Primary nasopharyngeal adenocarcinoma: A review

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Abstract

Primary nasopharyngeal adenocarcinoma (NAC) accounts for approximately 0.5% of all nasopharyngeal cancer. The diagnosis, staging and treatment of NAC has not been well described. This article presents a literature review on NAC and identifies its characteristics and management. The NAC group of diseases contains various pathological types and has a series of specific clinical characteristics, including slow progression, a low incidence of neck masses and frequent cranial neuropathy. The Epstein–Barr virus may not play an important role in NAC carcinogenesis. The rarity of the disease makes the staging classification and treatment strategies of NAC parallel to those recommended for nasopharyngeal squamous carcinoma. Some patients might benefit from surgery, and radiotherapy using precise techniques might achieve good control for treating NAC, but the roles of chemotherapy and target therapy are not clear. The proper staging system and optimal treatment strategies need to be established in NAC.

Key words: adenocarcinoma, management, nasopharynx, radiotherapy, surgery.

INTRODUCTION

Primary nasopharyngeal adenocarcinoma (NAC) is a very rare subtype of nasopharyngeal cancer (NPC). According to one of the largest retrospective studies from Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China) over 24 years (1978–2002), NAC contributed only approximately 0.48% (153/31791 patients) to all types of NPC.1 In comparative terms, nasopharyngeal non-keratinizing squamous carcinoma (NSC) constituted most of these cases in high-endemic regions and had a distinct geographical distribution, with an incidence of about 25 per 100 000.2 Most basic and clinical research focuses on NSC and most of the very few studies in English on NAC were case reports;3–12 large studies from a single institute are very rare.13–20

NAC is a special histological type different from NSC. Epstein–Barr virus (EBV) may not be closely associated with the carcinogenesis of NAC. The cervical node metastatic rate in NAC patients is not as high as that of NSC. A slowly rate of growth, a tendency for cranial nerve invasion, a high recurrence rate and a low distant metastatic rate are characteristic of NAC. Furthermore, the feasibility of applying the clinical tumor, node and metastases (TNM) staging system for NSC in NAC is worth discussing. The roles of surgery, radiotherapy, chemotherapy and target therapy in NAC are still unclear. Optimal treatment strategies of NAC have not been established. In this review, we extensively analyze the published literatures on NAC and further critically assess the particular clinical characters and treatment strategies of NAC.
INCIDENCE AND GEOGRAPHICAL DISTRIBUTION

Nasopharyngeal squamous carcinoma accounts for 95 to 98% of nasopharyngeal malignancies. In endemic NPC, the undifferentiated World Health Organization (WHO) type III accounts for more than 95%; in North America, WHO type I keratinizing differentiated squamous cell carcinoma (SCC) and WHO type II differentiated SCC accounts for 25 and 12%, respectively. Unlike NAC, NSC has a unique geographical distribution, particularly in the Cantonese population of China, or, more accurately, in Guangdong Province. In a recent study, Guo et al. updated the data of NAC from SYSUCC. It was found in a total of 40,719 NPC patients, constituting only 0.11% of all NPC. From data from Taiwan, the incidence was reported to be 1.3% by Kuo and Tsang, in Hong Kong, it was 0.38%. In another study, the incidence ranged from 0.0% in Uganda to 3.9% in the USA. Thus, the incidence of NAC is extremely rare even among defined ethnic groups. The geographical distribution of NAC is not distinct from that of NSC.

