Management of Extensive Cervical Nodal Metastasis in Nasopharyngeal Carcinoma After Radiotherapy

A Clinicopathological Study

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Objectives: To evaluate the efficacy of afterloading brachytherapy following radical neck dissection (RND) in the management of extensive cervical lymph node disease in nasopharyngeal carcinoma after radiotherapy; and to examine prospectively prognostic factors and the pathologic behavior of neck disease.

Patients: Twenty-seven patients with nasopharyngeal carcinoma who had extensive cervical lymph node metastasis following external radiotherapy were treated with RND. Thirteen of them also underwent afterloading brachytherapy with iridium wire (Ir 192). The RND specimens of the 27 patients were also examined with step serial whole-specimen sectioning.

Results: All patients survived and their wounds healed primarily. Pathologic examination revealed 183 tumor-bearing lymph nodes that contained tumors in the neck: level I, 4% (8/183); level II, 53% (96/183); level III, 34% (62/183); level IV, 5% (9/183); and level V, 4% (8/183). Extracapsular tumor extension was seen in 84% of patients. Multivariate analysis identified the number of tumor-bearing lymph nodes detected in the specimens to be the only significant factor that affected control of disease. Although the neck disease in the group of patients who had afterloading brachytherapy was more extensive, the 3-year actuarial tumor control for the groups with and without brachytherapy were 60% and 61%, respectively.

Conclusions: Recurrent cervical lymph nodes after radiotherapy in nasopharyngeal carcinoma are extensive and RND is mandatory for a successful salvage. When the nodal metastasis infiltrate or adhere to surrounding tissue, afterloading brachytherapy with iridium wire can provide satisfactory local tumor control.


THE INCIDENCE of nasopharyngeal carcinoma is high in the southern Chinese population and descendants who immigrate to Southeast Asia or other parts of the world. The primary treatment modality of the tumor is radiotherapy because most tumors are undifferentiated carcinoma, which is radiosensitive. The surface epithelium of the nasopharynx is richly endowed with lymphatics that freely cross the midline, so bilateral metastasis to the cervical lymph nodes is common on presentation. The neck is thus always included in the primary radiation field.

Despite good response to radiotherapy, the incidence of isolated recurrence or persistent disease in the neck ranges from 6% to 12% or even 16%. Management of these lymph nodes with additional radiotherapy has a low incidence of eradicating the disease and is associated with increased risk of accumulated irradiation injury. Surgical salvage for resectable disease in these patients, in the form of radical neck dissection (RND), has been shown to control disease in the neck in 66% of patients.

When recurrent or persistent disease in the cervical lymph nodes is large, extends to overlying skin, or infiltrates surrounding tissue, then RND alone may not be able to control the disease. For patients with extensive neck disease, afterloading brachytherapy after RND may be helpful. The present study prospectively examines the efficacy of this salvage modality, the prognostic factors, and the pathological nature of extensive neck nodal disease in patients with nasopharyngeal carcinoma after radical radiotherapy.

RESULTS

Of 27 patients, 18 were men and 9 were women. Their ages ranged from 33 to 68 years (median, 49 years). The lymph nodes in 5 necks were persistent disease and those in the remaining 22 necks were re-
PATIENTS AND METHODS

In the Head and Neck Division of the Department of Surgery, University of Hong Kong Medical Centre at Queen Mary Hospital, 27 patients (treated between 1990 and 1996) with nasopharyngeal carcinoma and large cervical lymph node metastasis after radical external radiotherapy were included in the study. The primary tumor in the nasopharynx was controlled in all patients, as verified by endoscopic examination and computed tomography. No distant metastasis was evident in all patients on routine metastatic screening.

