Clinical Research

Clinical features of 337 patients with recurrent nasopharyngeal carcinoma

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Abstract

Background and Objective: Although appropriate radiotherapy and combined treatments are widely used for the patients with primary nasopharyngeal carcinoma (NPC), local or regional recurrence rates are still high. According to clinical performance, pathology, and diagnostic imaging of the patients with the first recurrence of NPC, this study analyzed the clinical features of recurrent NPC to provide a reference for tracking the rules of recurrence after the treatment of patients with NPC. Methods: The clinical data of 337 patients diagnosed with recurrent NPC for the first time were collected. The diagnoses were based on pathology and/or Imaging and the patients were treated at the Sun Yat-sen University Cancer Center between January 1999 and December 2004. Data used for statistical analysis included clinical performance during the patient visit, the extension of the invasion as shown on Imaging, pathologic features, Epstein-Barr virus (EBV) serology, restaging, etc. Results: Patients were staged according to the system developed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) in 2002. Patients with diseases at stage I/II accounted for 25.2%, while those with stage III/IV accounted for 74.8%. The median interval of relapse was 25 months. Patients had local recurrence (69.4%), regional recurrence (4.5%), or both (26.1%). Epistaxis and headache were the most common symptoms. Ablative dysfunction and facial numbness induced by cranial nerve damage were the most common signs. The probability of invasion of structures adjacent to the nasopharynx, such as the oropharynx, the prestyloid space, and the carotid sheath area, was low in patients with recurrent NPC. By contrast, the probability of invasion of structures far from the nasopharynx, such as the base of the skull, the paranasal sinuses, cranial nerves, the cavernous sinus, the brain, the pterygopalatine fossa, the infratemporal fossa, the orbital apex, and the soft palate, was higher in recurrent NPC. Conclusions: The most common interval of relapse is about 2 years. The relapsed disease is usually more widespread and located deeper. Most recurrent NPC is advanced disease.

Key words: Nasopharyngeal neoplasm, neoplasm recurrence

Nasopharyngeal carcinoma (NPC) is a common malignant tumor in southern China, and radiotherapy is currently the primary treatment for patients with NPC. With improvements in radiotherapy and the continuous intensive awareness of comprehensive treatment, the 5-year overall survival rate is between 59.0% and 76.1%. However, local and regional recurrence is still the main treatment failure for NPC, and the 5-year cumulative rate of nasopharynx and cervical lymph node recurrence is 15.0%–22.0%. Domestic and foreign studies have indicated that the clinical features of recurrent NPC have multiple factors. Therefore, improving the recognition of the clinical features of recurrent NPC is of great significance to improving early diagnosis, early treatment, and the long-term survival rate for patients with recurrent NPC. This study summarized and retrospectively analyzed the relevant information of a large sample of patients with first-time recurrent NPC.

Patients and Methods

General clinical information

Between January 1999 and December 2004, 337 patients were diagnosed with their first recurrence of NPC at the Cancer center of Sun Yat-sen University. Either biopsy or imaging, [plain plus enhanced computed tomography (CT) or magnetic resonance imaging (MRI)], or both, were used to diagnose all patients. A total of 264 men (78.3%) and 73 women (21.7%) were included, with the male:female ratio of about 3.6:1. Patient age ranged between 21 years and 73 years, with a median age of 46 years. For 27 patients first treated at other hospitals, the stages were unknown. According to the 1992 Fuzhou staging criteria, 310 patients had clear pretreatment stages, of which
5.2% (16/310) had stage I disease, 31.3% (97/310) had stage-II, 46.5% (144/310) had stage-III, and 17.1% (53/310) had stage-IV disease.

**Statistical Methods**

SPSS version 16.0 was used for statistical processing. Variance analysis was used for processing the enumerated data, a χ² test was used for measurement data, and a rank-sum test was used for ranked data.

**Results**

**Recurrence time**

The time from the end of the first treatment to the first recurrence ranged from 4 months to 291 months, with a median recurrence time of 25 months, in which recurrence time less than 6 months accounted for 5.9% (20/337), 6 months to 12 months accounted for 17.8% (60/337), 12 months to 18 months accounted for 11.6% (39/337), and 18 months to 24 months accounted for 13.4% (45/337). The 2-year cumulative recurrence cases accounted for 48.7% (164/337). Recurrence from 24 months to 60 months accounted for 34.4% (116/337), from 60 months to 120 months accounted for 13.6% (46/337), and recurrence time more than 120 months accounted for 3.3% (11/337), as seen in Figure 1.

