Abstract: 

Background. Olfactory neuroblastoma (ONB) is a rare tumor arising from the olfactory neuroepithelium. There is no universally accepted staging system, and treatment approaches lack uniformity. We present one institution’s experience with this tumor and the results of therapy.

Methods. Thirty patients treated for ONB at The University of Texas M. D. Anderson Cancer Center between 1979 and 2002 were retrospectively reviewed. The diagnosis of ONB was histologically confirmed for each patient.

Results. The mean follow-up was 7.32 years. In 77% of cases, patients received treatment with surgery followed by postoperative radiation therapy. Sixteen percent received chemotherapy as part of their initial treatment. Overall 5-year and 10-year survival rates were 89% and 81%, respectively. Nine patients whose disease was initially stage C had a recurrence. The mean time for recurrence was 4.67 years.

Conclusions. The M. D. Anderson Cancer Center approach to ONB is complete surgical resection, usually involving a craniofacial approach, with postoperative radiation therapy. This approach seems to be curative in early-stage disease. Late recurrence warrants long-term follow-up. © 2005 Wiley Periodicals, Inc. Head Neck 27: 138–149, 2005

Keywords: olfactory neuroblastoma; esthesioneuroblastoma; craniofacial resection

Olfactory neuroblastoma (ONB) is a rare tumor of the nasal cavity, with approximately 945 cases having been described in the world literature.¹ Berger and Luc² described the first two cases of ONB in 1924. Schall and Lineback³ described the first cases in America in 1951.

Its incidence is 3% of all intranasal tumors.⁴ The sex distribution is roughly equal,¹,⁵ and it is generally a disease of white individuals.⁶ No etiologic basis has been determined. Several authors have demonstrated a bimodal distribution in age of diagnosis. These studies show peaks in age groups 11 to 20 years and 51 to 60 years.⁵,⁷ Other authors have found a unimodal distribution concentrating in the fifth decade of life.⁶
Diagnosis tends to be late, because early lesions are largely asymptomatic.

The most common presenting symptoms are unilateral nasal obstruction and epistaxis. Symptoms generally predate diagnosis by 6 months to 1 year. Some authors commonly report symptoms of orbital involvement, whereas others do not. Spaulding et al reported 53% of patients initially seen with orbital symptoms (proptosis, visual field defects, orbital pain, epiphora, and partial blindness), whereas Morita et al found very few with orbital symptoms (2%).

Esthesioneuroblastoma is a tumor of neuroectodermal origin, arising from olfactory epithelium. It is usually a polypoid mass high in the nasal cavity with paranasal extension, in close proximity to the cribriform plate. ONB is a locally aggressive malignancy that frequently invades the skull base and orbit. The incidence of metastasis is reportedly 10% to 33% at the time of diagnosis. The most common site of metastasis is the cervical lymph nodes, occurring in 10% to 33% of patients at the time of presentation. Distant metastasis occurs in 12% to 25% of patients, with lung, brain, and bone being the most common sites. Most studies examining the behavior of this tumor are retrospective reviews because of its rarity.

The most significant advance in the treatment of ONB occurred in the 1970s. In 1976, at the University of Virginia, Drs. Jane and Fitz-Hugh introduced craniofacial resection for treatment of ONB. This approach involved a craniofacial team, including an otolaryngologist–head and neck surgeon, a neurosurgeon, and a neuro-ophthalmologist. Their 5-year survival improved from 37.5% to 82% when extracranial surgical excision and craniofacial resection were compared.

Several staging systems have been proposed for ONB. The Kadish system (Table 1) is most commonly used; however, Biller et al presented an alternate system based on the more standard TNM system. These staging systems seek to describe ONB in a clinically relevant manner; however, there has been limited success in demonstrating prognostic value of any one staging system.

The purpose of this study was to review our experience with ONB at The University of Texas M. D. Anderson Cancer Center. Our study includes only histologically confirmed ONB and the time frame after the advent of craniofacial resection (CFR). Recommendations are made for management of ONB on the basis of our experience and review of the literature. We compare our results with several other large centers’ experiences.

