ENDONASAL ENDOSCOPIC RESECTION AND RADIOTHERAPY IN OLFACTORY NEUROBLASTOMA: OUR EXPERIENCE

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Accepted 5 December 2006
Published online 11 April 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20610

Abstract: Background. Our aim was to evaluate the efficacy of a bimodal method of treatment consisting in endoscopic resection followed by radiotherapy in patients with olfactory neuroblastoma (ON).

Methods. This is a retrospective review on 10 patients with ON treated at a tertiary referral center. All the patients were treated with endonasal endoscopic resection, and 1 refused postoperative radiotherapy.

Results. No mortality was observed. Local tumor control was obtained in all the patients. Follow-up ranged from 15 to 79 months (median, 37 months). One patient developed a regional recurrence and for this was treated with bilateral, modified type III radical neck dissection plus radiotherapy on the neck. All patients regained a good quality of life after the treatment.

Conclusions. This method of treatment causes minimal injury to the patients, reduces side effects, and improves the quality of life of those with olfactory neuroblastoma. ©2007 Wiley Periodicals, Inc. Head Neck 29: 845–850, 2007

Keywords: endonasal endoscopic surgery; olfactory neuroblastoma; radiotherapy; minimally invasive approach; esthesioneuroblastoma

Olfactory neuroblastoma (ON) is a rare malignant neoplasm of the nasal vault and is believed to arise from the olfactory epithelium. Basal cells of the olfactory neuroepithelium are presumably the progenitors of the esthesioneuroblastoma,1,2 although not all the authors link ON directly to olfactory epithelium.3 The incidence of this neoplasm is difficult to establish, even if it is reasonable to think that it represents about 3% to 5% of all malignant nasal tumors.4,5 ON presents a bimodal peak in the second and sixth decades of life6 and can occur in a very wide range of ages (3–90 years).4

Diagnosis tends to be made late because early-stage ONs are usually asymptomatic. The most common symptoms manifested are progressive nasal obstruction, epistaxis, and hypoanosmia.4,7 These symptoms are related to the site and local invasion of the tumor.4

The incidence of cervical metastasis varies from 10% to 33% at the time of diagnosis,1,7 whereas distant metastases occur in 12% to 25% of patients, in whom lung, brain, and bone are the areas most commonly involved.8,9 To date, no
universally accepted staging system has been adopted, though that proposed by Kadish et al.\textsuperscript{10} is the one most commonly used.\textsuperscript{7}

Moreover, there is no universally accepted therapy for ON, though many important authors\textsuperscript{2,7,11} have considered craniofacial resection plus radiotherapy to be the “gold standard” for these patients; the single-treatment method has not proven to be effective in ON patients.\textsuperscript{2,7} Based on the good results obtained by others\textsuperscript{12,13} and on considering that endoscopic surgical skills have improved greatly, we started to treat ON patients with a combined-therapy protocol, which foresaw an endonasal microendoscopic resection followed by radiotherapy.

**MATERIALS AND METHODS**

From 1999 to 2004, 10 patients (7 female and 3 male) with histologically confirmed esthesioneuroblastoma were treated with microendoscopic resection followed by radiotherapy. Patients’ ages at surgery ranged from 14 to 72 years (median, 58.5 years), and follow-up ranged from 15 to 79 months (median, 37 months). Patients were considered “assessable” if they had both surgical treatment and follow-up in our department. The criteria for exclusion included massive dural invasion and brain invasion or frontal sinus extension or invasion of the orbit. Focal involvement of the periorbit is not considered an exclusion criterion.

The Kadish system was used to stage the tumor, and Hyams’ grading was used to histologically differentiate the tumors.\textsuperscript{14} All patients underwent our preoperative protocol (Table 1). All patients were informed about the method of treatment and gave their consent to the therapy.

Presenting symptoms, site of origin, tumor staging and grading, method of treatment, intraoperative margins, length of hospitalization, complications, regional and distant metastases, recurrence, and survival rate were recorded and analyzed.

