Salvage Surgery for Recurrent Nasopharyngeal Carcinoma

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Objective: To evaluate the results of salvage surgery for patients with primary recurrence of nasopharyngeal carcinoma after radiotherapy.

Design: Cohort study.

Setting: Academic tertiary referral center.

Patients: Eighteen consecutive patients with primary recurrence of nasopharyngeal carcinoma after radiation failure underwent nasopharyngectomy for cure via a facial translocation approach from July 1, 1993, to December 31, 1999. Follow-up ranged from 3 to 71 months. Five patients with skull base invasion required a combined neurosurgical approach to treatment. Seven patients had additional postoperative radiotherapy.

Results: The actuarial 3-year survival was 57%, while the local control was 78%. Four of 5 patients who had skull base invasion achieved local control. There was no surgical mortality, and the morbidity was 22%.

Conclusion: Advances in skull base surgery make possible the effective control of primary recurrence of nasopharyngeal carcinoma, with acceptable mortality and morbidity.


NASOPHARYNGEAL carcinoma (NPC) is the most common cancer of the head and neck in the southeastern part of China, Taiwan, Hong Kong, and Singapore. Nasopharyngeal carcinoma refers to malignant tumor arising from the epithelial cells lining the nasopharyngeal space. Other malignant tumors, such as glandular tumors arising from the minor salivary glands or sarcomas and lymphomas, are not included in the category of NPC. Nasopharyngeal carcinoma is related to Epstein-Barr virus, and, contrary to epithelial tumors from other parts of the upper aerodigestive tract, the mainstay of NPC treatment is radiotherapy. This is because (1) most NPCs are undifferentiated or nonkeratinizing carcinomas, which are sensitive to radiotherapy, and (2) the complexity of the nasopharyngeal anatomy makes radical surgery difficult. However, in recent years, as we have better understood the anatomy and spread of nasopharyngeal tumors, and because of the advancements in skull base surgery, the nasopharynx is no longer considered a no-man’s-land. Herein, we report our experience of salvage surgery for recurrent NPC after radiation failure at the primary site.

RESULTS

Of the 18 patients, 15 had negative margins, while 3 had microresidual diseases. There was no surgical mortality, and the morbidity was 22% (4/18), including cerebrospinal fluid rhinorrhea in 1 patient, flap necrosis in 1, osteoradionecrosis (ORN) of the translocated facial bone graft in 1, and mild epiphora in 1 (Table 1). The patient who had postoperative cerebrospinal fluid rhinorrhea died of brain involvement 3 months after surgery. The patient with ORN was treated with 3 successive sequestrectomies and hyperbaric oxygen therapy and ultimately required a free flap to resolve the problem. The patient with flap necrosis underwent several debridements, and the oro-pharyngeal wound healed with a secondary intention. However, she died of massive bleeding from carotid artery blowout 15 months after surgery.

The 18 patients were followed up for 3 to 71 months (Table 1). To date, 3 patients have died of local disease (including 2 with microresidual disease), 2 have died of nodal metastases (1 neck and 1 ax-
MATERIALS AND METHODS

From July 1, 1993, to December 31, 1999, in the Second Division of Otolaryngology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan, Republic of China, we operated on 18 patients in whom local recurrence developed after radiotherapy for NPC. There were 13 men and 5 women (age range, 30-62 years). Previously, 17 patients had undergone a single course of radiotherapy with more than 6600 rad (66 Gy), while 1 patient had undergone a second course of radiotherapy for his primary recurrence. Four patients had undergone radiotherapy elsewhere. Our preferred method of preoperative radiologic diagnosis is magnetic resonance imaging scans; however, early in the study, 2 patients had computed tomography only.

Preoperatively, the tumors were classified as rT1 (8 patients), rT2b (1 patient), rT3 (5 patients), and rT4 (4 patients), according to the American Joint Committee on Cancer staging system.3 The clinical characteristics of the patients are summarized in Table 1. Two patients had previous sinus surgery, including 1 Caldwell-Luc operation and 1 functional endoscopic sinus surgery. One patient had persistent cervical metastasis after radiotherapy and underwent modified radical neck dissection before nasopharyngectomy. Another patient had recurrent neck disease after completion of nasopharyngectomy for his primary recurrence and subsequently underwent modified radical neck dissection. The nasopharyngectomies were carried out via a facial translocation approach. Five patients required a combined neurosurgical approach (3 subtemporal and 2 subfrontal) and appropriate neurosurgical resection. Seven patients who had tumor-positive or close surgical resection margins underwent a second course of radiotherapy postoperatively.