PATHOLOGICAL ORIGIN AND CLASSIFICATION

NAC is one of nasopharyngeal malignancies with a characteristic adenocarcinoma cell structure. It may have originated from the mucous epithelium of the nasopharynx or minor salivary gland, the ratio of low-grade to high-grade tumors has been estimated to be 1:1.5 or 1:2. In 1993, the WHO classified adenocarcinomas of the nasopharynx into papillary adenocarcinomas, mucoepidermoid adenocarcinomas (MEC), adenoid cystic adenocarcinomas (AAC) and polymorphous low-grade adenocarcinomas (PLGA). In 2005 the WHO published a series of pathological classifications of nasopharyngeal carcinomas, in which adenocarcinomas were excluded. NAC encompass a variety of histological types. NAC was first classified into traditional (conventional) adenocarcinomas and salivary gland-type adenocarcinomas by Zong et al. The former was further subdivided into acinic cell adenocarcinoma, papillary adenocarcinoma and tubular adenocarcinomas, and so on. Salivary gland-type adenocarcinomas include AAC, MEC and malignant mixed tumors. AAC is the most common subtype, especially in minor gland salivary cancer. MEC is more common in major gland salivary cancer. ACC accounted for 65%, followed by MEC and not otherwise specified (15%) reported by Schramm et al. In a recent study of 67 cases of primary salivary gland type carcinoma of the nasopharynx, ACC was reported in 25 (37.3%) patients, MEC in eight (11.9%) patients and traditional adenocarcinoma in 34 (50.8%) patients. Pathologists might have difficulties in the proper diagnosis of traditional NAC, compared with salivary gland type-NAC. There were fewer reports on traditional adenocarcinoma than on salivary gland type-NAC. He et al. reviewed all 208 cases of NAC reported from the 1970s. Of these 65 (31.25%) were traditional NAC, which could be further divided into low-grade and high-grade malignancies. Papillary adenocarcinoma was regarded as a type of low-grade malignancy. Pineda-Daboin et al. retrospectively analyzed 44 cases of NAC from the M.D. Anderson Cancer Center, Texas, USA, and suggested that NAC can be classified into two types: the conventional or surface origin type and the salivary type, which is consistent with the finding by Zong et al. Pineda-Daboin’s study found that 13 papillary NAC were invasive and are characterized by the presence of papillations with central fibrovascular cores. It was interesting that perineural, vascular or lymphatic invasion was not apparent, and therefore in Pineda-Daboin’s study, NAS was classified into: (i) surface origin type, usually papillary in configuration and of low-grade malignancy; (ii) salivary gland type. In summary, these classifications differ from each other in terms of the clinical manifestations, histomorphological features and behavior chosen to characterise each type (Table 1). We suggest that the different specific pathologic types of NAC should be studied as one group. A diagnostic standard should be established. Understanding and exploiting these complex pathological classifications and biological characteristics holds the promise of more effective therapies in the future.

Table 1 Subtypes of nasopharyngeal adenocarcinoma

| Traditional (conventional) adenocarcinoma | Salivary gland-type adenocarcinoma |
|------------------------------------------|-----------------------------------|
| Acinic cell adenocarcinoma               | Mucoepidermoid adenocarcinoma     |
| Papillary adenocarcinoma                 | Adenoid cystic adenocarcinoma     |
| Tubular adenocarcinoma                   | Polymorphous low-grade adenocarcinoma |
|                                          | Malignant mixed tumor             |
RELATIONSHIP BETWEEN NAC AND EBV VIRUS

EBV infection is closely associated with NSC carcinogenesis. Previous studies have shown that EBV-related antibodies, such as immunoglobulin (IgA) antibodies against viral capsid antigen (VCA-IgA), early antigen (EA-IgA), EBV- encoded RNA and EBV DNase antibody are useful makers in the screening, monitoring and prediction of the prognosis of NSC. Recently, the pre-treatment measurement of the EBV DNA level using a real-time polymerase chain reaction (PCR) technique was found to be more sensitive and specific than the PCR method. However, the relationship between NAC and EBV is still unclear. Common methods to identify the presence of EBV include the use of Epstein-Barr virus encoded RNA in situ hybridization (ISH) and LMP-1 gene by PCR analysis. Some investigators have detected EBV in salivary gland-type NAC, for instance, Kuo and Tsang found EBER ISH in nine of 15 patients (60%) and by PCR of the LMP-1 gene in 10 of 15 cases (67%). But He et al. reported that EBV had no close relationship in the carcinogenesis of nasopharyngeal AAC. Among 17 samples, nine had positive nuclear EBER. In another study, Liu et al. analyzed 26 patients with ACC of the nasopharynx. The prevalence of EA-IgA, VCA-IgA and EBV DNase antibody plasma level were 13.3, 25 and 42.9%, respectively.