MATERIALS AND METHODS

The medical records of all patients diagnosed with ONB at M. D. Anderson Cancer Center between 1979 and 2002 were retrospectively reviewed. This time frame was designed to encompass only the postcraniophial era introduced in the mid 1970s. This allows presentation of a more homogenous treatment group.

All pathologic specimens were reviewed and confirmed as ONB by one of the senior authors (AKE); specimens of neuroendocrine carcinoma were excluded. A total of 42 patients were identified. Patients were considered evaluable if they had their surgical treatment, radiation therapy, and follow-up at M. D. Anderson. Those who refused treatment or pursued it at outside institutions were excluded. Twelve patients were excluded on the basis of these criteria, and 30 patients were included in the study.

Most of the patients had no definitive treatment at outside institutions beyond biopsy and/or removal of the intranasal mass. In three cases,
prior local resections had left no evidence of residual disease, and no further surgery was performed at our institution. All three of these patients had early-stage disease (one stage A and two stage B), and all three had postoperative radiation performed at M. D. Anderson. In one case, a patient had had a frontal lobe mass resected 2 months before arrival at our institution, which established the diagnosis of ONB; she subsequently underwent CFR at M. D. Anderson to complete her surgical treatment.

The patients’ medical records were reviewed for demographic information, presenting symptoms, treatment regimen, tumor extent, regional and distant metastasis, microscopic margin status on final pathologic studies, tumor recurrence, salvage therapy, and survival. All patients’ imaging studies were reviewed to confirm staging according to the Kadish system. MRI and CT scans were used to judge response to chemotherapeutic agents.

Univariate analysis was performed to identify factors prognostic of survival and recurrence. The variables considered were sex, race, tobacco use, alcohol use, staging, cervical nodal involvement, treatment, and Kadish staging. \( P \) values of < .05 were considered significant.

The primary endpoints for this study were relapse-free survival and overall survival. These values were calculated on the basis of the actuarial method outlined in the American Joint Committee on Cancer (AJCC) criteria for reporting end results.\(^{18}\) Survival statistics were calculated from date of diagnosis. If the exact date was unknown, the first day of the month of diagnosis was used. Survival calculations included patients who died without disease and those lost to follow-up. Time until first recurrence was defined as the time between the date of treatment initiation and the date of the recurrence. Local control was defined as no clinical, radiographic, or pathologic evidence of persistent or recurrent tumor within the original tumor bed after therapy.

**RESULTS**

Three percent of the 30 patients had stage A disease, 33% had stage B, and 63% had stage C (Figure 1). The average follow-up time was 7.32 years (range, 0.35–20.46 years). The mean age at diagnosis was 47 years (range, 18–79 years) (Figure 2). Eighty-three percent of patients were white, and 17% were Hispanic. Sixty-three percent of patients were men, and 37% were women. Forty-three percent of patients had a history of tobacco use, and 37% had a history of occasional alcohol use. Nasal obstruction/congestion (67%), epistaxis (37%), headache (33%), and anosmia/hyposmia (20%) were the most common presenting symptoms (Table 2).

**Overall Survival and Disease-Free Survival.** Overall patient survival rates at 5 and 10 years were 89% and 81%, respectively. Overall relapse-free survival rates at 5 and 10 years were 69% and 38%, respectively (Figure 3).

Eleven patients had early-stage disease (Kadish stage A or B). Ten of these patients received surgery followed by postoperative radiation, with one patient also receiving preoperative chemotherapy. Five patients had CFR, two had lateral rhinotomy with medial maxillectomy, and three

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**FIGURE 1.** Stage distribution of patients with olfactory neuroblastoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIGURE 2.** Distribution of patients on the basis of their age at diagnosis of olfactory neuroblastoma. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
had endoscopic resection (one with Caldwell-Luc). All endoscopic surgeries were performed at outside hospitals, as previously mentioned in “Methods.” One patient with stage B disease received radiation and chemotherapy, because he was initially seen with cervical node metastasis.

