Radiother Oncol. 2015;2:3814.
17. Nandi M, Arun I, Bhattacharya A, Sen S, Ray S, Mallick I. Reporting of a primary sinonasal neuroendocrine small cell carcinoma in the paediatric age group. Head Neck Oncol. 2014;6:5.
18. Shunyu N, Lynah Z, Goyal A, Raphal V. Small-cell neuroendocrine carcinoma of the nasopharynx. Clin Rhinol. 2012;5:130-131.
19. Subba S. Neuroendocrine carcinoma of the nasopharynx: A case report. Med Health Sci J. 2011;9:101-103.
20. Lin IH, Hwang CF, Huang HY, Chien CY. Small cell carcinoma of the nasopharynx. Acta Otolaryngol. 2007;127:206-208.
21. Hatoum GF, Patton B, Takita C, et al.. Small cell carcinoma of the head and neck: The university of Miami experience. Acta Otolaryngol. 2011;131:206-208.
22. Lee LY, Chang KP, Hsu CL, Chen TC, Kuo TT. Small-cell neuroendocrine carcinoma of the nasopharynx: Report of a rare case lacking association with Epstein-Barr virus. Int J Surg Pathol. 2011;19:199-202.
23. Azevedo D, Rios E, Vendeira L, Sarmento C. Small cell neuroendocrine carcinoma of the nasopharynx: a rare case report. Autopsy Case Rep. 2017;7:31-35.
24. Bhardwaj N, Kakkar A, Iruku DVK. Small cell Neuroendocrine carcinoma: A rare nasopharyngeal malignancy with aggressive clinical course. Indian J Otolaryngol. 2018;70:454-458.
25. Wakasaki T, Yasumatsu R, Masuda M, et al. Small cell carcinoma in the head and neck. Ann Otol Rhinol Laryngol. 2019;128:1006-1012.
26. Hellmann MD, Nathanson T, Rizvi H, et al. Genomic features of resected head and neck advanced non-small-cell lung cancer. Cancer Cell. 2018;33:843-852.e4.
27. Ishida M, Sekine S, Fukagawa T, et al. Neuroendocrine carcinoma of the stomach: morphologic and immunohistochemical characteristics and prognosis. Am J Surg Pathol. 2013;37:949-959.
28. Syed BM, Green AR, Ellis IO, Cheung KL. Human epidermal growth receptor-2 overexpressing early operable primary breast cancers in older (≥70 years) women: biology and clinical outcome in comparison with younger (<70 years) patients. Ann Oncol: Official Journal of the European Society for Medical Oncology. 2014;25:837-842.

29. Hancke K, Denkinger MD, König J, et al. Standard treatment of female patients with breast cancer decreases substantially for women aged 70 years and older: A German clinical cohort study. Ann Oncol: Official Journal of the European Society for Medical Oncology. 2010;21:748-753.

30. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Stat Med. 1995;14:1707-1723.

31. Walenkamp AME, Sonke GS, Sleijfer DT. Clinical and therapeutic aspects of extrapulmonary small cell carcinoma. Cancer Treatment Reviews. 2009;35:228-236.

32. Altun M, Fandi A, Dupuis O, Cvitkovic E, Krajina Z, Eschwege F. Undifferentiated nasopharyngeal cancer (UCNT): current diagnostic and therapeutic aspects. Int J Radiat Oncol Biol Phys. 1995;32:859-877.

33. Berniker AV, Abdulrahman AA, Teytelboym OM, Galindo LM, Mackey JE. Extrapulmonary small cell carcinoma: Imaging features with radiologic-pathologic correlation. Radiographics. 2015;35:152-163.

34. Aly R, Gupta S, Potdar R. The role of immune checkpoint inhibitors in the treatment of extensive-stage extrapulmonary small cell carcinoma. Cureus. 2020;12.

35. Endris V, Buchhalter I, Allgäuer M, et al. Measurement of tumor mutational burden (TMB) in routine molecular diagnostics: in silico and real-life analysis of three larger gene panels. Int J Cancer. 2019;144:2303-2312.

36. Meléndez B, Van Campenhout C, Rorive S, Remmelink M, Salmon I, D’Haene N. Methods of measurement for tumor mutational burden in tumor tissue. Transl Lung Cancer Res. 2018;7:661-667.

37. Vanderwalde A, Spetzler D, Xiao N, Gatalica Z, Marshall J. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med. 2018;7:746-756.