CLINICAL MANIFESTATION AND DIAGNOSIS

The male to female ratio for NAC was reported to be 1:1.18:1, while the male to female ratio was reported to be 2:1 in NSC. The gender distribution varied in the different pathological types. The median age of patients ranged from 40 to 50 years. The slow rate of growth of NAC might be explained by the long duration of symptoms before patients sought medical attention. Schramm et al. reported the mean duration before seeking treatment was 19.3 months. NAC has specific clinical presentations that differ from NSC. Overall, patients with a nasopharyngeal neoplasm frequently present with at least four symptoms including nasal symptoms (epistaxis, nasal obstruction), neck masses, otological symptoms (tinnitus, deafness) and cranial nerve palsies (Table 2). Epistaxis, another frequent symptom in NSC, presented later in NAC. Neck masses are uncommon in NAC due to its low rate of cervical node metastasis. However, cranial nerve deficits in NAC are higher than in NSC. The most common type of NAC is ACC which has a tendency of perineural spreading and local recurrence. These symptoms are highly suggestive of the presence of local advanced disease and such patients should have a physical examination for assessment. In a large respective analysis of symptoms of NSC, neck mass (75%) and nasal dysfunction (73%) were the most common, followed by aural dysfunction (62%) and headache (35%). Cranial nerve palsy was uncommon (20%). In a study by Pineda-Daboin et al., nasal obstruction and cranial nerve symptoms were very common in patients with NAC, being found in 50 and 40% of them, respectively. The trigeminal nerve was the most commonly invaded. Schramm et al. found that 14 patients presented with sinonasal symptoms and 11 patients presented with cranial neuropathy in 25 nasopharyngeal salivary gland malignancies, and in more than the half (9/17) of patients with cranial neuropathy the V2 ramus in the trigeminal nerve was affected. A recent study of 67 patients with primary salivary gland carcinomas of the nasopharynx, found that 38.8% of them had a skull base invasion and 19.4% had a cranial nerve invasion as well. It is well recognized that node disease at presentation is uncommon in minor salivary gland carcinoma, constituting approximately 15% of patients, according to the literature, compared with an average of 50% with head and neck SCC. Cross-sectional imaging with computed

| Type     | Clinical manifestation (%) [reference] |
|----------|----------------------------------------|
|          | Nasal symptom | Neck mass | Otological symptoms | Cranial nerve palsy (nasal obstruction) |
| NAC      | 50<sup>18</sup> | 15<sup>15</sup> | 28.4<sup>16</sup>; 15<sup>14</sup> | 55<sup>13</sup> |
| NSC      | 76<sup>17,18</sup> | 75<sup>17,18</sup> | 62<sup>17,18</sup> | 19.4<sup>14</sup>; 15<sup>17</sup> |

Table 2 Clinical manifestation of nasopharyngeal adenocarcinoma (NAC) versus nasopharyngeal non-keratinizing squamous carcinoma (NSC) (%)
tomography or magnetic resonance imaging should be undertaken to define the tumor size as part of cancer staging. A nasopharyngeal fibreoptic endoscopy and a biopsy from the nasopharynx tumor needed to be taken. Pathologists can identify the subtypes based on its morphological features. Immunohistochemical analysis is a valuable method for the sub-classification of NAC.

**STAGING SYSTEM**

The TNM stage system is commonly used to guide oncologists to adopt the correct treatment and offer information on prognosis. The International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification is used extensively in the Europe and North America. In endemic regions of NPC, the clinical staging of NPC can be done were of NAC. Pineda-Daboin et al. reported that poly-

The staging system for NAC should take a number of prognostic factors into account, such as cranial nerve invasion, skull base erosion and the presence of positive cervical nodes. Schramm et al. disagreed that most patients with cranial neuropathy should be classified as T4 stage, so they proposed a new staging system for salivary gland nasopharyngeal malignancies. Minor salivary gland carcinomas represent a more complicated group. Interestingly, from the study reported by Vander Poorten et al., the presence of nodal metastases does not affect prognosis in minor salivary gland carcinoma. Recently, Erovic et al. found that the T stage at presentation was a predictor of patients’ disease-free survival, but N stage was not. Further, we suggest that prognostic factors related to NAC should be analyzed. N staging might be considered to divide into N0 and N+ in the NAC staging system.

**TREATMENT AND PROGNOSIS**

Treatment and prognosis always mainly depended upon tissue type, histological grading and TNM staging. Over past 30 years, there have been few large-scale clinicopathological studies for NAC (Table 3). In a study by Pineda-Daboin et al., the authors found that polymorphic low-grade adenocarcinomas, hyalinating clear cell carcinomas and acinic cell carcinomas in NAC had good prognosis. Patients with these tumors were alive and free of recurrence or metastasis in a median follow-up period of 9 years. In endemic areas, NPC constituted more than 95% of all NPC cases and is sensitive to radiotherapy and chemotherapy, so radiotherapy instead of surgery is the first choice for localized tumors. Radiotherapy alone can cure early-stage disease, and radiotherapy in combination with chemotherapy is the main treatment for local advanced tumors. Due to the rarity of NAC, there is still no standard treatment. In developed countries, surgical excision is the treatment choice and radiotherapy is recommended as a post-operative treatment for patients who are at high risk of postoperative recurrence. Schramm et al. reported that the 5-year and 10-year survival rate were 67 and 48%, respectively. In 15 patients with clinical N0 who were given surgery of the ipsilateral neck, 47% (7/15) had lymph nodes metastases. In high-incidence endemic regions, especially southern China, the treatment of most NAC is similar to that of NSC. It is of interest that NAC can be well controlled by radiotherapy with and without chemotherapy. In a study at SYSUCC by Guo et al., the local control rate and the 5-year disease-free survival rate were 79 and 75% (P = 0.724) in the radiotherapy-treated group (n = 32), and 90 and 89% (P = 0.724) in the surgery plus radiotherapy (n = 10) group, respectively. Early-stage disease (T1 or T2) has been shown to be equally well controlled with either radiotherapy or surgery alone, but for advanced-stage (T3 or T4) disease, combination radiotherapy following by surgery may significantly improve locoregional control rates. ACC has a higher locoregional control rate (LRCR) than other histological types. From recent data, the 5-year LRCR was 59.5 in patients with ACC and 29.2% in patients with MEC and 39.1% in patients with traditional adenocarcinomas, respectively. Distant metastases were uncommon and the most common site of distant metastasis is the lung. In future, large multicenter studies should be conducted to further evaluate the treatment policy of NAC. In particular a high-dose radiotherapy using a precise technique might be recommended.