Clinical examination of the neck was performed, and the number, size, mobility, and location of the cervical lymph nodes were recorded. Salvage surgery was only performed 3 months after completion of radiotherapy when the lymph nodes showed no further reduction in size (persistent lymph node disease). Recurrent lymph node disease was diagnosed if the nodes resolved after radiotherapy and reappeared later. All 27 patients underwent RND, removing the sternomastoid muscle, internal jugular vein, spinal accessory nerve, and soft tissue in the neck en bloc. For 13 patients, postoperative afterloading brachytherapy was planned before RND. They were selected prospectively, when on clinical examination either the skin over the neck nodes was affected or one of the nodes was fixed to the underlying tissue.

During surgery, the skin overlying the node was removed together with the neck dissection specimen. Hollow nylon tubes were positioned precisely over the tumor bed 1.0 cm from each other for high-dose rate remote control afterloading brachytherapy (Figure 1). A deltopectoral flap or a pectoralis major myocutaneous flap was used to resurface the skin defect (Figure 2). By postoperative day 7, when the neck wound would have healed, iridium wires (Ir 192) cut to the appropriate length were inserted into the nylon tubes to deliver an additional 5400 rad (54 Gy) of radiation to the tumor bed. At completion of brachytherapy, all the iridium wires and nylon tubes were removed under local anesthesia.

For the remaining 14 patients, RND alone was performed, and it was considered to be adequate for salvage. After removal, the RND specimen was spread out and stretched and pinned onto a foam board. The whole specimen was then immersed in 10% buffered formalin for fixation. The entire neck dissection specimen was then cut into multiple blocks with a sharp knife at 3-mm intervals. The blocks were then processed and embedded in paraffin. From each paraffin block a histologic section was cut with a microtome and stained with hematoxylin-eosin for examination.

All patients were followed up monthly for the first 3 months and then every 2 months until the end of the second year. They were then followed up every 3 months until the end of the fifth year, and then every 6 months. Follow-up ranged from 8 months to 6 years (median, 29 months).

Survival was analyzed using the preoperative factors, operative findings, and pathological features. Sex, age, recurrent or persistent nodal disease, and number, size, and mobility of the lymph nodes were determined before and during surgery. Pathological features included the status of the resection margin, tumor infiltration of skin, number and size of lymph nodes identified histologically, extracapsular extension of tumor, and proximity to the spinal accessory nerve. Five-year actuarial local tumor control and survival rates were used for the whole group and for comparison of results between the 2 groups of patients (ie, those with and those without brachytherapy). Statistical Product and Service Solutions software (version 6.0; SPSS Inc, Chicago, Ill) was used for analysis of results.

current disease. All patients survived RND and were discharged from the hospital. For 13 patients who were given postoperative afterloading brachytherapy, their wounds also healed primarily, and the brachytherapy caused no additional morbidity.

Clinical examination before surgery showed that 25 patients had a solitary cervical lymph node, 1 had 3 nodes, and 1 had 7 nodes. Nodes ranged from 0.5 to 10.0 cm in diameter (median, 2.5 cm). In 22 (82%) of 27 necks, 1 or more of the lymph nodes were located in the upper part of the neck, level I, level II, and the upper part of level V. In 20 patients, at least 1 lymph node was regarded to have some adhesion fixation to the underlying tissue, and in 13 of these 20 patients the neck skin overlying the node was clinically infiltrated by tumor. In the remaining 7 patients the lymph nodes were mobile. All of the lymph nodes were on one side of the neck. Eleven patients underwent right and 16 underwent left RND. A MacFee incision was used for all RNDs, and when part of the neck skin was removed, an additional incision was used appropriately.

During surgery, the total number of positive lymph nodes detected in the 27 patients was 60 (range, 1-8; median, 1 node per patient). Forty-four nodes (73%) were located in the upper cervical level, 8 (13%) were in the middle neck, and the remaining 8 (13%) were in the lower cervical region. At the time of surgery, 1 or more lymph node in 19 necks were adherent to one of the surrounding structures, including the carotid sheath, internal jugular vein, spinal accessory nerve, sternomastoid muscle, and floor of the posterior triangle. The lymph nodes in the remaining 8 necks were mobile and not adherent to any of these important structures in the neck.