There were no instances of recurrence in this group, with a mean follow-up of 9.31 years. Five-year and 10-year overall survival was 91% (Figure 4). The one death occurring 2.3 years after initial diagnosis was not attributable to ONB; this patient had no evidence of disease at a clinic visit 7 months before death. Disease-specific survival for early-stage disease is 100% at 5 and 10 years.

Nineteen patients had Kadish stage C disease. Thirteen of these patients (68%) received a combination of surgery and radiation. Thirteen of these had surgery with postoperative radiation, whereas one received radiation followed by surgery. All surgeries performed on patients with stage C disease were CFR. Two of these patients treated with surgery and postoperative radiation also received preoperative chemotherapy. Of the remaining six patients with stage C disease, two patients received surgery alone, two received radiotherapy alone, and two were treated definitively with chemoradiation. For patients with stage C disease, 5-year and 10-year survival rates were 88% and 75%, respectively. Relapse-free survival at 5 and 10 years was 61% and 0%, respectively (Figure 5). All cases of recurrence occurred in patients whose disease was initially Kadish stage C.

**Table 2. Presenting symptoms of patients with olfactory neuroblastoma.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. patients (n = 30)</th>
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<tbody>
<tr>
<td>Nasal obstruction</td>
<td>21</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
</tr>
<tr>
<td>Anosmia/hyposmia</td>
<td>7</td>
</tr>
<tr>
<td>Sinusitis/sinus pain</td>
<td>3</td>
</tr>
<tr>
<td>Epiphora</td>
<td>2</td>
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<tr>
<td>Facial swelling</td>
<td>2</td>
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<tr>
<td>Otalgia</td>
<td>2</td>
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<tr>
<td>Rhinorrea</td>
<td>2</td>
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<tr>
<td>Seizure</td>
<td>2</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1</td>
</tr>
<tr>
<td>Facial pain</td>
<td>1</td>
</tr>
<tr>
<td>Visual changes</td>
<td>1</td>
</tr>
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</table>

**Prognostic Factors.** Sex, tobacco use, alcohol use, presentation with regional disease, margin status at time of initial resection, and treatment variations did not show prognostic significance with regard to recurrence or survival. Kadish staging was prognostically significant for 2-year ($p = .028$) and 5-year survival ($p = .032$). Kadish staging was also prognostic for regional and local recurrences combined ($p = .024$) but not statistically significant for local ($p = .114$) and regional ($p = .176$) recurrence when evaluated separately.

**Surgical Management.** Surgery was used as part of initial management in 87% (26 of 30) of our
patients (Figure 6). Of the 23 operations performed at M. D. Anderson, 21 (91%) were CFR. No elective neck dissections were performed, but one patient, who was initially seen with cervical metastasis, had a selective neck dissection performed as initial management.

Two patients received surgery alone, without adjuvant therapy. In one case, the surgery was fatal secondary to an epidural hematoma (January/1991). This patient would have received postoperative radiation if he had survived. The other patient was initially misdiagnosed with a meningioma and treated with surgery alone. He had a local recurrence 1.49 years after his initial surgery, at which time a diagnosis of ONB was recognized. He was salvaged with further surgery (CFR) and postoperative radiation. This patient is currently disease free 1.69 years from his salvage therapy.

Seventy-seven percent of patients (23 of 30) were managed with a combination of surgery and postoperative radiation. Gross eradication of disease was achieved in all 23 patients. Local control was obtained in 83% of these patients (19 of 23), with a mean follow-up of 7.0 years (range, 0.35–20.46 years). Seventeen percent of patients (four of 23) treated with surgery and postoperative radiation had local recurrence develop. Local recurrence occurred an average
Seventeen percent of these same patients (four of 23) have had regional recurrences develop in the neck an average of 5.4 years after initial treatment (range, 0.29–12.91 years). All patients had regional disease develop while their primary site was controlled. Two of them went on to have a local recurrence develop shortly after their regional recurrence was recognized. The other two patients have had enduring cures after management of their regional recurrences with postsalvage follow-ups of 20.16 and 9.53 years.