**Radiotherapy**

The role of radiotherapy in treating NAC is an area of discussion. In previous reports of patients with minor salivary gland carcinoma who were unfit for surgery, radiotherapy alone could gain high local control. Wang et al. reported that a total of 20 patients (15 patients from previous studies) with nasopharyngeal adenoid cystic carcinoma received definitive radiotherapy. The 5-year local control rate was 45.5% and the 5-year and 10-year survival rates were 78 and 49.5%, respectively. In another study of Yin et al., 10
patients with nasopharyngeal cylindroma treated with radiotherapy had survival rates of 86 and 50% at 5 years and 10 years, respectively. The authors recommended a radiotherapy dose was between 8000 Gy and 10 000 Gy. Radiation-induced damage of the surrounding normal tissue can now be minimized by more precise techniques, such as 3-dimensional conformal radiotherapy, intensive modulated radiotherapy (IMRT) and image-guided radiotherapy. High dose of radiotherapy can now be delivered to the tumor avoiding the surrounding normal organs. IMRT had been reported to improve local control and also spares radiation-induced damage to the parotids. On the other hand, high-liner energy transmission radiotherapy might help to improve the outcome. It has been reported that patients treated with neutron therapy had good local control. Huber et al treated 75 local advanced, recurrent or incompletely resected ACC patients who were treated with photon, neutron or mixed beam radiotherapy; the 5-year local control rate was 75% for neutron radiation and 32% for the other two types of radiation.

**Surgery**

The structure of the nasopharynx is complex anatomically. It is surrounded by an array of important tissues and organs including the brain stem, the spinal cord and cranial succquet’s canal, so that total or near-total
resection is hard to achieve. Surgery is technically challenging for the nasopharynx.59 Though endoscopic or endoscopic-assisted treatment may be a helpful technique, it is unclear whether these methods are better than open surgical techniques or not.59 On the other hand the known perioperative risks include cerebrovascular injury, the incidence of stroke and wound infections. The lateral infratemporal middle fossa approach has been used as a surgical technique to manage nasopharyngeal tumors by Schramm et al.19 Facial paresis (n = 13) and trismus (n = 14) were the most common early and late complications, respectively, following surgery. About 70% of NSC patients had cervical node metastasis, so radiotherapy oncologists prefer to deliver a high radiation dose (60–66 Gy) for positive neck nodes. Even for patients without nodal metastasis, the radiation dose should be at least 50 Gy. Cervical node metastasis in NAC is relatively lower than in NSC. A 47% rate of occult disease was noted by Schramm et al.19 therefore, they recommended noted that elective neck dissection was indicated when managing nasopharyngeal salivary gland malignancy. Though Guo et al.’s study showed that surgery could gain better local control and overall survival than radiotherapy, their study was limited by the fact that the stage distribution was unbalanced, and more advanced stage patients were in the radiotherapy group.17 Some centers still consider surgery to be the first-line treatment for NAC,47 especially for MEC, as it is viewed as radiosensitive tumor.15

