Nasopharyngectomy and Surgical Margin Status

A Survival Analysis

Alexander C. Vlantis, FCS(SA)ORL; Raymond K. Y. Tsang, FRCS(Edin)(ORL); Brian K. H. Yu, FRCR; Michael K. M. Kam, FRCR; Michael C. F. Tong, FRCS(Edin)(ORL); Phoebe S. Y. Lo, MSc; C. Andrew van Hasselt, MMed(Otol)

Objective: To explore whether the margin status at surgical salvage nasopharyngectomy for local residual or recurrent nasopharyngeal carcinoma affects patient survival.

Design: Retrospective case series review.

Setting: Academic tertiary referral center.

Patients: Seventy-nine consecutive patients with operable local residual or recurrent nasopharyngeal carcinoma after failure of primary treatment with radiotherapy with or without chemotherapy underwent surgical salvage nasopharyngectomy with curative intent between November 28, 1987, and November 17, 2003. Sixty-one patients were men and 18 were women. Their mean age was 48 years (age range, 26-70 years).

Intervention: Surgical salvage nasopharyngectomy.

Main Outcome Measures: The status of the closest margin at surgery was assessed as clear, close, or positive. Survival time was measured from the date of surgery to the date of the last follow-up, to the date of an event occurrence, or to the date of death. The Kaplan-Meier method was used to estimate the probability of local progression-free survival and overall survival at 5 years. Differences in survival rates between surgical margin statuses were assessed using the log-rank test.

Results: Five-year overall survival for patients with clear margins was 77%, for patients with close margins was 46% (P = .05), and for patients with positive margins was 23% (P < .001).

Conclusion: Clear surgical margins at the time of surgical salvage nasopharyngectomy for residual or recurrent nasopharyngeal carcinoma positively affect patient survival.

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Primary nasopharyngeal carcinoma is treated with radiotherapy, with or without chemotherapy. Local failures occur in 9% to 40% of patients after primary treatment. Patients who receive salvage treatment for an isolated early-stage local failure have a significantly better overall survival (OS) rate than patients who do not. Salvage of local failures using external beam radiotherapy (EBRT) leads to further 5-year survival of 7% to 36%, but severe late radiotherapy complications occur in 20% to 57% of these patients. Alternatively, surgical nasopharyngectomy can be used to salvage local failures with or without postoperative radiotherapy, resulting in 5-year OS of 40% to 60%.

Previously published data showed that nasopharyngectomy resulted in better survival and local control for recurrent early-stage tumors (rT1 and rT2) than did irradiation using EBRT. Although clear surgical margins are a principle in oncologic surgery, one of the main risks of nasopharyngectomy is in the lateral dissection of the specimen, which is performed to achieve clear surgical margins. This may cause inadvertent injury to the internal carotid artery (ICA), which lies lateral to the nasopharynx. The mucosal space of the nasopharynx reflects off the carotid space or sheath so that the mucosa of the nasopharynx and the ICA are separated only by a layer of connective tissue. Injury to or exposure of the ICA at the time of nasopharyngectomy may predispose to an ICA rupture. Safe lateral dissection of the nasopharynx is limited by the close proximity of the ICA.

There are few data in the literature regarding the significance of surgical margin status at nasopharyngectomy on the outcome of the procedure and on the survival of the patient. We performed this study to explore whether surgical margin status at salvage nasopharyngectomy for local nasopharyngeal carcinoma failure affects patient survival.
METHODS

A retrospective medical record review was performed for 80 patients who underwent nasopharyngectomy with curative intent as a salvage procedure for residual or recurrent nasopharyngeal carcinoma after receiving primary radiotherapy with or without chemotherapy. Surgery was performed at the Prince of Wales Hospital in Hong Kong, an academic tertiary referral center, between November 28, 1987, and November 17, 2003. The date of data analysis completion was March 20, 2007.

Residual disease was defined as the presence of disease within 24 weeks of completion of primary radiotherapy. Recurrent disease was defined as the presence of disease 24 weeks or more after completion of primary radiotherapy and where results of the first postradiotherapy biopsy, usually performed 8 to 12 weeks after radiotherapy to allow for a possible delay in histologic remission, were negative. The term recurrent is inclusive of residual tumors and recurrent tumors in this article unless defined separately.

