EFFICACY OF NECK DISSECTION FOR LOCOREGIONAL FAILURES VERSUS ISOLATED NODAL FAILURES IN NASOPHARYNGEAL CARCINOMA

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Abstract: Background. Neck dissection has been shown to be effective in controlling nodal failures in nasopharyngeal carcinoma. Its efficacy in controlling the disease in patients with synchronous locoregional failure is, however, not documented.

Method. A retrospective review of all patients who underwent neck dissection for nodal failures with or without treated local failure within 6 months was conducted for this study. The survivals of these 2 groups of patients were analyzed.

Results. The 5-year overall survival of the whole cohort was 58%. There was no difference in 5-year disease specific survival (68% vs 40%; \( p = .121 \)) and 5-year progression free survival (44% vs 36%; \( p = .334 \)) when comparing patients with isolated nodal failures and synchronous locoregional failures. Multivariate analysis showed that only the initial N classification affects survival.


Keywords: nasopharyngeal carcinoma; locoregional recurrence; nodal recurrence; neck dissection; salvage surgery

The management of nasopharyngeal carcinoma (NPC) has markedly improved after the introduction of concurrent chemoradiation.1 Isolated nodal failures after chemoradiation are now uncommon, ranging from 3.5% to 6.9%.2,3 Surgical salvage, in the form of radical neck dissection, has been shown to be more effective than reirradiation in controlling the nodal disease. Sham and Choy4 reported that the overall 5-year survival of only 19.7% of patients with nodal recurrence were treated by a second course of external radiotherapy. Our center has reported a 5-year actuarial survival of 38% after radical neck dissection for control of nodal disease after radiotherapy 20 years ago.5 In our center, radical neck dissection has been the standard treatment for regional failure for patients with NPC. Occasionally, a patient who presented with nodal recurrence also had local recurrence. Chua et al6 reported that 12% of patients with local recurrence of NPC also had synchronous nodal recurrence. In patients with synchronous locoregional failures, the treatment decision can be difficult. Although both the local and regional disease itself is amenable to salvage treatment, the combined morbidity of managing both local and regional disease might be significant. The treatment approach to one site may be affected by the choice of treatment to the other site. Finally, synchronous locoregional disease may carry a significantly worse prognosis even after successful salvage, thus less radical treatments were usually used in this group of patients.

We reviewed the outcome of patients undergoing neck dissection for nodal failures after NPC treatment and reviewed if patients with locoregional recurrence have significantly worse prognosis after neck dissection than patients with isolated nodal failure. The primary objective is to determine whether there is any difference in survival in patients with NPC who had concurrent locoregional failures compared with patients with isolated nodal failure after treatment with salvage neck dissection. The second objective was to analyze any factors that would influence survival, including initial stage of disease, recurrent stage of disease, age, sex, recurrent or persistent disease, the presence of extracapsular spread, and the use of brachytherapy after neck dissection.

PATIENTS AND METHODS

From January 1999 to December 2008, 64 consecutive patients had neck dissection with a curative intent for salvage of nodal failures after radiotherapy for nasopharyngeal carcinoma in the Department of Surgery, University of Hong Kong Medical Centre. Among the 64 patients, there were 42 men and 22
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women. Median age was 46.5 and ranged from 26 to 71 years old. Follow-up of patients who survived ranged from 8 to 129 months with median follow-up of 6 years. Patients who had neck dissection and treatment of local recurrence within 6 months were considered as synchronous locoregional recurrence. Thirty-four patients had isolated nodal recurrence. Eighteen patients had synchronous locoregional recurrence. Seven patients had local recurrence more than 6 months before the nodal recurrence and all were local disease-free when they received the neck dissection. Five patients developed isolated recurrence at the nasopharynx more than 6 months after neck dissection for nodal recurrence and are considered as disease progression. The 12 patients from the last 2 groups were grouped together in the group of isolated nodal recurrence during analysis.

All patients have undergone evaluation for their locoregional failures, which included clinical examination, nasopharyngoscopy and biopsy of the nasopharynx, ultrasonography of the neck, and fine-needle aspiration of the suspicious lymph nodes. Blood was taken for complete blood count, renal and liver biochemistry, and creatinine clearance. Chest x-rays were also performed. All patients with suspected local recurrence would have cross-sectional imaging performed in addition, either a CT scan or MRI of the nasopharynx. The 18-fluorodeoxyglucose (FDG) positron emission tomography scans were frequently used in recent years.