Chemotherapy and molecular target therapy

To our knowledge, there had been no previous reports concerning chemotherapy for NAC. We investigated the role of chemotherapy by referring adenocarcinoma or salivary gland carcinoma of head and neck. Contrary to the belief that adenocarcinoma of head and neck is resistant to cytotoxic drugs,60-62 several reports have confirmed that these tumors are sensitive to chemotherapy.63-68 From some publications, platinum, 5-fluorouracil and anthracyclines seemed to be effective single agents,63-68 but gemcitabine has not been proven to be active in ACC of head and neck from an EORTC 24982 study.69 Some effective combination chemotherapy regimens include cisplatin, 5-fluorouracil,64 and CAP (cyclophosphamide, doxorubicin and cisplatin).66-68 However, the response rates of chemotherapy reported from the literature were variable. The CAP regimen is the most consistent combination chemotherapy, and response rates were reported to be 25–33%. Similarly, with locoregionally advanced NSC, concurrent chemoradiotherapy is the standard treatment strategy. More and more studies now confirm the potential benefits of concurrent chemotherapy and radiotherapy (CRT) following surgery in locally advanced salivary gland carcinomas. In Katori and Tsukuda’s study, patients gained a pathological complete response of 24% with CRT.70 Tanvetyan et al. reported that 3-year survival rates of CRT versus radiotherapy alone were 83 versus 44%.71 Schoenfeld et al. conducted a study to treat patients with salivary gland tumors using IMRT and concurrent chemotherapy and the local control rate was very satisfactory.72

For adenocarcinomas of the head and neck, c-Kit and epidermal growth factor receptor (EGFR) have been evaluated as potential therapeutic targets. KIT is a transmembrane cell surface receptor encoded by the c-kit proto-oncogene and plays a role in regulating cell growth, differentiation and migration. KIT expression can be found in over 80% of salivary gland carcinoma patients.73,74 Imatinib mesylate is a drug used for gastrointestinal stromal tumors that works by inhibiting KIT tyrosine kinase receptor and Bcr-abl, platelet-derived growth factor receptor, and is now being re-evaluated in ACC. Alcedo et al.75 conducted two studies on patients with unresectable ACC using imatinib, and all gained a well response. However, in a phase II study, nine of 16 patients had stable disease, though the overexpression of wild-type c-kit was detected before treatment.76 EGFR expression had been reported in head and neck squamous cell77 and NSC.78 For adenocarcinomas of the head and neck, the EGFR expression was as high, being about 17–35%.79,80 Cetuximab, an EGFR inhibitor, provided a 50% clinical benefit rate in a phase II study of salivary gland tumors.81 There were clear differences in the molecular expression of each subtype, a finding that was supported by Gibbons et al.82 However, no comprehensive studies of molecular expression have been that include patients with NAC, and it clarification of the specific target in different subtypes is needed.82

CURRENT CHALLENGE AND FUTURE DIRECTION

NAC is a rare yet clinical challenging cancer to treat, diagnose and classify. The rarity of this disease makes the prospective evaluation of NAC very difficult. Most data are derived from retrospective analyses. NAC comprises a series of sub-pathological types, including ACC, MEC and PLGA. Further multicenter studies are
absolutely needed to better understand the biological characteristics of the different sub-pathological types, to establish accurate clinical staging system and optimal treatment guideline.

**CONCLUSION**

In summary, compared with NSC, NAC is very rare, but NAC is a group of disease including a various pathological types. NAC differs from NSC in its propensity for a slow rate of growth, a low incidence of neck node metastases and the frequent occurrence of cranial neuropathy. Currently, NAC is staged similarly to NPC in the TNM staging system. Minimally invasive surgery may have a role in minimizing perioperative risk in the treatment of NAC. 3D-conformal radiotherapy techniques may improve local control in NAC. The role of chemotherapy and molecular target therapy remain to be defined. We have a tendency to treat NAC the same way as head and neck cancer. While surgery or radiotherapy can be used for early-stage disease, for advanced-stage unresectable patients, concurrent chemoradiotherapy should be considered. A proper staging system and optimal treatment strategies for NAC needed to be established in the future.