After histologic confirmation of the local failure, patient selection for salvage and the method to be used was based on the extent of the disease. This was assessed clinically using nasopharyngoscopy and radiologically using computed tomography initially and then magnetic resonance imaging with gadolinium and fat suppression when it became available in 1995. For the purposes of the review, the primary tumor (T) and the residual or recurrent tumor (rT) were restaged for uniformity according to the American Joint Committee on Cancer criteria.18

Patients were offered surgical salvage of local disease if there was no intracranial extension of the tumor, there was no evidence of distant metastases, the ICA was not involved with the tumor, and it was considered possible to resect the tumor without injuring the ICA. At surgical resection of the nasopharynx, frozen section histologic analysis was performed to assess the surgical resection margins. Surgical resection continued until the frozen section margins were negative or until further resection of tissue was not possible or was deemed unsafe. Further resection of tissue was deemed unsafe if it put the ICA at significant risk of being injured. The aim of surgery was, therefore, to safely achieve clear surgical resection margins. Our policy is not to resect carcinoma at the expense of the ICA.

At the end of the surgical resection, the nasopharynx is lined by a variety of dressings and tissues, depending on the surgeon’s preference, that includes the mucosa of the inferior turbinate, a split-thickness skin graft, or a free flap. The cavity is then packed with antiseptic-impregnated gauze for 7 to 10 days. The status of the closest surgical margin was assessed on histologic examination as being either clear (≥3 mm), close (>1 and <3 mm), or positive (≤1 mm). All the patients received postoperative radiotherapy, either intracavity brachytherapy if technically possible or EBRT, except for those who refused. All the patients were followed up regularly according to the protocol for these patients, which included endoscopic examination of the nasopharynx and radiologic imaging.

Distributions of clinical characteristics, such as T category, N category, and postoperative radiotherapy, among the margin groups were tested using either χ² or Fisher exact tests. The end points of the study were OS, local progression-free survival (LPFS), and locoregional PFS (LRPFS). The OS was calculated from the date of surgery to the date of death from any cause or was censored at the date of the last follow-up. The LPFS was defined as patients surviving with no evidence of local recurrence on follow-up evaluations, and the LRPFS as patients surviving with no evidence of local or regional recurrence on follow-up evaluations. The Kaplan-Meier method was used to estimate the probability of survival at 5 years. Comparisons of the survival rates of clear, close, and positive margins were assessed using the log-rank (Cox-Mantel) test. The significance level was set at P < .05.

RESULTS

The surgical margin status of 1 patient was unknown, and so the patient was excluded from the analysis. The study patients consisted of 61 men and 18 women, with a median age of 46 years and a mean age of 48 years (age range, 26-70 years) at the time of surgery. Thirteen patients had a residual tumor and 66 a recurrent tumor. The median interval between the end of primary radiotherapy and the date of the recurrence was 29 months (mean, 42 months; range, 1-235 months). Patient characteristics of sex, age, initial T category, initial N category, recurrent T category, recurrent N category, and postoperative radiotherapy according to surgical margin status of clear, close, or positive are given in Table 1.

A variety of surgical approaches were used to access the nasopharynx depending on the tumor location. Twenty-five patients underwent a maxillary swing approach popularized by Wei et al,19 33 underwent a mid-
The main goal of surgery is complete but safe surgery with or without a mandibular split. Incidents involving the ICA occurred in 3 patients. In 1 patient, the artery was damaged and so was ligated to prevent a possible future blowout. The patient recovered uneventfully. In a second patient, the carotid was exposed at the time of surgery and, despite dressing the nasopharynx in the usual way, ruptured 2 days later and was then ligated. The patient experienced a stroke but died 4 months later free of disease. A third patient developed a leaking ICA in the postoperative period that was repaired as the nasopharynx had been approached via a transmandibular-transpalatal route.

The nodal status of patients at their initial and recurrence presentations are given in Table 1. There was no significant difference between patients with clear or close margins vs positive margins presenting with a negative or positive neck at either the initial presentation (P = .83) or the recurrence presentation (P = .86) (Table 2). Patients were followed up for a median of 47 months (mean, 55 months; range, 3-163 months) or until death.

The main goal of surgery is complete but safe surgical resection of the tumor with clear surgical margins. However, close surgical margins still remain preferable to positive margins. Because there was no significant difference in the survival rates between clear and close surgical margins, we grouped them together for the analysis against the positive margin group to facilitate the requirement of the Fisher exact test in exploring the differences in clinical factors. Results showed that the initial T category (P = .51), initial N category (P = .83), recurrent N category (P = .86), and postoperative radiotherapy (P = .23) were comparable between the margin groups (Table 2). However, there were significantly fewer patients with recurrent advanced tumors (rT3-rT4) in the clear or close margin group (3 patients; 6%) than in the positive margin group (9 patients; 30%) (P = .008). Initially in the series, imaging was less sophisticated and developed than it is now, and we operated on 10 rT3 patients and 2 rT4 patients in whom the imaging understaged the tumors, especially relating to bone invasion, which we are now better able to differentiate from radiotherapy changes. It is not surprising that 8 of the 10 rT3 patients (80%) that we operated on had positive margins, as did 1 of the 2 rT4 patients (50%).