In 13 patients, microscopic residual tumor was present at the end of surgery, and hollow nylon tubes were placed over the tumor bed for afterloading brachytherapy with iridium Ir 192. For these 13 patients, the skin overlying the neck node was excised for tumor clearance or in preparation for brachytherapy. For resurfacing this cutaneous defect, a deltopectoral flap was used for 11 patients, and a pectoralis major myocutaneous flap was used for the remaining 2.

All patients survived surgery, and the associated morbidity was minimal. There was no hematoma or prolonged leakage of chyle. The skin flap remained intact with no wound infection or necrosis. For 13 patients with brachytherapy and replacement of the neck skin, all the
deltopectoral and pectoralis major myocutaneous flaps remained intact. All of these patients completed the course of brachytherapy with no complications.

The neck dissection specimens were examined using the step serial sectioning method; for each specimen, the number of histologic sections obtained ranged from 24 to 38 (median, 29 sections). The total number of sections for the 27 specimens was 783, and from these the total number of lymph nodes examined was 2016. The number of lymph nodes studied in each patient ranged from 31 to 109 (median, 52).

Metastatic tumor cells were identified in 183 nodes; for each specimen, the number of tumor-bearing lymph nodes ranged from 1 to 34 (median, 6). Of the 27 specimens, 22 had more than 1 tumor-bearing lymph node. This was significantly more than the preoperative finding, which showed that only 2 of 27 specimens had more than one lymph node \( P < .001 \).

Pathologic examination revealed moderately differentiated carcinoma in the nodes of 25 necks and well-differentiated nodes in 1 patient. The remaining patient presented with a persistent upper cervical lymph node 2 cm in diameter; pathologic examination of the whole specimen revealed 109 lymph nodes. Examination of the lymph nodes showed no malignant cells in any of the nodes, and the large persistent lymph node only exhibited reactive hyaline fibrosis.

Lymph nodes that contained tumor cells were distributed in the neck in the following pattern: level I, 4% (8/183); level II, 53% (96/183); level III, 34% (62/183); level IV, 5% (9/183); and level V, 4% (8/183).

Extracapsular tumor spread was seen in 133 (73%) of 183 lymph nodes. The capsule sometimes disappeared, and tumor cells were among the soft tissue (Figure 3). In 19 patients, at least 1 lymph node exhibited this pathological feature. In the other 7 patients, the capsule of all the tumor-bearing lymph nodes was intact. Histologic examination also showed that in 13 (50%) of the 26 specimens with malignant lymph nodes, 1 or more of the tumor-bearing lymph nodes were infiltrating or lying within 1 mm of the spinal accessory nerve (Figure 4).

The 3-dimensional resection margin was also determined using step serial whole-specimen sectioning. Positive resection margins were identified in 13 (50%) of the 26 specimens that contained malignant lymph nodes (Figure 5). This factor correlated with infiltration of neck skin by the node \( P = .02 \), extracapsular spread of tumor \( P < .02 \), and the size of the largest lymph node \( P < .001 \). Postoperative afterloading brachytherapy was given to these patients.

Univariate analyses were performed for all the clinical and pathological factors in relation to the probability of tumor control in the neck. The results showed that the number of lymph nodes identified before sur-

Figure 1. A, After radical neck dissection and removal of the overlying skin, the tumor bed was marked (arrow). B, Hollow nylon tubes were placed accurately over the tumor bed.

Figure 2. A deltopectoral flap was used to cover the skin defect, and afterloading brachytherapy was administered.
gery, the number of malignant lymph nodes detected histologically in the specimens, and the location of the nodes to within 1 mm of the spinal accessory nerve were significant factors. Multivariate analysis, however, identified the number of tumor-bearing lymph nodes in the specimen to be the only significant factor that affected the control of disease in the neck. A positive margin was not a significant factor; as for these 13 patients, additional afterloading brachytherapy was given.