**REFERENCES**

1. He JH, Zong YS, Luo RZ et al. Clinicopathological characteristics of primary nasopharyngeal adenocarcinoma. Ai Zheng 2003; 22: 753–7.
2. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005; 365: 2041–54.
3. Lee DJ, Smith RR, Spaziani JT, Rostock R, Holliday M, Moses H. Adenoid cystic carcinoma of the nasopharynx. Case reports and literature review. Ann Otol Rhinol Laryngol 1985; 94: 269–72.
4. van Hasselt CA, Ng HK. Papillary adenocarcinoma of the nasopharynx. J Laryngol Otol 1991; 105: 833–4.
5. TS L. Minor salivary gland tumors of the nasopharynx. Zhonghua Zhong Liu Za Zhi 1990; 12: 127–9.
6. Wenig BM, Hyams VJ, Heffner DK. Nasopharyngeal papillary adenocarcinoma. A clinicopathologic study of a low grade carcinoma. Am J Surg Pathol 1988; 12: 946–53.
7. Wenig BM, Harpaz N, DelBridge C. Polymorphous low-grade adenocarcinoma of seromucous gland of the nasopharynx. Am J Clin Pathol 1989; 92: 104–9.
8. Carrizo F, Luna MA. Thyroid transcription factor-1 expression in thyroid-like nasopharyngeal papillary adenocarcinoma: report of 2 cases. Ann Diagn Pathol 2005; 9: 189–92.
9. Ohe C, Sakaida N, Tadokoro C et al. Thyroid-like low-grade nasopharyngeal papillary adenocarcinoma: report of two cases. Pathol Int 2010; 60: 107–11.
10. Sillings CN, Weathers DR, Delgaudio JM. Thyroid-like papillary adenocarcinoma of the nasopharynx: a case report in a 19-year-old male. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: e25–28.
11. Lengel E, Somogyi A, Godeny M et al. Polymorphous low-grade adenocarcinoma of the nasopharynx. Case report and review of the literature. Strahlenther Onkol 2000; 176: 40–2.
12. Nojeg MM, Jalaludin MA, Jayalakshmi P. Papillary adenocarcinoma of the nasopharynx - case report and review of the literature. Med J Malaysia 1998; 52: 104–16.
13. Wang CC, See LC, Hong JH, Tang SG. Nasopharyngeal adenoid cystic carcinoma: five new cases and a literature review. J Otalaryngol 1996; 25: 399–403.
14. Liu TR, Yang AK, Guo X et al. Adenoid cystic carcinoma of the nasopharynx: 27-year experience. Laryngoscope 2008; 118: 1981–8.
15. Qiu F, Hua YJ, Guo L et al. Mucoepidermoid carcinoma of nasopharynx: a report of twelve cases. Ai Zheng 2005; 24: 362–4.
16. Liu TR, Chen FJ, Qian CN et al. Primary salivary gland type carcinoma of the nasopharynx: therapeutic outcomes and prognostic factors. Head Neck 2010; 32: 435–44.
17. Guo ZM, Liu WW, He JH. A retrospective cohort study of nasopharyngeal adenocarcinoma: a rare histological type of nasopharyngeal cancer. Clin Otalaryngol 2009; 34: 322–7.
18. Pineda-Daboin K, Neto A, Ochoa-Perez V, Luna MA. Nasopharyngeal adenocarcinomas: a clinicopathologic study of 44 cases including immunohistochemical features of 18 papillary phenotypes. Ann Diagn Pathol 2006; 10: 215–21.
19. Schramm VL Jr, Imola MJ. Management of nasopharyngeal salivary gland malignancy. Laryngoscope 2001; 111: 1533–44.
20. Kuo T, Tsang NM. Salivary gland type nasopharyngeal carcinoma: a histologic, immunohistochemical, and Epstein–Barr virus study of 15 cases including a psammomatus mucoepidermoid carcinoma. Am J Surg Pathol 2001; 25: 80–6.
21. McGuire LJ, Lee JCK. The histopathologic diagnosis of nasopharyngeal carcinoma. Ear Nose Throat J 1990; 69: 229–36.
22. Resta L, Ricco R, Santangelo A. Morphologic and classificatory considerations about 140 cases of carcinoma of the nasopharynx. Tumori 1983; 69: 313–21.
23. Batsakis JG, Solomon AR, Rice DH. The pathology of head and neck tumors: carcinoma of the nasopharynx, part 11. Head Neck Surg 1981; 3: 511–24.
24. Spiro RH, Thaler HT, Hicks WF, Kher UA, Huivos AH, Strong EW. The importance of clinical staging of minor salivary gland carcinoma. Am J Surg 1991; 162: 330–6.
32 Ho S, Teo P, Kwan WH, Choi P, Tjong J, Johnson PJ et al. A morphologic and follow-up study on the nasopharyngeal lymphoid hyperplasia and its relation to the cancer. Chin Med J (Engl) 1989; 102: 625–9.

33 Lin JC, Wang WY, Liang YM et al. Quantification of plasma Epstein–Barr virus DNA in patients with advanced nasopharyngeal carcinoma. N Engl J Med 2004; 350: 2461–70.

34 Twu CW, Wang WY, Liang WM et al. Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 2007; 67: 130–7.

35 He JH, Zong YS, Zhang M, Zhong BL, Liang YJ, Liang XM. Primary adenoid cystic carcinoma of the nasopharynx and its relation to Epstein–Barr virus infection. Zhonghua Bing Li Xue Za Zhi 2003; 32: 234–7.