All patients treated surgically had grossly negative margins at the time of surgery. Five patients had microscopically positive margins after review of the histologic findings. All five patients were treated with postoperative radiation, and none has had a local recurrence, with mean follow-up of 7.77 years (range, 3.67–15.96 years).

Radiotherapy. Ninety percent of our patients (28 of 31) received radiation as part of their initial treatment. All radiation treatments were performed at M. D. Anderson, except with one patient who received the second half of his treatment at an outside institution. No elective neck irradiation was performed on N0 necks. The mean dosage of radiation therapy was 59.4 cGy.

Twenty-three of these patients were treated with surgery and postoperative radiation as explained earlier. In cases of postoperative radiation, patients were treated to a mean of 56.9 cGy (range, 50.0–67.2 cGy). The remaining five cases included one case of radiation before surgery, two cases of radiation alone, and two cases of combination chemotherapy and radiation.

Two patients with stage C disease received radiation alone. One patient had a complete response by imaging studies but had a local recurrence 7.80 years after completion of radiation therapy. This patient was salvaged successfully with surgery at an outside institution (University of Virginia). The other patient died from a myocardial infarction 2 months after completing radiation. He was 79 at the time of diagnosis and not an optimal surgical candidate. He did not have any imaging after his radiation, so it is impossible to comment on the success of his treatment. One patient received radiation before surgical resection but did not respond, according to imaging studies. Viable tumor was found in the surgical specimen.

Two patients received combinations of radiation and chemotherapy as initial therapy. One patient, who had stage C disease and cervical metastasis, had radiation without response followed by seven cycles of vincristine, doxorubicin, and cyclophosphamide with an enduring complete response (22.73 years). The other patient, who also had stage C disease, was treated with chemotherapy, four cycles of vincristine, doxorubicin, and ifosfamide with near-complete response that was followed by radiation with a complete response. The follow-up on this patient has been...
short (1.75 years), but there has been no evidence of recurrence.

**Chemotherapy.** Chemotherapy was used as initial management in 17% of patients (five of 30). Four of these had stage C disease, and one had stage B disease. Regimens of chemotherapy were continued as long as the patients clinically responded. Chemotherapy was never used independently, always in combination with other treatment modalities.

Two patients were treated definitively with chemotherapy and radiation as described earlier. Three patients were managed with chemotherapy before surgery. Preoperative chemotherapy was used to reduce the tumor size before resection. One patient had a decrease in the size of the tumor (stage B), one had no change (stage C), the other had progression of the tumor (stage C with cervical metastasis). The patient who responded received two cycles of cisplatin and etoposide. One patient, who did not respond, received several different regimens of chemotherapy, including two doses of 5-fluorouracil (5-FU) and leucovorin; two doses of intra-arterial cisplatin; and one dose of vincristine, doxorubicin, and cyclophosphamide. The other patient had progression of disease during therapy. This patient was treated with three cycles of vincristine, doxorubicin, cyclophosphamide, and dimethyltriazenoimidazolecarboxamide (DTIC). All three patients had viable tumor in their surgical specimens.

Chemotherapy was used in five instances of recurrence. One patient, who had local recurrence 6.82 years after diagnosis, was treated with chemotherapy with three cycles of cisplatin and etoposide. There was no response, and the patient did not tolerate the treatment well; further interventions were discontinued.

Another patient had neck metastasis develop 0.29 years after initial surgery and postoperative radiation. He was treated with 16 cycles of vincristine, doxorubicin, cyclophosphamide, and DTIC. The patient had a complete response after the first treatment, but treatment was continued to ensure an enduring cure. He has been disease free 18.78 years after recurrence.

Another patient received 10 cycles of vincristine, doxorubicin, cyclophosphamide, and DTIC after resection of a left temporal lobe recurrence. The patient had another local recurrence/metastasis develop in the left parietal lobe 1.82 years after discontinuing treatment. This patient then received two cycles of etoposide and ifosfamide preoperatively before another resection. The response is unknown, because films are not available.