All patients had biopsy-proven primary recurrence. A systemic workup with chest x-ray, abdomin al sonography, and technetium Tc 99m bone scan was carried out before the operation, and if any of these examinations had positive findings, the patient entered a second radiotherapy protocol and did not have surgery. The contraindications for cranial base surgery for recurrent NPC in our division are (1) extensive intradural invasion, (2) cavernous sinus involvement, and (3) pharyngobasilar fascia invasion. We do not consider bony destruction of the cranial base unresectable.

The cutoff point for study data was May 31, 2001. Statistical analysis was carried out using commercially available software (SPSS version 7.5; SPSS Inc, Chicago, Ill). The actuarial overall survival and local control were calculated by the Kaplan-Meier method. Five patients who had skull base or intracranial extension needed a combined neurosurgical resection; 1 died of local recurrence in the brain and 1 died of axillary nodal metastases. Four (80%) of the 5 patients had local control.

Of the 18 patients, 16 had undifferentiated carcinomas (World Health Organization type 3), and 2 had keratinizing squamous cell carcinomas (World Health Organization type 1). In 3 patients, no cancer was found in the surgical specimens, although preoperative biopsies had demonstrated recurrent cancer.

The mainstay of NPC treatment is radiotherapy, as most NPCs are undifferentiated or nonkeratinizing carcinomas, which are radiosensitive. Nasopharyngeal carcinoma, compared with other epithelial cancers of the upper aerodigestive tract, has a high incidence of distant metastasis. However, locoregional failure is still the main cause of death. For example, in our tumor registry, 1002 (35%) of 2860 registered patients with NPC died of local disease or local recurrence, despite radical radiotherapy.4

Although the incidence of local persistent or recurrent disease has decreased following introduction of concurrent chemoradiotherapy,5 such occurrences lead patients to a dismal prognosis. Treatment of primary recurrence can be accomplished by additional external beam radiotherapy or by skull base surgery. Reirradiation of the primary recurrence of NPC has been reported,6,9 but it was accompanied by significant morbidity caused by complications such as severe xerostomia, trismus, deafness, and neurological sequelae.8,9 Other pitfalls include the complications of ORN following reirradiation.10,11 The patient may experience foul odor, severe pain, and massive bleeding. Furthermore, it cannot be assumed that NPC cells surviving the first course of radiotherapy will respond to further radiotherapy.

The surgical approach to the nasopharynx has been the focus of interest since the development of skull base surgery. Fisch12 used an infratemporal fossa approach to resect nasopharyngeal tumors. However, in this lateral approach, mastoidectomy must be accomplished before attacking the nasopharynx. Transpalatal approaches have been favored by Fee13 and Hsu14 and their colleagues; however, only small mucosal tumors in the central roof of the nasopharynx are suitable for this approach. A mandibular swing approach attacks the tumor from below, but we have found the exposure of the skull base to be limited with this approach, especially when the tumor has invaded the foramen ovale or touched the pterygoid plate base. Nevertheless, it has been claimed that this method offers control of the ascending internal carotid artery and allows resection of the tumor in the parapharyngeal space medial to the artery.14 Wei et al,15 from Hong Kong, used the maxillary swing approach to resect these difficult tumors. This approach is ideal for tumors confined to the mucosal surface of the nasopharynx or tumors with paranasopharyngeal space invasion.13,16 In our study, a facial translocation approach was used exclusively.17 And this approach can be combined with neu-

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rosurgical craniotomy for tumors with skull base invasion.18

In the facial translocation approach, the facial osteotomy can be localized based on the location of the tumor. If the tumor is confined to the nasopharynx or has paranasal extension, a nasoorbitomaxillary osteotomy will suffice, and the infraorbital neurovascular bundle can be preserved. However, when the tumor has invaded the parapharyngeal space, a larger facial osteotomy, optionally including part of the zygoma, is created to remove the tumor.

If the tumor has invaded the pterygoid plate base, a combined preauricular infratemporal subtemporal approach is used.19 This approach offers superior and lateral approaches to the nasopharyngeal and parapharyngeal space. After temporal craniotomy, the temporal lobe is retracted to expose the temporal base. The foramen ovale can be decompressed, and the transverse portion of the petrous internal carotid artery lying behind the foramen ovale is located and protected. The tumor can then be removed from the superior, lateral, and anterior directions. However, it is difficult to differentiate bony invasion by cancer from ORN intraoperatively.20 Confirmation of clear margins of skull base bone requires histopathological analysis. After the tumor is resected, the temporalis muscle is split and its anterior half is transposed to fill the defect, covering the exposed subtemporal dura and separating the neurocranium from the underlying upper aerodigestive tract. Anterior craniofacial resection is carried out if NPC involves the cribriform plate or the planum sphenoidale.