36 Buchholz TA, Shimotakahara SG, Weymuller EA Jr, Laramore GE, Griffin TW. Neutron radiotherapy for adenoid cystic carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 1993; 119: 747–52.

37 Lee AWM, Foo W, Law SCK et al. Nasopharyngeal carcinoma – presenting symptoms and duration before diagnosis. HK Med J 1997; 3: 355–61.

38 Ozyar E, Atahan IL, Akyol FH, Gırı'kaynak M, Zorlu AF. Cranial nerve involvement in nasopharyngeal carcinoma: its prognostic role and response to radiotherapy. Radiat Med 1994; 12: 65–8.

39 Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972; 29: 1446–9.

40 Wei WI, Sham JS, Zong YS, Choy D, Ng MH. The efficacy of fiberoptic endoscopic examination and biopsy in the detection of early nasopharyngeal carcinoma. Cancer 1991; 67: 3127–30.

41 Greene FL, Page DL, Fleming ID et al. AJCC Cancer Staging Manual, 6th edn. Springer-Verlag, New York, NY 2002.

42 American Joint Committee on Cancer. AJCC Cancer Staging Manual, 5th edn. Lippincott-Raven, Philadelphia, PA 1997; 37.

43 Union Internationale Contre le Cancer. Pharynx. In: Spiessl B, Beahrs OH, Herkeman P (eds). TNM Atlas: Illustrated Guide to the TNM Classification of Malignant Tumors, Vol. 3. Springer-Verlag, Berlin 1992; 20–31

44 Min HQ, Hong MH, Ma J et al. A new staging system for nasopharyngeal carcinoma in China. Int J Radiat Oncol Biol Phys 1994; 30: 1037–42.

45 Vander Poorten VL, Balm AJ. Stage as major long term outcome predictor in minor salivary gland carcinoma. Cancer 2000; 89: 1195–204.

46 Erovic BM, Schopper C, Pammer J et al. Multimodal treatment of patients with minor salivary gland cancer in the case of recurrent disease. Head Neck 2010; 32: 1167–72.

47 Wen SX, Tang PZ, Xu ZG, Qi YF, Li ZJ, Liu WS. Therapeutic modalities of nasopharyngeal adenoid cystic carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2006; 41: 359–61.

48 Mendenhall WM, Morris CG, Amdour RJ, Werning JW, Hinerman RW, Villaret D et al. Radiotherapy alone or combined with surgery for adenoid cystic carcinoma of the head and neck. Head Neck 2004; 26: 154–62.

49 Brown J, Choi EC, Fee WE JF. Nasopharyngectomy for recurrent high-grade mucoepidermoid carcinoma after radiation failure. Otolaryngol Head Neck Surg 1999; 120: 564–6.

50 Garden AS, Weber RS, Ang KK, Morrison WH, Mentre J, Peters LJ et al. Postoperative radiation therapy for malignant tumors of minor salivary glands. Cancer 1994; 73: 2563–9.

51 Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988; 15: 613–7.

52 Jenkins DW, Spaulding CA, Constable WC, Cantrell RW et al. Minor salivary gland tumors: the role of radiotherapy. Am J Otolaryngol 1989; 10: 250–6.

53 Yin ZY, Wu XL, Hu YH, Gu XZ et al. Cylindroma of the nasopharynx: a chronic disease. Int J Radiat Oncol Biol Phys 1986; 12: 25–30.
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54 Pow EH, Kwong DL, McMillan AS et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006; 66: 981–91.

55 Kam MK, Leung SF, Zee B et al. Prospective randomized study of intensity modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007; 25: 4873–9.

56 Douglas JG, Laramore GE, Austin-Seymour M, Koh W, Stelzer K, Griffin TW. Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy. Int J Radiat Oncol Biol Phys 2000; 46: 551–7.

57 Huber PE, Debus J, Latz D et al. Radiotherapy for advanced adenoid cystic carcinoma: neutrons, photons, or mixed beam? Radiother Oncol 2001; 59: 161–7.

58 Wei WI, Lam KH, Sham JST. New approach to the nasopharynx: the maxillary swing approach. Head Neck 1991; 13: 200–7.

59 Devaiah AK, Lee MK. Endoscopic skull base/sinonasal adenocarcinoma surgery: what evidence exists? Am J Rhinol Allergy 2010; 24: 156–60.

60 Suen JY, Johns ME. Chemotherapy for salivary gland cancer. Laryngoscope 1982; 92: 235–9.

61 Posner MR, Ervin TJ, Weichselbaum RR, Fabian RL, Miller D. Chemotherapy of advanced salivary gland neoplasms. Cancer 1982; 50: 2261–4.