Of the evaluable cases of chemotherapy use (those with imaging studies to judge response), there were four responders and five nonresponders (Table 3). Responders were treated with combinations of vincristine, doxorubicin, cyclophosphamide or ifosfamide with or without DTIC (three patients) or cisplatin and etoposide (one patient). The five patients who did not respond received combinations of vincristine, doxorubicin, cyclophosphamide or ifosfamide with or without DTIC (two patients), or leucovorin and 5-FU (one patient), or cisplatin and etoposide (one patient), or intra-arterial cisplatin (one patient).

**Recurrence.** Nine (30%) of our 30 patients had recurrent disease develop. All recurrences occurred in patients whose disease was initially Kadish stage C. Three patients had multiple recurrences develop. Initial recurrences included five regional and four local recurrences (Figure 7). All patients with recurrence had grossly and microscopically negative margins at the time of their initial surgery, and all had no evidence of disease after initial treatment. The mean time to initial recurrence was 4.67 years (range, 0.29–9.52 years).

Six patients had local recurrence develop; salvage therapy varied significantly. One patient was managed with palliative radiation and lived 3.16 years; he died of causes unrelated to ONB. Another patient received chemotherapy unsuccessfully for local recurrence. Three patients were successfully salvaged with surgical resection. The tumor in one of these cases had been previously misdiagnosed as a meningioma; salvage therapy consisted of CFR and postoperative radiation.

<table>
<thead>
<tr>
<th>Table 3. Olfactory neuroblastoma response to chemotherapy.</th>
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<tr>
<td>Agent</td>
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</tr>
<tr>
<td>Vincristine, doxorubicin, cyclophosphamide, or ifosfamide</td>
</tr>
<tr>
<td>Etoposide and cisplatin</td>
</tr>
<tr>
<td>Etoposide and ifosfamide</td>
</tr>
<tr>
<td>5-Fluorouracil and leucovorin</td>
</tr>
<tr>
<td>Intra-arterial cisplatin</td>
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*Abbreviation: DTIC, dimethyltriazenoimidazolecarboxamide.*
The final patient had a local recurrence develop three times. She was treated with three different regimens over the course of 9.66 years. The salvage treatments involved combinations of surgery, chemotherapy, and radiation. Although these treatments did not ultimately cure, they contributed to this patient’s prolonged survival.

**Neck Management.** The overall incidence of neck nodal metastasis over the course of the study was 23% (seven of 30) (Figure 8). Seven percent of patients (two of 30) initially had neck metastasis. One of these patients had a complete response to a combination of radiation and chemotherapy. The other received preoperative chemotherapy followed by neck dissection and postoperative radiation. Both management approaches were successful.

Eighteen percent of patients (five of 28) who were initially seen with N0 necks had regional recurrences develop. Recurrence in the neck developed a mean of 4.86 years after initial diagnosis (range, 0.29–9.52 years). Twenty-eight percent of patients with Kadish stage C disease with N0 necks (five of 18) had nodal metastasis develop as a form of recurrence.

Three patients with neck recurrences were managed successfully with neck dissection and postoperative radiation. These patients have had no further disease in the treated neck, with a mean follow-up of 3.74 (range, 1.52–9.53 years). One patient who had cervical metastasis develop 0.29 years after initial therapy was treated successfully with chemotherapy, as described earlier. The final patient was salvaged with radiation to the neck. This patient’s disease was controlled regionally for 9.50 years before she had new local disease and distant metastasis develop.

**Complications.** Thirty-two percent of patients (10 of 31) had complications related to their treatment (Table 4). Levine et al have previously...
reported an overall complication rate of 40%. The most common complication was epidural hematoma (n = 3), with one being fatal. Two of the three instances of epidural hematoma, including the one fatality, and all other neurologic complications listed, occurred before 1992. Since 1992, only one instance of intracranial hypotension with resultant pneumocephalus and epidural hematoma has occurred. No permanent neurologic sequelae ensued after treatment.

**DISCUSSION**

Similar to Resto et al, our review of ONB includes only cases with histologically confirmed ONB. We have excluded cases of neuroendocrine carcinoma and other high-grade neoplasms of the nasal cavity. The work of Hyams et al and Taxy et al illustrates the microscopic and immunohistochemical overlap of these entities. Other investigators have included neuroendocrine carcinoma in their analyses, because they consider these two entities as part of a histologic spectrum of the same disease. Several authors, however, have described the different pathophysiology of these two tumors.