**Diagnosis of the first recurrence**

Of the 337 patients, 76.9% (259/337) were diagnosed on pathology as having recurrence: 91.9% (238/259) had World Health Organization (WHO) type III, 7.3% (19/259) had WHO type II, and 0.8% (2/259) had WHO type I. Some patients with only intracranial and skull base recurrence who were unable to have a biopsy performed were diagnosed by MRI, CT, and positron emission tomography (PET)-CT, at 12.8% (43/337), 8.3% (28/337), and 2.1% (7/337), respectively.

The positive rate of EBV-VCA IgA in whole group was 98.6%, and the geometric mean titer of VCA-IgA was 1:169.8. The positive rate of EA-IgA was 65.6%, and the geometric mean titer was 1:31.8. The geometric mean titers of VCA-IgA and EA-IgA were 1:224.7 and 1:35.5, respectively, when patients were newly diagnosed in this group. The four sets of titer values were transformed logarithmically, and examined by Wilcoxon signed rank test. It was found that the Z value of log VCA-IgA between the first diagnosis and recurrence was -2.768, which was statistically significant \( (P = 0.006) \); the Z value of log EA-IgA between the first diagnosis and recurrence was -1.487, which was not statistically significant \( (P = 0.137) \).

The common invasion sites of recurrent NPC revealed by imaging in the whole group included the base of the skull base, accounting for 54.6% (184/337), the prestyloid space for 44.2% (149/337), the carotid sheath area for 32.3% (109/337), the anterior group of cranial nerves for 28.2% (95/337), the cavernous sinus for 26.1% (88/337), the paranasal sinuses for 22.8% (77/337), the oropharynx for 19.3% (65/337), the nasal cavity for 18.1% (61/337), intracranial invasion for 12.8% (43/337), the pterygomaxillary fossa for 11.0% (37/337), the posterior group of cranial nerves for 5.9% (20/337), the infratemporal fossa for 5.3% (18/337), the orbital apex for 5.0% (17/337), the soft palate for 3.3% (11/337), the cervical vertebrae for 2.1% (7/337), and the hypopharynx for 0.6% (2/337). Sites of primary and recurrent tumor invasion were compared by McNemar test (Table 1). The results showed that the invasion
rates of the oropharynx, the prestyloid space, and the carotid artery sheath by the primary tumor were significantly higher than those by the recurrence. Conversely, the invasion rates of the skull base, the paranasal sinuses, the cranial nerves, the cavernous sinus, the intracranial space, the pterygomaxillary fossa, the infratemporal fossa, the orbital apex, and the soft palate by recurrent tumors were significantly higher than those by the primary tumor.

**Clinical stages in patients with recurrent disease**

Patients were restaged by the 1992 Fuzhou staging criteria as follows: stage I accounted for 7.4% (25/337), stage II 11.6% (39/337), stage III 27.0% (91/337), stage IVa 47.2% (159/337), and stage IVb 6.8% (23/337) (Table 2). As restaged by the 2002 staging system developed by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), stage I accounted for 6.8% (23/337), stage IIa 1.5% (5/337), stage IIb 16.9% (57/337), stage III 23.4% (79/337), stage IVa 42.4% (143/337), stage IVb 2.1% (7/337), and stage IVc 6.8% (23/337) (Table 3).
Discussion

Do sex, age, clinical manifestations, invasion sites, and clinical stage of the first case of recurrent NPC have different characteristics than primary NPC? According to reports with large numbers of patients, the median age of patients with recurrent NPC is 43.8 years to 48 years, with a median recurrence time of 2 years, which is similar to this study. As reported by Lee et al. and Cui et al. the male:female ratio was about 2.5:1 and was similar with primary NPC. In this study the male:female ratio was 3.6:1 and was very close to the 3.7:1 reported by Li et al.8 The results showed that the incidence of recurrent NPC was higher in men than in women, and the male:female ratio was even higher than it was 10 years ago. The ratio of recurrent cases declined gradually following the extended interval from the end of treatment. Patients with recurrent disease at 3 years after the initial diagnosis accounted for 63.5%, which were considered at high risk for recurrence. Patients with recurrent disease between 3 years and 6 years was 23.7%, which decreased by nearly two-thirds compared to patients with recurrence at 3 years. Patients with recurrence at 6 years to 10 years accounted for only 9.5%, which indicated a low-risk period. Only very few patients were seen with disease recurrence after 10 years (3.3%), who belonged to the stable period of cured NPC.