62 Belani CP, Eisenberger MA, Gray WC. Preliminary experience with chemotherapy in advanced salivary gland neoplasms. Med Pediatr Oncol 1988; 16: 197–202.

63 Licitra L, Marchini S, Spinazze S et al. Cisplatin in advanced salivary gland carcinoma: a phase II study of 25 patients. Cancer 1991; 68: 1874–7.

64 Hill ME, Constenla DO, A’Hern RP et al. Cisplatin and 5-fluorouracil for symptom control in advanced salivary adenoid cystic carcinoma. Oral Oncol 1997; 33: 275–8.

65 Jones AS, Phillips DE, Cook JA, Helliswell TR. A randomized phase II trial of epirubicin and 5-fluorouracil versus cisplatinum in the palliation of advanced and recurrent malignant tumour of the salivary glands. Br J Cancer 1993; 67: 112–4.

66 Dreyfuss AI, Clark JR, Fallon BG, Posner MR, Norris CM Jr, Miller Det al. Cyclophosphamide, doxorubicin and cisplatin combination chemotherapy for advanced carcinomas of salivary gland origin. Cancer 1987; 60: 2869–72.

67 Licitra L, Cavina R, Grandi C et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma: a phase II trial of 22 patients. Ann Oncol 1996; 7: 640–2.

68 Tsukuda M, Kokatsu T, Ito K, Mochimatsu I, Kubota A, Sawaki Set al. Chemotherapy for recurrent adenocarcinoma and adenosquamous carcinoma in the head and neck. J Cancer Res Clin Oncol 1993; 119: 756–8.

69 van Herpen CM, Locati LD, Buter J et al. Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982). Eur J Cancer 2008; 44: 2542–5.

70 Katori H, Tsuchida M. Concurrent chemoradiotherapy with cyclophosphamide, pirarubicin, and cisplatin for patients with locally advanced salivary gland carcinoma. Acta Otolarzynol Jpn 2006; 126: 1309–14.

71 Tanvetyanon T, Qin D, Padiya T et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major salivary gland carcinoma. Arch Otolarzynol Head Neck Surg 2009; 135: 687–92.

72 Schoenfeld JD, Sher DJ, Norris CM Jr et al. Salivary gland tumors treated with adjuvant intensity-modulated radiotherapy with or without concurrent chemotherapy. Int J Radiat Oncol Biol Phys 2010 (2012; 82: 308–14.

73 Holst VA, Marshall GE, Mosaluk CA, Frierson HF Jr. KIT protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma. Mod Pathol 1999; 12: 956–60.

74 Jeng YM, Lin CY, Hsu HC. Expression of the c-kit protein is associated with certain sub-types of salivary gland carcinoma. Cancer Lett 2000; 154: 107–11.

75 Alcedo JC, Fabrega JM, Arosemena JR, Urrutia Aet al. Imatinib mesylate as treatment for adenoid cystic carcinoma. Mod Pathol 2009; 12: 956–60.

76 Hotte SJ, Winquist EW, Lamont E et al. Imatinib mesylate in patients with adenoid cystic cancers of the salivary glands expressing c-kit: a Princess Margaret Hospital phase II consortium study. J Clin Oncol 2005; 23: 585–90.

77 Grandis JR, Melhem MF, Gooding WE et al. Levels of TGF alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. J Natl Cancer Inst 1998; 90: 824–32.

78 Chua DT, Nicholls JM, Sham JS, Au G et al. Prognostic value of epidermal growth factor receptor expression in patients with advanced stage nasopharyngeal carcinoma treated with induction chemotherapy and radiotherapy. Int J Radiat Oncol Biol Phys 2004; 59: 11–20.

79 Dori S, Vered M, David R, Buchner Aet al. HER2/neu expression in adenoid cystic carcinoma of salivary gland origin: an immunohistochemical study. J Oral Pathol Med 2002; 31: 463–7.

80 Gibbons MD, Mannu U, Carroll WR, Peters GE, Weiss HL, Grizzle WE et al. Molecular differences in mucoepidermoid carcinoma and adenoid cystic carcinoma of the major salivary glands. Laryngoscope 2001; 111: 1373–8.

81 Locati LD, Bossi P, Perrone F et al. Cetuximab in recurrent and/or metastatic salivary gland carcinomas: a phase II study. Oral Oncol 2009; 45: 574–8.

82 Gupta AK, Wilke WW, Taylor EN et al. Signaling pathways in adenoid cystic cancers: implications for treatment. Cancer Biol Ther 2009; 8: 1947–51.