Earlier studies report a bimodal age distribution of ONB. In a more recent study, in which ONB was histologically controlled for, the age peak was unimodal in the fifth decade of life. Our distribution similarly shows a unimodal peak in the fourth and fifth decades of life. Most of our patients were men (63%), whereas other authors have reported nearly equal distributions between male and female patients.

All investigations of ONB have striven to identify prognostic indicators. Early reports identified older age (>50 at presentation), female sex, disease recurrence, nodal and distant metastasis, and tumor extension beyond the nasal cavity as poor prognostic factors. Resto et al showed that the most significant predictor of overall survival was positive surgical margins. Others found histologic differentiation (Hyam’s grading) to be a predictor of local recurrence and survival, even though several earlier reports failed to demonstrate this.

Above all, there has been a search for clinical staging that is prognostically significant. Most authors have not found Kadish staging reflective of this. Resto et al report that the Kadish system was prognostic only in regard to relapse-free survival, but not for overall survival. They found that the Biller staging system (TNM) provided more descriptive information that correlated better with prognosis. Polin et al conversely report that Kadish stage is predictive of disease-related mortality.

In this study, we found the Kadish staging system to be prognostically significant for 2-year and 5-year survival. There were no significant differences between groups with regard to 10-year survival. Kadish staging was also prognostic for recurrence. In our review, all recurrence occurred in patients whose disease was initially Kadish stage C. These findings indicate that early-stage disease (stages A and B) has improved survival and a lower incidence of recurrence compared with stage C disease.

No consensus exists regarding the treatment of ONB. Review of the available literature indicates that ONB is a surgical disease, but the role of adjuvant therapies remains uncertain. The advent of craniofacial resection has clearly improved disease-free survival. Radiotherapy alone has been proposed as primary treatment in ONB, because ONB is believed to be a radiosensitive tumor. Elkon et al found that the results of radiation alone were equivalent to surgery alone and combination therapy in early-stage lesions. Similarly, reviews from the Mayo Clinic showed no significant difference in survival rates between patients who had radiotherapy alone and those who had surgery alone. However, recurrence rates of up to 67% have been cited when radiation alone was used.

At our institution, we have not advocated management with radiation alone since 1980, even in cases of early-stage lesions. Two patients in our series received radiation alone as primary treatment. One patient had a complete response initially but had a local recurrence develop 7.80 years later.

**Table 4. Complications related to treatment of olfactory neuroblastoma.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural hematoma</td>
<td>3</td>
</tr>
<tr>
<td>Nasal stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>1</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>1</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
</tr>
<tr>
<td>Radiation necrosis of the frontal lobe</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimal duct obstruction</td>
<td>1</td>
</tr>
<tr>
<td>Intractable maxillary pain</td>
<td>1</td>
</tr>
<tr>
<td>Pituitary hypofunction</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>1</td>
</tr>
<tr>
<td>Seizure disorder</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Complications related to treatment of olfactory neuroblastoma.
later and required surgical salvage. The other patient was managed with radiation alone, because he was a poor surgical candidate; he died from causes unrelated to ONB 3 months after completing radiation.

Other authors have recommended surgery alone in early-stage disease. Biller et al.17 advocated craniofacial resection alone with negative margins as treatment for patients with Kadish stage A/B disease. They suggested that radiation should be reserved for incomplete tumor excision, recurrence, and nonsurgical candidates. Similarly, Morita et al9 reported that surgical resection alone is effective for low-grade tumors if tumor-free margins can be achieved.

Although our experience is limited, surgery alone does not seem to be effective for local control. Our one patient treated with surgery alone, because of a misdiagnosis of meningioma, had a local recurrence develop just 1 year after surgery. However, this lesion was stage C, so we cannot comment directly on management of early-stage lesions with surgery alone.