### Table 1. Clinical Characteristics of Patients With Recurrent Nasopharyngeal Carcinoma at the Primary Site*

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Retreatment Stage</th>
<th>Approach</th>
<th>Margins</th>
<th>Pathologic Findings</th>
<th>Complications</th>
<th>Follow-up, mo/Outcome Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/38</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>14/DLD</td>
</tr>
<tr>
<td>2/M/42</td>
<td>rT3</td>
<td>FT and ST</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>21/NER</td>
</tr>
<tr>
<td>3/M/35</td>
<td>rT2b</td>
<td>FT</td>
<td>+</td>
<td>UD</td>
<td></td>
<td>31/DLD</td>
</tr>
<tr>
<td>4/M/42</td>
<td>rT4</td>
<td>FT and SF</td>
<td>−</td>
<td>UD</td>
<td>Cerebrospinal fluid rhinorrhea</td>
<td>3/DLD</td>
</tr>
<tr>
<td>5/M/46</td>
<td>rT4</td>
<td>FT and ST</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>18/Died of distant metastasis</td>
</tr>
<tr>
<td>6/M/59</td>
<td>rT3</td>
<td>FT and ST</td>
<td>−</td>
<td>UD</td>
<td>Epiphora</td>
<td>31/NER</td>
</tr>
<tr>
<td>7/F/30</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>69/DRN</td>
</tr>
<tr>
<td>8/M/42</td>
<td>rT3</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>33/NER</td>
</tr>
<tr>
<td>9/M/58</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>20/NER</td>
</tr>
<tr>
<td>10/M/56</td>
<td>rT3</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td>Osteoradionecrosis</td>
<td>71/NER</td>
</tr>
<tr>
<td>11/M/62</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>54/NER</td>
</tr>
<tr>
<td>12/F/32</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>49/NER</td>
</tr>
<tr>
<td>13/F/41</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>59/NER</td>
</tr>
<tr>
<td>14/M/44</td>
<td>rT4</td>
<td>FT and SF</td>
<td>+</td>
<td>UD</td>
<td></td>
<td>36/DRN</td>
</tr>
<tr>
<td>15/M/41</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>18/NER</td>
</tr>
<tr>
<td>16/M/43</td>
<td>rT1</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>18/NER</td>
</tr>
<tr>
<td>17/F/40</td>
<td>rT3</td>
<td>FT</td>
<td>+</td>
<td>UD</td>
<td>Flap necrosis</td>
<td>15/Died of carotid artery blowout</td>
</tr>
<tr>
<td>18/F/62</td>
<td>rT4</td>
<td>FT</td>
<td>−</td>
<td>UD</td>
<td></td>
<td>18/NER</td>
</tr>
</tbody>
</table>

*FT indicates facial translocation; −, negative; +, positive; UD, undifferentiated carcinoma; ellipses, none; DLD, died of local disease; ST, subtemporal; NER, no evidence of recurrence; SF, subfrontal; DN, died of nodal disease; and WD, well-differentiated carcinoma.

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Figure 1. Actuarial survival of patients who underwent nasopharyngectomy for primary recurrence of nasopharyngeal carcinoma.

Figure 2. Actuarial control of disease in the nasopharynx after resection.
TUMOR EXTENSION

The nasopharynx lies deep and central in the skull. Its roof is the undersurface of the sphenoid sinus floor. The posterior wall is separated from the basiocciput and clivus by the pharyngobasilar fasciae. The lateral wall of the nasopharynx consists of the torus tubarius, surrounded by the superior constrictor muscle, and is pierced by the sinus of Morgagni, in which pass the eustachian tube and tensor veli palatini muscle. The nasopharynx communicates freely with the posterior nasal choanae. Nasopharyngeal carcinoma is notorious for submucosal extension. It commonly resides in the Rosenmüller fossa and may extend laterally through the sinus of Morgagni to invade the parapharyngeal space. Skull base extension by destruction of the pterygoid base is common, and the tumor may extend superiorly to involve the cavernous sinus or go laterally to involve the foramen ovale. The pharyngobasilar fasciae are tough fasciae and can be a strong barrier against tumor. In rare instances, NPC may invade these fasciae to involve the clivus.