We further compared survival rates between margin groups by stratifying the recurrent tumor into early (rT1-rT2) or advanced (rT3-rT4) (Table 3). In the analysis of early recurrences, rT1 or rT2 (n = 67), the OS, LPFS, and LRPFS rates of patients with clear or close surgical margins were significantly better than those of patients with positive margins (P ≤ .001 for all). In the analysis of advanced recurrences, rT3 or rT4 (n = 12), there were no significant differences in the OS, LPFS, and LRPFS rates between the clear or close margin group and the positive margin group (P > .05 for all). We are now circumspect about offering surgery to rT3 patients who have bone invasion.

When we analyzed only patients with clear and positive margins (n = 66), we found that there was a marginally significant association between surgical margins and postoperative radiotherapy (P = .047). However, the adjuvant radiotherapy did not seem to give an additional benefit because the clear margin group, of whom only 61% received postoperative radiotherapy, showed a better survival rate than the positive margin group, of whom 83% received postoperative radiotherapy. When we analyzed only close and positive margins (n = 43), we found that there was no significant association with postoperative radiotherapy (P = .30). In analyzing the whole study group, there were no significant differences in the OS (P > .99), LPFS (P = .28), and LRPFS (P = .47) rates between patients who received postoperative radiotherapy and those who did not.
Five-year OS was 51%, LPFS was 62%, and LRPFS was 57%. The OS rates for patients with clear, close, and positive surgical margins were 77%, 46%, and 23%, respectively (clear vs close margins, \( P = .05 \); clear vs positive margins, \( P < .001 \); and close vs positive margins, \( P = .16 \)). (Figure 1). Five-year LPFS rates for patients with clear, close, and positive surgical margins were 85%, 72%, and 31%, respectively (clear vs close margins, \( P = .42 \); clear vs positive margins, \( P < .001 \); and close vs positive margins, \( P = .01 \)) (Figure 2). The LRPFS rates for patients with clear, close, and positive surgical margins were 82%, 50%, and 31%, respectively (clear vs close margins, \( P < .11 \); clear vs positive margins, \( P < .001 \); and close vs positive margins, \( P = .06 \)).

**COMMENT**

Achieving clear surgical margins is a function of anatomy. The surgical margin status at surgery depends on the relationship between the tumor and the tissues of the nasopharynx. The limits of surgical resectability depend on the ability to remove the tumor posteriorly, superiorly, laterally, and inferiorly. The prevertebral muscles, clivus, and vertebral bodies limit posterior excision of the tumor; the sphenoid and basisphenoid limit superior excision of the tumor; and the ICA limits lateral excision of the tumor. Determining the involvement of these structures preoperatively using magnetic resonance imaging determines which patients are more likely to have clear, close, or positive margins when surgery is possible. We offer salvage surgery to patients whom we assess as having a surgically resectable tumor based on imaging. The other provisos for surgery are that the tumor must not abut the ICA, there must be a plane for surgical excision between the ICA and the tumor, and there must not be overt bone involvement.

Primary nasopharyngeal carcinoma is currently treated in Hong Kong with external radiotherapy using 2-dimensional or 3-dimensional conformal radiotherapy or intensity-modulated radiotherapy, with or without chemotherapy. Intracavity brachytherapy or stereotactic radiotherapy is used for adjuvant dose escalation. Local failures occur in 9% to 40% of patients after primary treatment. In Hong Kong, local failure occurs in 12% of patients, as reported in a study of 2687 consecutive patients treated in all public oncology centers in Hong Kong between 1996 and 2000.

Although treatment of a local failure with EBRT will lead to further 5-year survival of 7% to 36%, severe late radiotherapy complications occur in 20% to 57% of these patients. To minimize treatment complications and improve tumor control, alternative radiotherapy techniques have been used, such as EBRT with brachytherapy, brachytherapy alone, stereotactic radiosurgery, and intensity-modulated radiotherapy. Alternatively, surgical nasopharyngectomy has been used to salvage a local failure.

Yu et al studied 2915 consecutive patients treated in all public oncology centers in Hong Kong between 1996 and 2000 to determine whether salvage treatment of local nasopharyngeal carcinoma failures prolongs survival in view of the complications associated with salvage treatment. They showed on univariate and multivariate analyses that patients with an isolated early-stage local failure who received salvage treatment had a significantly better OS rate than those who did not. They also showed that there was no significant difference in OS rates between patients treated with radical radiotherapy or nasopharyngectomy. Because patients who undergo salvage surgery for a local failure avoid the potential complications of a second course of EBRT, and because previously published data from this institution showed...
that for rT1 and rT2 patients nasopharyngectomy resulted in better survival and local control than reirradiation using EBRT, we offer patients with local recurrences nasopharyngectomy as salvage. For local recurrent disease, nasopharyngectomy with or without postoperative radiotherapy results in further 5-year OS rates of 40% to 60%.\(^9\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\)\(^6\) In the present series, 5-year OS rates were 51%, LPFS rates were 62%, and LRPFS rates were 57%.