All patients had their initial disease and recurrent disease restaged with the 2002 Union Internationale Contre le Cancer (UICC) staging system. For the initial staging of the nasopharyngeal carcinoma, 1 patient (1.6%) had stage I disease, 20 patients (31.3%) had stage II disease, 18 patients (28.1%) had stage III disease, and 9 (14.1%) patients had stage IV disease. Staging information was missing in 16 patients (25%) as they were referred for salvage treatment from other institutions. We arbitrarily define persistent nodal disease as failure diagnosed within 6 month after primary radiotherapy. Using this definition, there were 6 patients with persistent disease, with 1 patient having concurrent local and regional persistent disease. For the staging of the nodal failures, 5 patients (7.8%) had no tumor in the neck dissection specimen. The decision to proceed to neck dissection in this group of patients was based on clinical and radiological suspicion and findings of atypical cells on fine-needle aspiration. Forty-six patients (71.9%) had rN1 disease, 10 patients (15.6%) had rN2 disease, and 3 patients (4.7%) had rN3 disease. Seven patients had extensive nodal disease with close or positive resection margin and received brachytherapy in the form of iridium-192 wire after-loading at the time of radical neck dissection. Four patients had bilateral nodal failures and received bilateral modified radical neck dissections. Pathological examination of the neck dissection specimens showed that 5 patients had positive resection margin and 16 specimens showed 1 or more lymph nodes having extracapsular spread.

For recurrent or residual disease at the primary site, aggressive salvage procedures were carried out for these patients whenever applicable. Salvage treatment was either in the form of gold grain implant or nasopharyngectomy via a maxillary swing approach. Five patients received gold grain implants and 12 patients received nasopharyngectomy. One patient developed local recurrence 3 months after neck dissection and refused treatment to the local recurrent disease. The clinical oncologist and head and neck surgeon jointly decided on the choice of treatment for local failure. Later in the series, the radioactive gold grain was not done and all local recurrences were salvaged with nasopharyngectomy via a maxillary swing approach.

All patients were followed up monthly in the first year after treatment, every 2 months in the second year, and every 3 months from the third year onward. For the calculation of disease-specific survival (DSS), patients that died not due to the recurrent cancer would be considered as censored at the date of death and not counted as died of disease. For the calculation of progression-free survival (PFS), the date of detection of any recurrent local or nodal disease or distant metastasis would be counted as disease progression.

The overall survival (OS), DSS, and PFS rates were calculated using the Kaplan–Meier method. Univariate analysis of survival between groups was calculated with the Kaplan–Meier method and log-rank test. The Cox proportional hazard regression model was used for multivariate analysis of survival. The chi-square and Fisher exact test were used in calculation of significance in cross-tabulations. Statistical significance is defined as \( p < .05 \). All statistics are calculated with SPSS 18.0 (Chicago, IL).

RESULTS

Disease-specific Survival and Progression Free Survival. There was no 30-day postoperative mortality. One patient, who underwent a nasopharyngectomy together with a neck dissection, died of carotid blow out in the nasopharynx 2 months after treatment. Three patients died of other causes, 43, 89, and 96 months after the neck dissection. The mean interval and median interval between the completion of radiotherapy to regional failure in recurrent disease were 48.9 months and 34 months (range, 7–240 months).

For the whole cohort of 64 patients, the overall 5-year survival was 58%. The 5-year DSS rate was 60%; the 5-year PFS rate was 42%. Figure 1 and Figure 2 showed the DSS and PFS plots of the whole cohort. Analyzing the subgroup with isolated nodal failures, the 5-year DSS was 68%; the 5-year PFS was 44%. For the group of patients with synchronous locoregional disease, the 5-year DSS was 40%; the
5-year PFS rate was 36%. Table 1 summarizes the results of the survival analysis. Using the Kaplan–Meier model for analysis of difference in survival, the survival rates of the 2 groups were not statistically significant ($p = .121$ for DSS and $p = .334$ for PFS, log-rank tests). Figure 3 and Figure 4 showed the Kaplan–Meier plot of DSS and PFS of the 2 groups.

**Multivariate Analysis.** Multivariate analysis using the Cox regression model showed that only the initial N classification affects the DSS, (relative risk, 2.04; 95% confidence interval [CI], 1.15–3.61; $p = .011$). Both the age and the recurrent N classification affect the PFS. The relative risk of age on the PFS was 1.07 (95% CI, 1.02–1.14; $p = .026$) and relative risk of recurrent N classification was 2.23 (95% CI, 1.12–4.44; $p = .046$). Table 2 and Table 3 summarized the statistics of the Cox regression analysis of the prognostic factors.

**Relapse and Disease Progression.** Of the whole cohort, 29 of the patients (45.3%) were disease free at the time of the study. The mean and median survival after relapse was 19.5 and 11.5 months, but ranged from 1 month to a maximum of 96 months. Eight patients (12.5%) presented with local recurrence, whereas 9 patients (14%) had their relapse presented as distant metastasis. Nodal recurrence was the commonest form of failure with 18 patients (28.1%) suffering from nodal relapse.