With understanding of the anatomy of the nasopharynx and the natural extension of NPC, nasopharyngectomy can be accomplished by removing most of the nasopharyngeal mucosa, the ipsilateral torus tubarius, and the medial pterygoid plate and its base by a nasoorbitomaxillary osteotomy. Further lateral extension necessitates a combined subtemporal approach. In our study, anterior craniofacial resection via a subfrontal approach was carried out in patients with anterior cranial base tumors. The posterior half of the nasal septum was commonly removed to gain access to the contralateral Rosenmüller fossa. Currently, the contraindications in our division for salvage surgery for NPC are (1) extensive indurated invasion, (2) cavernous sinus involvement, and (3) pharyngobasilar fasciae invasion. Preoperatively, magnetic resonance imaging scans are the imaging methods of choice to define the local extension of the primary recurrence, which is important for surgical planning. Magnetic resonance imaging scans are also valuable in differentiating sinus invasion by cancer from obstructing sinusitis. Its excellent soft tissue resolution also reveals cavernous sinus or foramen ovale involvement. Based on our experience with the first 2 patients in this series, computed tomographic scans are no longer used to define skull base extensions.

En bloc resection of NPC is not always possible, and, as with other difficult lesions of the skull base, the resection is often completed piece by piece. However, if the tumor is confined to the nasopharynx, en bloc resection can be easily accomplished by fracturing down the sphenoid sinus floor, cutting the eustachian tube, removing the medial pterygoid plate, and stripping the tumor off the posterior pharyngobasilar fasciae. The resulting nude surface of the nasopharyngeal space is left to reepithelialization, which takes about 3 months. During this time, diligent endoscopic cleansing and local hygiene maintenance are crucial.

COMPLICATIONS

Four patients had postoperative complications, including 1 cerebrospinal fluid rhinorrhea, 1 flap necrosis, 1 ORN of the translocated facial bone, and 1 mild epiphora. In the patient with ORN, a free facial bone graft technique via a facial translocation approach was used. Despite diligent sequestrectomies and hyperbaric oxygen therapy, the ORN persisted and the patient required a free flap to obliterate the paranasal cavity, thereby resolving the ORN. Based on our experience with this patient, we now use the vascularized facial bone graft technique exclusively in facial translocation for patients who have had previous radiotherapy.

In the immediate postoperative period, patients may experience crust formation and accumulation in the hollow paranasal and nasopharyngeal cavities. Regular self-cleansing and irrigation with warm isotonic sodium chloride solution are important to improve the condition.

Fee et al described 9 patients with primary recurrence of NPC; 7 were treated for cure and 2 for palliation. Five of the 7 lived free of disease for 6 to 48 months. The authors concluded that surgery produced results as good as those of reirradiation, if not better. In a follow-up study, Fee and colleagues reported that long-term survival (>3 years) after surgical resection for recurrent NPC was possible; however, salvage surgery had only slightly better results than reirradiation. Wei et al described 26 patients who underwent maxillary swing approaches to their nasopharyngeal or paranasopharyngeal tumors, 18 of which were recurrent NPC. At 3½ years after surgery, 9 were alive without disease, and the actuarial local control of recurrent NPC was 42%. Hsu et al described 24 patients with primary recurrence of NPC, in whom various surgical approaches were used based on the location and invasion of NPC. In their series, 14 patients (58%) survived after surgery during a median 18 months of follow-up. The authors postulated that cranial nerve invasion was a surgical contraindication but that salvage surgery otherwise was a reasonable alternative to reirradiation. King et al recently described 31 patients with primary recurrence of NPC, among whom 7 had cervical metastases in addition to their primary recurrences, requiring nasopharyngectomy and neck dissection. In their series, 9 patients had tumor-positive margins, and there was no significant difference in disease-free survival between them and patients with clear surgical margins. The actuarial 3-year overall survival was 47%, and the authors concluded that postoperative radiotherapy significantly enhanced survival and tumor control.

In our series, the actuarial 3-year survival of 57% and local control of 78% compared favorably with those of the other series. Postoperative radiotherapy was administered in only 7 patients (39%) who had tumor-positive or close surgical resection margins. Further-

Table 2. Two-Year Survival According to rT Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Patients</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>rT1</td>
<td>8</td>
<td>87.5</td>
</tr>
<tr>
<td>rT2b</td>
<td>1</td>
<td>100.0</td>
</tr>
<tr>
<td>rT3</td>
<td>5</td>
<td>80.0</td>
</tr>
<tr>
<td>rT4</td>
<td>4</td>
<td>50.0</td>
</tr>
</tbody>
</table>

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more, we conclude that intracranial invasion is resectable. Superior dissection around the sphenoid sinus and pterygoid base and lateral dissection around the foramen ovale through a combined anterior facial and superior neurosurgical approach are crucial to control primary recurrence of NPC with skull base invasion. In our series, we achieved local control in 4 of 5 patients with skull base or intracranial involvement. With the concerted efforts of radiologists, radiation oncologists, head and neck surgeons, and neurosurgeons, nasopharyngectomy can be a safe and oncologically sound approach to treatment of primary recurrence of NPC. Further effort should be directed to early detection of local recurrence by molecular biology techniques.

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