The addition of radiation to surgery seems to significantly improve local control. Dulgherov and Calcaterra8 reported 86% local control with combined treatment compared with 17% with surgery alone. O’Connor et al25 saw a 75% recurrence rate after surgery alone compared with none after the combined approach. Morita et al9 had local recurrence develop in 55% of patients with total resection alone versus only 19% in patients with total resection and postoperative radiation. Similarly, Foote et al15 reported that local control improved from 72.7% to 85.9% when postoperative radiation was added. Notably in this study, patients who received postoperative radiation had more advanced tumors. Foote et al strongly advocated the use of postoperative radiation to improve local control.

At our institution, we consider surgery with postoperative radiation the standard of care for all lesions. Twenty-four of our 30 patients were treated with a combination of surgery and radiation. Most of these were treated with surgery followed by postoperative radiation. Twenty of these 24 patients had no evidence of local recurrence, with a mean follow-up of 7.18 years (range, 0.35–20.46 years). Three of these 20 patients had recurrences develop in the neck but have been successfully salvaged.

As recommended by Chao et al,26 combined-modality treatment is preferred even in patients with Kadish A/B disease. All 11 patients with stage A/B disease in our series were treated with surgery and postoperative radiation. One of these patients also received preoperative chemotherapy because of nodal metastasis. For early-stage disease, our disease-specific survival is 100%, with no instances of local or regional recurrence and a mean follow-up 8.31 years (range, 1.67–17.66).

Five patients with microscopically positive margins received postoperative radiation, and all remain free of disease, with a median follow-up of 7.77 years. This is consistent with numerous other reports of improved survival with surgical resection and postoperative radiation. Although some authors have found margin status to be a significant indicator of overall survival,6 this was not found in our study. All five patients who had a local recurrence develop after surgery had microscopically negative margins after their initial resections.

Numerous authors have commented on the effectiveness of chemotherapy in the treatment of ONB. Most authors report partial responses with preoperative or salvage chemotherapy.6,24,26 McElroy et al27 reviewed a 20-year experience of chemotherapy for ONB at the Mayo Clinic. They found that only two of eight patients responded, with both responding patients having high-grade tumors. They recommended chemotherapy in patients with advanced, high-grade lesions but cautioned that it is not curative. Even though these high-grade tumors were sensitive to chemotherapy, overall survival of those patients was still shorter.

In our series, there were four cases of significant response to chemotherapy. Two cases involved patients treated definitively with chemotherapy and radiation. In both cases, the chemotherapeutic agents generated most of the tumor response. Vincristine and doxorubicin were used in combination with an alkylating agent (cyclophosphamide or ifosfamide). Similarly, another patient’s neck recurrence was treated successfully with a combination of vincristine, doxorubicin, cyclophosphamide, and DTIC. The combination of cisplatin and etoposide was also successful in reducing the size of a stage B tumor preoperatively in one patient. However, there are five cases in which chemotherapy did not generate a response with the aforementioned agents and others.

Three patients in our study were treated with preoperative chemotherapy. One patient responded, whereas two did not. Viable tumor was found in all surgical specimens. Contrary reports by Polonowski et al28 have reported the absence of
viable tumor in surgical specimens after treatment with preoperative chemotherapy with cisplatin and 5-FU.

The preceding approach is similar to the University of Virginia’s experience with patients with Kadish stage C disease. As outlined by Spaulding et al in 1988, their treatment for stage C disease includes preoperative chemotherapy with two to three cycles of cyclophosphamide and vincristine (with or without DTIC) followed by radiation and CFR. Investigators from the University of Virginia believe that preoperative adjuvant therapy changes unresectable lesions to resectable lesions. According to their data, patients who respond to adjuvant therapy before surgery have a higher chance of obtaining disease-free survival.24,29

Reviewing their experience, Polin et al reported that 14 of 21 patients showed a significant reduction in tumor burden with preoperative adjuvant therapy. However, six of these 14 responders had stage A/B disease and received only preoperative radiation. Eight responders had stage C disease and received preoperative chemotherapy and radiotherapy. All seven non-responders had stage C disease and received chemotherapy and radiotherapy. This leaves only 53% (eight of 15) of patients with stage C who responded to preoperative chemotherapy and radiation, and from their data, it is difficult to determine which of these two modalities generated the response. For stage C disease, their 1-year, 5-year, and 10-year survival rates are 96%, 71%, and 44%, respectively. These data are similar to our stage C survival rates, without the addition of preoperative chemoradiation.