**Surgical Technique.** All the surgical procedures were performed by the senior author (P.C.). In Kadish A tumors, where a dura resection is not foreseen, sodium fluorescein is administered intratecally before surgery to increase intraoperative identification of cerebrospinal fluid (CSF) leak. Initially, the lesion is divided into sections suitable for histological assessment. In the major lesions, we first perform a cavitation with a microdebrider to reduce the volume of the neoplasm while respecting the boundaries of the mass. Then the base of implant of the tumor is removed using a subperiosteal dissection plane, with the centripetal technique. In this manner, we obtain a clean surgical field with an excellent visualization of all the margins. The skull base is then drilled, usually with a diamond burr, and last, after resection of the ethmoidal roof and the fovea ethmoidalis, we remove the dura mater of the olfactory cleft and the olfactory bulb. During the procedure, we normally map the surgical field with many samplings to minimize the risk of recurrence. This mapping is extremely valuable because, in cases of massive dura involvement or frontal sinus involvement, the endoscopic surgical procedure is converted into an open external approach with bifrontal craniotomy. The same surgical approach described earlier is used in all the patients, but obviously, surgical resection is tailored to the patient’s local conditions. In fact, a lesser resection is performed for a Kadish A neoplasm than would be done for Kadish C lesion, which necessitates a greater resection; in this sense, when the nasal septum is in contact only with the tumor, we perform a wide subperiosteal dissection and an extensive drilling of the bone plate. When the septum is infiltrated by the ON, it is resected. As for the whole procedure, the dura resection is also tailored to the neoplasm extension and is guided by frozen sections. In all the patients, it was possible to anatomically spare the contralateral olfactory cleft. The key points of our surgical procedure are:

dissection of the lesion,
centripetal technique,
removal of dura mater and olfactory bulb,
freezing sections, and
multilayer duraplasty.

**Radiotherapeutic Technique.** Patients underwent postoperative radiotherapy starting 6 to 8 weeks following surgery. A volume encompassing the preoperative extent of the tumor, plus a 5-mm margin, was irradiated at a total dosage of 54 to 60 Gy in 2 Gy daily fractions. All patients were treated by 3-dimensional conformal radiotherapy,
including 2 to 3 nonaxial 6 MV photon beams in most cases in order to spare the ocular structures and chiasm, as well as the brain and hypophysis. A narrow-spaced (3 mm) CT scan was acquired for target contouring and planning of treatment, the patient’s head being immobilized by means of a thermoplastic facemask. Field conformation was achieved by means of customized blocks or multi-leaf collimators.

RESULTS

Presenting Symptoms. Nine patients complained of nasal obstruction either alone or associated with other symptoms. Nasal obstruction was the only symptom in 3 patients, whereas it was associated with epistaxis in another 4. One patient was completely symptom free at the time of diagnosis. One patient complained of mucous rhinorrhea with progressive nasal dyspnea.

Site of Origin. Nine tumors arose in the olfactory cleft (8 right side, 1 left side), and 1 arose in the right ethmoid sinus.

Stage. According to the Kadish classification, disease in 3 patients was classified as stage A, 4 patients as stage B, and 3 patients as stage C. All the Kadish C patients in this series had intracranial extension with a focal invasion of the dura of the cribiform plate. No invasion of the dura of the lateral lamella was observed.

Hyams’ Grading. Pathologic differentiation according to the Hyams’ criteria revealed 4 Hyams’ grading I, 4 Hyams’ II, and 2 Hyams’ III tumors. Grade I and II tumors were considered as low-grade ON while grade III tumors were considered as high-grade ON. Grade IV was not used because this entity is controversial.

Treatment. Only 1 patient was administered systemic chemotherapy postoperatively, due to the peri orbital extension and the young age. One patient refused postoperative radiotherapy. The mean dosage administered was 56.1 ± 5 SD Gy, with the technique previously described.

Intraoperative Margins. In all of these cases, surgical margins were free of disease. No dura trespassing was observed, so no tumor could be considered intradural.

Length of Hospitalization. Length of hospitalization ranged from 4 to 21 days (median, 5 days). All but 1 patient stayed in hospital for less than 10 days. One patient had a lengthier hospitalization due to a suspected CSF leakage that required careful observation and evaluation, including an examination under general anesthesia.

Surgical Complications. No serious complications were observed in this series of patients. As far as minor discomfort was concerned, almost all patients complained of nasal crusting during the first months after the procedure.