**SURGICAL MARGINS**

Hsu et al\(^1\)\(^2\) performed salvage nasopharyngectomy on 24 patients in a series reported in 1997. Of 8 patients with positive margins (33%), 4 died of local disease, 2 had a local recurrence, and 2 remained disease free. In a follow-up study\(^3\) of 60 patients by the same group, 28 (47%) had clear margins and 32 had either close or positive margins. Twenty-nine patients in their series died of uncontrolled local disease.

Shu et al\(^1\)\(^2\) reported a series of 28 patients in 2000. Seven patients (29%) had positive margins, of whom 1 patient survived disease free, 4 developed local recurrences, and 2 died. Wei\(^1\)\(^3\) reported in 2001 that clear tumor margins were achieved in 60 of 78 patients (77%) who underwent nasopharyngectomy in that series. In the series of 37 patients with nasopharyngeal carcinoma reported by Fee et al\(^1\)\(^4\) in 2002, 78% had clear margins; 5 of 8 patients with positive margins developed a local recurrence.

Hao et al\(^1\)\(^5\) described 18 patients who underwent nasopharyngectomy for nasopharyngeal carcinoma in 2002. All 3 patients who had positive margins died: 1 of local disease, 1 of regional disease, and 1 of a carotid rupture. The outcome of 4 patients with close margins in their series was not specifically discussed further.\(^1\)\(^6\) Chang et al\(^1\)\(^7\)\(^8\)\(^9\) reported on a series of 38 patients who underwent salvage nasopharyngectomy in 2004. Twenty-five of the 30 patients (83%) with clear margins were alive and disease free, whereas only 3 of the 8 patients with close or positive margins were alive and disease free.

In the series of 11 patients undergoing nasopharyngectomy reported by Bridger et al\(^1\)\(^8\) in 2005, all 4 patients who died had positive surgical margins, whereas of the 7 survivors, 6 remained disease free. Three of the 6 disease-free survivors had clear margins, 2 had positive margins on frozen section and subsequent negative margins, and 1 had the bony margin drilled away. The 1 patient who was alive with local disease also had positive margins. Of the 8 patients described by Choi and Lee\(^1\)\(^9\) in 2005, all 6 patients with clear margins (75%) were alive and disease free, whereas both patients with positive surgical margins developed local recurrences.

In the present series, the final surgical margin status was clear in 45% of patients (36), close in 16% (13), and positive in 38% (30). These final surgical margin status values may reflect a bias toward operating on patients with more advanced disease, as occurred earlier in the series, but this needs to undergo further study to be objective. These data suggest that clear surgical margins positively affect patient survival. Since November 2003, we have continued to accumulate cases because further studies are needed with a bigger cohort and multivariate analysis to confirm these preliminary findings.

**INTERNAL CAROTID ARTERY**

Two of 16 patients described by Wei et al\(^1\)\(^9\) in 1995 developed subsequent bleeding from the ICA. One patient died and 1 survived after the ICA was ligated. Both patients had received nylon tubes for postoperative brachytherapy for close surgical margins at the time of resection.

In the series by Shu et al,\(^1\)\(^2\)\(^2\) of 28 patients died of ICA rupture. One patient has been mentioned previously herein, dying 2 months after the ICA was exposed and covered with temporalis muscle. A second patient, in whom the tip of the petrous bone was drilled out and the pulsation of the ICA visualized during surgery, died of ICA rupture 4 days later. Two additional patients died of ICA rupture 5 months after surgery. Fee et al\(^1\)\(^5\) reported in 2002 that 1 of their 37 surgical patients died of an intraoperative carotid injury. Two of 38 patients reported by Chang et al\(^1\)\(^7\)\(^8\)\(^9\) in 2004 died of a carotid rupture, 1 at 7 months and 1 at 15 months.

In the present series, the ICA was exposed or injured in 3 patients. In 2 patients the artery was ligated; 1 patient recovered uneventfully and the other, who developed a stroke, died 4 months later, free of disease. A leaking ICA in a third patient was repaired uneventfully.

In conclusion, these data suggest that the surgical margin status at the time of surgical salvage nasopharyngectomy for residual or recurrent nasopharyngeal carcinoma seems to affect the OS, LPFS, and LRPFS rates of patients. Patients with clear or close margins seem to have better survival rates than patients with positive surgical margins.

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Correspondence: Alexander C. Vlantis, FCS(SA)ORL, Department of Otorhinolaryngology, Head and Neck Surgery, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin NT, Hong Kong (lexvlantis@cuhk.edu.hk).

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