Clinical Research Paper

Clinical analysis of 53 cases of esthesioneuroblastoma

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Background and Objective: The prognosis of esthesioneuroblastoma (ENB) is poor. This study was to analyze prognostic factors and explore a rational treatment for ENB. Methods: Clinical data of 53 ENB patients, treated at Sun Yat-sen University Cancer Center from 1980 to 2003, were analyzed retrospectively. The correlation of prognostic factors to clinical features and treatment approaches were analyzed using the Kaplan-Meier method. Efficacy of different treatment modalities was compared. Results: The five-year overall survival (OS) was 41% of all ENB patients. The five-year OS of the surgery group, radiotherapy group, chemotherapy group, surgery combined with radiotherapy and (or) chemotherapy group, chemoradiotherapy group were 42%, 38%, 0, 56%, 0, respectively, which were statistically significant (p < 0.05). The five-year OS of Kadish stage A, B, C patients were 100%, 37%, 31%, respectively (p < 0.05). The recurrence rate over the entire period was 51%. The five-year OS of the recurrence group and recurrence-free group were 42% and 48%, respectively (p > 0.05). Conclusions: ENB is a malignant tumor with high rates of locoregional recurrence and distant metastasis. Surgery-based multimodality is a relatively reasonable method. The prognosis of ENB is associated with the clinical stage and treatment modalities.

Esthesioneuroblastoma (ENB) is a rare malignant tumor originating from the olfactory epithelium in the nasal cavity. The disease is latent; most patients referred to the hospital are at the advanced stage. The tumor spreads to the intracranium and damages ethmoid sinus, frontal sinus and orbital plate, which leads to the destruction of basion. The single treatment of surgery, radiotherapy or chemotherapy could hardly cure the disease. Surgery cannot completely excise the lesions, so the recurrence rate is high. This study was to analyze prognostic factors and explore a rational treatment for ENB.

Patients and Methods

Patients. Clinical data of 53 patients with pathologically confirmed ENB treated at Sun Yat-sen University Cancer Center from January, 1980 to December, 2003 were enrolled, including 30 males and 23 females, with a sex ratio of 1.3:1. The patients were aged between 6 to 73 years (median, 39 years). Ten patients had neck lymph node metastases, and 43 did not. No distant metastases were observed when they were initially referred to the hospital. According to the Kadish Staging System, five cases were classified as stage A, 25 as stage B, and 23 as stage C. All patients had complete medical records. The follow-up period started from the initial therapy and ended in December, 2007. The survival time started from the initial therapy to the date of death or the end of the follow-up. The invasion of ENB was determined by imaging examinations or surgery.

Clinical symptoms. When ENB invaded the nasal cavity, patients had nasal blockage or painless nasal hemorrhage, which was often misdiagnosed as nasal polyps. Anosmia frequently occurred at the advanced stage of ENB resulting from the invasion of olfactory epithelium by ENB. When ENB invaded the intraorbital area, it caused exorbitism, diplopia, vision loss and even blindness. When ENB invaded maxillary sinus, swollen cheek and facial numbness appeared; when it invaded intracranium, symptoms of intracranial hypertension such as headache and vomiting, were observed. Some patients showed lymph node enlargement. And one patient suffered from dysphagia due to swollen retropharyngeal lymph nodes.

Treatments. Patients were divided into several groups based on the treatment modalities. Nine were included in the single surgery group, 12 in the single radiotherapy group, four in the single chemotherapy group, 18 in the group of surgery plus radiochemotherapy, and 10 in the radiochemotherapy group. The radiation sites in the single radiotherapy group included 11 cases of the primary tumor and one case of the primary tumor plus neck metastasis. The radiation dose was 38Gy to 85Gy, with an average of 66 Gy. Radiotherapy was performed using the 60Co or linear accelerator. The used chemotherapy regimens are IFO+DTIC+THP-ADM, DDP+CTX+ADM, CTX+THP-ADM+VCR, DDP+VP16 and VM26+IFO+DDP. The chemotherapy period lasted 4–12 cycles.

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Statistical analysis. The SPSS 13.0 statistical package was applied for analyses. The Kaplan-Meier method was adopted to calculate the survival and plot survival curves. The survival comparison was performed by the log-rank test. p < 0.05 indicated a significant difference.