Radiotherapeutic Complications and Sequelae. Radiation was well tolerated in all patients, without undue breaks in treatment. According to Common Toxicity Criteria, the worst acute toxicity ranged from G0 to G1 for oropharyngeal mucositis (always restricted to the hard and soft palate and to the nasopharynx), G1 to G2 for nasal mucositis, G0 to G1 for conjunctivitis, and G0 to G1 for skin erythema. Radiotherapy-induced epiphora was observed in 1 patient. No other significant late radiation damage was found.

Local Recurrence. To date, no local recurrences have been observed.

Regional and Distant Metastases. One patient developed regional metastasis in the neck 21 months after the initial treatment for a Kadish B, Hyams’ III ON. She underwent a bilateral type III modified radical neck dissection followed by radiotherapy on the neck. To date, no distant metastasis has developed. No regional metastases have been observed in the other patients.

Survival. At the time of writing, all the patients are alive and free of disease. Follow-up ranged from 15 to 79 months (median, 37 months), but in 5 patients, the follow-up is still too short (less than 3 years) to draw any conclusion. Every patient regained his or her normal daily activities with excellent quality of life. Olfactory function was preserved in every patient.

DISCUSSION

ONs are thought to arise from neuroepithelial cells of the nasal vault and are intimately related to the cribiform plate. Typically, ONs are 1-sided, broad-based, and friable tumors. Patients with ON usually complain of unilateral progressive nasal obstruction, epistaxis, and hypoanosmia. Other complaints depend on involvement of the surrounding areas.

The behavior of these tumors varies greatly: some patients survive with the disease for more...
than 20 years, whereas in others, survival is limited to few months due to catastrophic progression and dissemination.\(^4\)

From a prognostic point of view, invasion of surrounding areas, mainly brain and orbit, has proven to worsen prognosis.\(^11\) Although not universally accepted, Hyams’ grading has been demonstrated to be of prognostic value.\(^4,7\) Moreover, in a report by Diaz et al, all the recurrence occurred in patients with Kadish stage C tumors, and the Kadish staging system has been demonstrated to be of prognostic value for recurrence and survival.\(^7\) The stage attributed at the initial presentation is highly predictive of survival.\(^4\)

Nevertheless, it is logical to think that the high incidence of local recurrence is directly related to inadequate resection margins.\(^12\) In fact, the most frequent recurrence is local,\(^6,13\) and only 33\% to 50\% of these patients can be managed successfully.\(^2\)

Unfortunately, until now, many patients with ON have been treated with surgery or radiotherapy alone.\(^4\) Surgery alone seems to be ineffective for local control,\(^7\) and Foote et al suggest the use of postoperative radiotherapy in order to reduce the risk of local failure.\(^16\) Surgery alone or combined treatment may account for 50\% and 33\% of local recurrence rates, respectively.\(^13\) Dulgerov et al, in their excellent review, demonstrated that there is a significant difference in survival rates between combined treatment and radiotherapy alone.\(^2\)

Actually, craniofacial resection followed by radiotherapy has been considered the gold standard treatment against which other approaches must be judged.\(^11\) Other authors confirm this statement.\(^2,7\) Although craniofacial resection is routinely performed in many centers, it still remains an invasive procedure with serious complications (intracranial hemorrhage, CSF leakage, pneumocephalus, and infection) and morbidity.\(^17\) In recent years, many authors have begun treating ON with a minimally invasive approach, obtaining good results.\(^12,13,18\) Walch et al\(^12\) were the first to treat ON patients with combined endoscopic resection and radiosurgery. Based on these data and considering that endoscopic surgical skills have improved greatly, we too have begun treating ON patients with a minimally invasive protocol.

Regarding the overall survival, all the patients in our series are still alive at the time of writing; however, we observed a regional recurrence in the neck of a patient with a Kadish B, Hyams’ III tumor, 21 months after the initial treatment. The patient has been treated with a bilateral type III modified radical neck dissection followed by radiotherapy on the neck. Until now, no distant metastasis and no regional recurrence have been seen.

In the remaining 9 patients, neither local failure nor regional recurrence has been observed.