Two types of recurrence, including local nasopharyngeal recurrence and regional cervical lymph node recurrence, are present in patients with recurrent NPC. The incidence of these two types of recurrence has changed significantly over time. In the late 1970s, lymph node recurrence alone accounted for 43.4% of all patients with recurrent NPC, reported by Cao et al. In the late 1980s, lymph node recurrence was 25.7%, reported by Cui et al. In this group, nasopharyngeal recurrence alone was the most common, while lymph node recurrence alone accounted for only 4.5%. The reason is very likely that (1) the advancement of radiotherapeutic equipment and technology improved the local control rate of cervical lymph node metastases, and (2) combined chemotherapy and radiotherapy improved local control rates, especially for huge lymph nodes receiving radiotherapy after induction chemotherapy.

It was reported in patients with primary NPC, cervical lymph node enlargement was the first symptom in about 40% to 50% of patients, followed by epistaxis, nasal obstruction, and tinnitus, etc. However, in this group, because nasopharyngeal recurrence alone accounted for the vast majority, neck mass only accounting for 14.8% of chief complaints, patients with recurrent disease reported headaches significantly more often than newly diagnosed patients, which might be due to late stage, destruction at the base of the skull, and/or intracranial invasion. In addition, the incidence of cranial nerve injury is 10.4% to 19.8% in primary NPC, but our data showed that in patients with recurrent disease, the incidence of cranial nerve injury occurred in one-third (35.3%) of the patients, which is significantly higher than its incidence in newly diagnosed patients. This may be relevant to the wide variation in patients with recurrent NPC.

The results showed the pathologic type of recurrent NPC was still mainly WHO type III, which was similar to the pathologic type of newly diagnosed patients in regions with high incidence. The base of the skull is the most common site of recurrence, but it is hard to perform biopsy due to the deep position and the complicated surrounding anatomical structure. So in this group, patients with skull base or intracranial recurrence alone could only be diagnosed by combined clinical manifestations and imaging data.

In terms of the serological tests of EBV, Cao et al. reported that VCA-IgA and EA-IgA levels correlated with clinical stages in newly diagnosed patients—the higher the stage, the higher the antibody level—while the antibody levels of different clinical stages had no significant difference in this group. However, we found that the VCA-IgA geometric mean titer of recurrent NPC was lower than that of primary disease, and the difference was statistically significant (P=0.006). Therefore, a lower level of VCA-IgA does not equate with a decreased risk of recurrence.

By comparing the invasion sites between primary and recurrent tumors, specifically structures adjacent to the nasopharynx, such as the oropharynx, the pre-styloid space, and the carotid artery sheath, the probability of invasion can be observed to be significantly lower in recurrent NPC. Conversely, regarding the structures far from the nasopharynx, such as the skull base, the paranasal sinuses, the cranial nerves, the cavernous sinus, the intracranial cavity, the pterygomaxillary fossa, the infratemporal fossa, the orbital apex, and the soft palate, the probability of invasion is significantly higher in recurrent disease than in primary disease. Areas neighboring the nasopharynx were in the high-dose area during the first treatment, while the areas far away from the nasopharynx were in either low- or no-dose areas. So we speculate that the possible reasons for the above-mentioned phenomena are: (1) the tumor cells of subclinical lesions in low-dose areas receive mostly sub-lethal damage, and can be repaired, survive, continue to split, and lead to tumor recurrence; or (2) the patients carry genes susceptible to NPC, and had a tendency of recurrence under external factors, but the normal structure of the areas adjacent to the nasopharynx was destroyed by high-intensity rays at the first treatment, with the local blood supply reduced and unfavorable for tumor growth, so the tumor relocates and occurs far away from the nasopharynx.

The follow-up of patients with cancer is very important. Follow-up should be performed every 3 months in the first 3 years after treatment, and every 6 months thereafter, and imaging examinations should be performed every year to discover metastasis or recurrence before clinical symptoms appear. However, our data showed that the early diagnosis of patients with recurrent NPC was still unsatisfactory. Based on the 1992 Fuzhou staging criteria or 2002 UICC/AJCC staging system, early-stage patients (stages I/II) accounted for only about one-quarter, while the vast majority of patients were at middle- and late-stages of disease. These patients have broader lesions and may have developed radiation encephalopathy or other consequences after their first treatment, so the area and dose of re-irradiation is restricted, making it difficult to apply radical
radiotherapy for some patients. Therefore, it is necessary and crucial to emphasize the importance of follow-up for patients to strive for early detection and early diagnosis, and to advance the early diagnosis of recurrent NPC, to improve the survival rate after retreatment.

References