Results

Survival for ENB patients. Fifty-three patients were followed up until December, 2007. Thirty-five died and 18 survived. The three- and five-year survival rates for the 53 ENB patients were 48% and 41%, respectively (Fig. 1).

Prognostic factors of ENB. Comparison of survival in patients with different stage classifications. According to the Kadish Staging System, the average survival time for patients with stage A ENB was 140 months, with stage B ENB was 50 months, and with stage C ENB was 32 months. The three- and five-year survival rates for stage A patients were both 100%, for stage B patients were 47% and 37%, and for stage C patients were 37% and 31%. Differences were significant among different stages of classification ($\chi^2 = 6.796$, p < 0.05) (Fig. 2).

Survival for patients with or without lymph node metastases. The average survival rates of 10 patients with and 43 patients without lymph node metastasis were 28 months and 56 months, respectively. The five-year survival rate was higher in patients with lymph node metastasis than those without (42% vs. 20%) ($\chi^2 = 0.967$, p > 0.05).

Survival of patients with different sites of recurrence. Twenty-three patients relapsed while 22 did not. The five-year survival rates of the two groups were 42% and 48%, respectively. The recurrence time ranged from two to 264 months (medium, 15 months). ENB relapsed in 11 patients within one year after the treatment. The survival rate was not significantly different between patients with or without recurrence ($\chi^2 = 0.951$, p > 0.05). The five-year survival for eight patients who did not receive other control modalities after the initial therapy was 0. The five-year survival rates for 10 patients suffering from local recurrence, three patients suffering from regional recurrence, and two patients having both local and regional recurrence were 80%, 0 and 0, respectively. Eight patients who had distant metastases died within three years. Significant difference was noted in the survival for these three groups of patients with metastasis ($\chi^2 = 13.471$, p < 0.05) (Fig. 3).

Survival for patients receiving different treatment modalities. The average survival time for the single surgery group, the single radiotherapy group, the single chemotherapy group, the group of surgery plus radiochemotherapy and the group of radiotherapy combined with chemotherapy group were 58 months, 50 months, 18 months, 69 months and 35 months, respectively; the five-year survival for these five groups were 42%, 38%, 0, 56% and 0, respectively. Significant differences were observed in these groups ($\chi^2 = 11.277$, p < 0.05) (Fig. 4).

Discussion

ENB originates from the neuroepithelial cells in the olfactory mucosa of the upper nasal cavity. With the improved diagnostic capacity, an increasing number of ENB cases have been reported. ENB is classified according to the staging system proposed by Kadish et al.1 Stage A tumors are limited to the nasal cavity; stage B tumors are tumors invading the nasal cavity and sinus; stage C tumors consisting of tumors extending beyond the nasal cavity and sinus, such as eroding into the orbit and the intracalvarium, or distant metastases.

Choice of treatment modalities. ENB often arises in the upper nasal cavity. It is latent with atypical symptoms, which makes early diagnosis difficult. Prognosis of ENB patients at the early stage is good after surgery, chemotherapy or radiotherapy. The five-year survival rate for five patients with stage A ENB in the study was 100%. However, unfortunately, most patients suffered from stage B or stage C ENB when they were admitted to the hospital, thus, single treatment of surgery, radiotherapy or chemotherapy could not cure ENB. Many researchers propose to use the combination treatment of surgery and postoperative radiotherapy or chemotherapy in treating ENB.2,3
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Meta-analysis showed that the five-year survival rate was 48.0% in 87 patients treated with single surgery and 65.0% in 169 patients treated with surgery plus chemotherapy, which implied significant differences between the two modalities. Most researchers agree to choose different surgery modalities for primary tumors of ENB based on the stage classification. Patients at the early stage are recommended to receive intranasal endoscopic resection, while patients at the advanced stage are recommended to undergo craniofacial resection plus postoperative chemotherapy, because the surgical margin is a key prognostic factor. Ferlito et al. proposed cervical lymph node dissection for patients with advanced ENB to avoid cervical lymph node recurrence. Zafero et al. conducted a 25-year study on 18 patients with ENB and found that in the four patients with local N0 advanced tumors, two suffered from recurrence in the neck after preventive neck radiotherapy and the other two who had no recurrence in the neck suffered from regional recurrence, though preventive neck radiotherapy had been applied. Four patients with stage N+ ENB underwent cervical lymph node dissection, three of which continued to receive radiotherapy after surgery while the other one did not. The four patients did not show cervical lymph node recurrence and achieved a 10-year survival rate of 80%. Therefore, cervical lymph node dissection is suggested for N0-ENB, and postoperative radiotherapy is recommended for patients with more than one positive cervical lymph node detected by pathological examination.