Although these are excellent results, we must keep in mind that in 5 patients the follow-up is less than 3 years and is therefore too short to draw any conclusion. Although somewhat anecdotal, the recurrence in our series developed in a patient with Hyams’ grade III tumor. Local recurrence and nodal and distant metastases are reported to occur more frequently in patients with high-grade tumors.\(^6\) Other reports do not seem to confirm this statement.\(^19\) Unfortunately, our series cannot be useful in this controversy because we had only 1 regional recurrence, and therefore no serious conclusion can be drawn.

From a therapeutic point of view, given the difficulty obtaining complete confidence in the adequacy of surgical margins, we think that postoperative radiotherapy is necessary in almost all patients in order to reduce the risk of local recurrence. However, the real role of the surgical margins cannot be evaluated from our data, given the absence of positive margins in all the patients. Obviously, it must be stressed that it is necessary to obtain clear margins during the surgical procedure in order to increase the chance of local control.

Microendoscopic surgical resection can spare the contralateral cribiform plate and consequently the sense of smell. In our series, we were able to spare the healthy cribiform plate in all the patients (Figure 1) and therefore preserve the sense of smell, partially at least; in fact, in the postoperative period, all the patients, when asked, confirmed the maintenance of their sense of smell. If necessary, even the olfactory bulb can be resected. In our series, this extended technique was performed in 2 patients. Hence, we think that microendoscopic surgery represents, in skilled hands, a valid alternative to traditional techniques. In fact, with this technique it is possible to resect the entire sinonasal skull base, if necessary, between the frontal sinus and the clivus and in a coronal view between the 2 orbits. Given the fact that “complete resection” means a resection made in healthy tissue, we are convinced that this technique permits a complete and radical resection because all the intraoperative margins, verified with frozen sections, are free of disease. Moreover, the magnification offered by the endoscope permits a very careful examination of
the surgical field. Based on our experience, we think that endonasal procedures allow a complete and radical resection of the lesion and usually require only brief hospitalization. In our series, the length of hospitalization ranged from 4 to 21 days (median, 5 days), and all patients but 1 stayed in the hospital for less than 10 days.

We have observed no fatal complications related to the surgical procedure. We suspected a CSF leak in 1 patient, but endoscopic evaluation performed under general anesthesia proved negative. No other major complications have been observed; this aspect has to be pointed out due to the relatively high incidence of complications in craniofacial series. Almost all patients have complained of minor discomfort due to nasal crusting during the first months after the procedure. Moreover, radiotherapy was well tolerated by all the patients; the patients complained of only minor discomfort due to nasal and oropharyngeal mucositis and conjunctivitis. In 1 patient, a radiotherapy-induced epiphora was observed. At the time of writing, no other late significant radiation damage has been reported. We think that stereotactic fractionated conformal radiotherapy can be regarded as the optimal approach to the postoperative treatment of ON, as it allows the delivery of high dosages while improving both target coverage and sparing of the organs at risk as compared with conventional radiotherapy.

Single-dose stereotactic radiotherapy (radiosurgery) has also been suggested as a postoperative treatment combined with endoscopic surgery. Because the ablative effect of radiosurgery is typically suited for well-demarcated, visible gross disease, its use as a postoperative adjuvant in patients without macroscopic residual disease calls for further analysis. In our opinion, radiosurgery may result in being a justified choice in patients with small-volume macroscopic residual disease not in close proximity to the optic pathways.

Our treatment protocol, while requiring further confirmation with regard to efficacy, allows a rapid return to normal daily activities and a minimization of morbidity and hospitalization. All the patients in our series regained an excellent quality of life with preservation of the olfactory function. These aspects are not to be underestimated.

FIGURE 1. MR images of a patient with a right olfactory neuroblastoma. (A) Preoperative sagittal view; (B) Postoperative sagittal view; (C) Preoperative coronal view; (D) Postoperative coronal view.
Although preliminary, our data seem to confirm the effectiveness of this technique and, given the absence of local recurrence at the time of writing, we believe that this kind of procedure is worthy of examination and evaluation.

Finally, it must be stressed that recurrence can be seen even 10 or more years after treatment,6,8 and for this reason the follow-up has to be extended over the entire life of the patient.

CONCLUSION

This method of treatment minimizes injury to the patient, improves the quality of life, and permits good control of the disease. A lengthier follow-up and a larger sample of patients are required to confirm these excellent results.

REFERENCES