Our limited data suggest that ONB does respond to chemotherapy in some cases. In 11 documented instances in which chemotherapy was used to treat histologically confirmed ONB at our institution, four patients responded. In three of these cases, the patients were treated definitively with enduring cures. Further research will be needed to determine which tumors will respond to chemotherapy.

Locoregional recurrence was the most common cause of failures. There were six cases of local recurrence in our group of 30 patients. Sixteen percent of patients (four of 24) treated with surgery and radiation had local recurrences develop, whereas both patients managed with radiation or surgery alone had local recurrences develop. Although the numbers are small, surgery with postoperative radiation therapy seems to be superior to single-modality treatment.

In stage C disease, 10-year relapse-free survival is 0%, whereas overall survival is 74%. This reflects the effectiveness of salvage therapy. As alluded to by Spaulding et al and Elkin et al, salvage therapies play an important role in control of ONB.5,7 All five of the patients with stage C disease who have been followed for greater than 10 years have had recurrences develop. Of these five, four have been rendered disease free, whereas one has had multiple recurrences and at the last clinic visit was alive with disease. This reflects the tendency for stage C tumors to recur and the success of salvage treatment.

The incidence of cervical node metastasis in our patients over the course of the study was 23% (seven of 30). Eighteen percent of patients with N0 necks had cervical nodal metastasis develop after initial treatment, and all were initially stage C. Elkon et al had previously noted this high rate of lymph node metastasis in patients with stage C disease. Neck recurrences were commonly salvaged with neck dissection and postoperative radiation.

Neck recurrences tend to be late, with a mean time of 4.86 years after initial treatment. With the long delay between diagnosis and neck failure, it is difficult to clinically assess the neck on initial evaluation. The significant rate of neck metastasis in patients with stage C disease (26%) stresses the importance of long-term follow-up. In our experience, salvage therapy with neck dissection and postoperative radiation has been successful.

In Beitler et al’s review of 110 patients, they found that 9% of patients had recurrences in the neck with local control. They theorized that these patients could have been cured if their initial management had addressed the neck. They recommended elective neck therapy in those patients managed radically, although they found only two reported cases of elective neck management in the literature.

None of our patients were initially seen with distant metastasis. Other authors have reported an incidence between 12% and 25%, with lung and brain being the two most common sites. However, these studies did not control for histologically confirmed ONB. Only one of our patients had distant metastasis to her spine develop 12.91 years after her initial diagnosis. This patient had a complicated course involving one regional recurrence and three local recurrences, all of which were treated before distant metastasis developed. On the basis of our experience,
histologically confirmed ONB may not be as prone to metastasize distally as previously reported.

Recurrence can be late. The mean time until recurrence in several articles is approximately 2 years,7,9,11,15 but the range extends up to 10 years. Eden et al11 noted that 39% of recurrences occurred later than 5 years from diagnosis. In our study, we found the mean time to recurrence to be 4.67 years, and 55% occurred 5 years after completion of initial therapy. Follow-up should involve routine imaging with MRI or CT scans. These should initially be performed every 6 months and then extended to a yearly basis based on the clinician’s impression. Long-term follow-up should be the rule in cases of ONB.

CONCLUSION

The M. D. Anderson approach to ONB is complete surgical resection, usually involving a craniofacial approach, with postoperative radiation therapy. Our relapse-free and overall survival is 100% with this approach in early-stage lesions (stage A/B). All incidences of recurrence were found in patients whose disease was initially stage C. Patients with stage C disease tend to have both local and regional recurrences develop during long-term follow-up, but salvage therapy is successful for prolonging survival and ultimately cure in some cases. Chemotherapy is effective in some cases, but our experience is limited. Late recurrence warrants long-term follow-up of these patients with routine imaging.

REFERENCES