In recent years, chemotherapy is widely accepted for the treatment of patients with advanced ENB. Zafero et al. reported that 35% of the patients with advanced ENB were cured after chemotherapy.

We found that surgery-based comprehensive modalities yielded a higher five-year survival rate than the single surgery, single radiotherapy, single chemotherapy and the combination of radiotherapy and chemotherapy (p < 0.05), which were in line with other studies.

It is worth mentioning that one patient recovered from the primary tumor after radical radiation therapy; 15 months later, the neck lymph node metastasis was cured after radical dissection plus postoperative radiotherapy; 26 months later, he was referred to the hospital because of discomfort swallowing. MRI image indicated retropharyngeal lymph node metastases and lymph node metastases in the neck area II on the opposite side. After 12 courses of chemotherapy, the patient received stem cell transplantation (SCT) and was recovering from SCT. We propose that chemotherapy plays an important role in treating patients with ENB, especially patients with locally advanced tumors which can hardly be excised, or patients who could not receive radiotherapy because of a wide range of tumors and short intervals between radiotherapy courses.

Analysis of prognostic factors. The prognosis of ENB is correlated with clinical stage classification. The five-year survival rate for the five patients (9.4%) with stage A ENB in this study was 100%. Because most patients with ENB referred to the hospital were at the advanced stage of the disease, even though effective comprehensive treatments were applied, the survival rate of these patients was lower than that of patients at the early stage (p < 0.05). Timely diagnosis of ENB at the early stage is a key factor affecting the prognosis. Additionally, we should pay attention to the lump in the nasal cavity and perform biopsy when necessary, so that favorable treatment regimens could be used.

ENB is easy to recur. The recurrence rate of ENB was 51% in our study, which was similar to 47% as reported by other groups. Patients could survive a long time after active treatments for ENB recurrence. Kim et al. reported that the recurrence rate was 47% and the success rate of salvage therapies, such as surgery, radiotherapy or chemotherapy after surgery was 50%. Zhao et al. reported that the five-year survival rate for 24 patients receiving salvage treatment after recurrence was 28.8% and one patient lived more than 13 years.

In this study, 13 patients underwent salvage therapies after recurrence. Three received single surgery, two received single radiotherapy, three received chemotherapy, and five had surgery combined with radiotherapy and/or chemotherapy. The survival...
after recurrence ranged from five months to 227 months (median, 36 months). Therefore, comprehensive and active treatments should be recommended for recurrent patients after the initial therapy based on the health conditions. Eleven patients (50%) recurred within one year. Thus, patients with ENB should be closely followed up within one year after initial therapy for early diagnosis and treatment.

The recurrent sites are closely correlated to the prognosis of ENB. The prognosis of patients with local recurrence was significantly better than that of patients with regional recurrence, of patients with combined local and regional recurrence, and of patients with distant metastasis. It is advisable to treat the cervical lymph node metastases. In this study, three patients with stage C ENB underwent neck preventive radiation and did not suffer from lymph node metastases until the end of follow-up.

Dulguerov et al. reported that the five-year survival for patients with or without neck lymph node metastases were 29.0% and 64.0%, which implied significant differences. Our data indicated that the five-year survival rates for patients with or without initial diagnosis of neck lymph node metastases were 20% and 42%, however, neck lymph node metastasis was not a prognostic factor of ENB, which might be due to limited study subjects enrolled.

In summary, ENB is a highly malignant tumor with a high recurrence tendency. The prognosis of ENB is correlated to the clinical stage, treatment modalities and recurrence sites. Surgery-based multimodality is a relatively reasonable method.

References