**DISCUSSION**

Neck dissection has been shown to be superior to reirradiation in controlling nodal failures in NPC.\(^4\,\,12\) Previous irradiation limits the amount of radiation that can be given in re-treatment without significant toxicities to vital structures like the spinal cord. Moreover, the tumor cells had survived previous radiotherapy to present as relapse; this clone of tumor cells might be radioresistant. Reirradiation is also associated with significant early and late morbidities. Surgery, in the form of radical neck dissection, is still the treatment of choice for nodal failures in NPC. A report from our institution 20 years ago showed a 5-year nodal control rate of 66% and a 5-year OS rate of 38%.\(^5\) In our current series, the 5-year OS had increased to 58%. This improvement in survival may be due to improved imaging techniques.
and early detection of nodal failures, leading to more successful salvage. Alternatively, newer palliative treatment may slow down the disease progression and prolong the OS of patients with recurrent disease, but we have no data to prove this assumption.

Our institution has previously reported on a series of 13 patients treated with interstitial brachytherapy in addition to radical neck dissection for salvage of nodal failures in NPC in a 7-year period from the year 1990 to 1996. There have only been 7 cases of interstitial brachytherapy in addition to radical neck dissection for salvage of nodal failures in the current 10-year cohort. The drop in usage of interstitial brachytherapy in conjunction with neck dissection is likely due to the efficacy of concurrent chemoradiation in controlling bulky nodal disease and the improvement in diagnostic imaging allowing nodal diseases to be detected before the disease becomes fixed to skin or neck structures.

It was reported in the literature that 8% to 28% of patients with local failures also have regional nodal failures, leading to more successful salvage. Alternatively, newer palliative treatment may slow down the disease progression and prolong the OS of patients with recurrent disease, but we have no data to prove this assumption.

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failures.\textsuperscript{6,14–16} Although aggressive treatment is usually offered to patients with either local or regional failures, efficacy of similar aggressive treatments to both local and regional disease in patients with synchronous locoregional failures was not defined. This is because we are uncertain about the prognosis of patients with concurrent locoregional failure and the fear of excessive treatment-related morbidities. In this cohort, we are unable to show any statistical difference in survival of patients with isolated nodal failures who have received neck dissection and patients with synchronous locoregional failures who have received neck dissection and treatment to the local disease. From the multivariate analysis, the only significant predictor of DSS is the initial N classification. On the other hand, the recurrent N classification predicts PFS. From the data, we are not able to provide a satisfactory explanation of the findings in the multivariate analysis. Although age has been shown to be a statistically significant predictor in PFS, the relative risk is very low (1.07, 95% CI, 1.02–1.14) and is clinically not significant.

There has been 1 report in the literature on the use of concurrent chemoradiation to treat locoregionally recurrent NPC.\textsuperscript{17} The response rate was 58% and the reported 5-year OS and PFS was 26% and 15% only. Grade 3 to 4 late toxicities were significant, up to 23%. In that series of 35 patients, there were 23 patients with advanced (rT3–rT4) local disease. The advanced local disease may explain the worse survival when compared with the current cohort. Further studies are required to compare the efficacy and toxicities of surgery versus reirradiation with concurrent chemotheraphy in patients with NPC with small locoregional failures.

In our unit, the treatment of choice for small local recurrence of NPC was nasopharyngectomy. The operative risk is small and long-term morbidity of patients who have received this operation is acceptable.\textsuperscript{18} With suitable precaution and meticulous surgery, the morbidity of radical neck dissection is low and is more effective than radiotherapy in controlling nodal failures in patients with NPC. Our current cohort demonstrated that 1 in 3 patients with synchronous locoregional failure survived for 5 years after radical treatment. We would advocate an aggressive approach in managing synchronous locoregional failures in NPC. For patients with small local disease and resectable nodal disease, we advocate a combined nasopharyngectomy and radical neck dissection aiming for a cure. For patients with unresectable recurrent disease in the nasopharynx, it is uncertain that radical neck dissection together with external beam reirradiation to the nasopharynx would offer survival benefits. Further studies in this subgroup of patients would be required before we can advocate an aggressive surgical approach.

In summary, there is no statistical difference in the survival of patients with NPC with synchronous locoregional failure who have received a radical neck dissection and curative treatment to the local disease when compared to patients with NPC with isolated nodal failures who have received radical neck dissection. The 5-year OS of patients with NPC who have received radical neck dissection for salvage of nodal failure is 58%. Radical neck dissection is effective in controlling nodal failures in patients with NPC.

\textbf{REFERENCES}