Five-year actuarial control of disease in the neck, disease-free survival, and overall survival were 72%, 64%, and 48%, respectively. Seven patients died of local recurrence in the neck alone, 4 died of subsequent distant metastasis, and 2 died of other medical diseases. The clinical and pathological factors in the 2 groups were analyzed using the χ² test (Table 1).

Survival rates were also determined for patients with and without postoperative brachytherapy. Five-year actuarial tumor control rate in the neck for the groups with and without brachytherapy were 60% and 61%, respectively (P = .29). Five-year disease-free survival was 41% for the group with brachytherapy and 61% for the group with RND alone (P = .06). Statistically, there was no difference between the 2 groups in local tumor control rate and disease-free survival.

In the present study, recurrent or persistent status of the lymph nodes does not have any bearing on the outcome. This may be related to the fact that all these patients exhibited extensive lymphadenopathy and the outcome was more related to other features of these lymph nodes. The small number of patients in the persistent lymph node group also contributed to the findings of the analysis.

Preoperative examination showed that 82% of the lymph nodes were located in the upper neck, and this was also confirmed at surgery. This is in accordance with the pattern or spread of lymph nodes.8 The extensive local infiltrating nodes in nasopharyngeal carcinoma after

<table>
<thead>
<tr>
<th>Factors</th>
<th>Radical Neck Dissection Alone (n = 14)</th>
<th>Radical Neck Dissection and Brachytherapy (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, y</td>
<td>47</td>
<td>51</td>
<td>.49</td>
</tr>
<tr>
<td>Sex, M/F</td>
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<td>9/4</td>
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<tr>
<td>Before surgery</td>
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<td>13</td>
<td>.06</td>
</tr>
<tr>
<td>At surgery</td>
<td>36</td>
<td>24</td>
<td>.08</td>
</tr>
<tr>
<td>In specimen</td>
<td>89</td>
<td>94</td>
<td>.25</td>
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<td>Positive margin, No.</td>
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<td>.007</td>
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<tr>
<td>Extracapsular spread, No.</td>
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<td>12</td>
<td>.04</td>
</tr>
<tr>
<td>Close to accessory nerve, No.</td>
<td>6</td>
<td>8</td>
<td>.08</td>
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</tbody>
</table>

COMMENT

In the present study, recurrent or persistent status of the lymph nodes does not have any bearing on the outcome. This may be related to the fact that all these patients exhibited extensive lymphadenopathy and the outcome was more related to other features of these lymph nodes. The small number of patients in the persistent lymph node group also contributed to the findings of the analysis.

Preoperative examination showed that 82% of the lymph nodes were located in the upper neck, and this was also confirmed at surgery. This is in accordance with the pattern or spread of lymph nodes.8 The extensive local infiltrating nodes in nasopharyngeal carcinoma after
radiotherapy were located mainly in the upper part of the neck, close to the accessory nerve, internal jugular vein, and sternomastoid muscle. The location and invasive nature of the disease suggests that these structures should be removed to achieve tumor clearance.

The most frequent location of the pathologically positive cervical lymph nodes was level II, followed by level III, and then the other levels. This is in accordance with the pattern of metastatic tumor in nasopharyngeal carcinoma.8

When tumor infiltration of the overlying skin is clinically suspected, the skin should be removed en bloc with the RND specimen. Because the neck has been irradiated, the thin neck skin preserved after removal of tumor might not be viable. Because brachytherapy would probably be used for local tumor control, it was better to replace the overlying skin that was close to the tumor. The number of lymph nodes detected was higher at surgery than at preoperative evaluation, demonstrating the limitation of clinical examination, especially in the irradiated neck. In 20 (74%) of 27 neck dissections, at least 1 lymph node was fixed to the surrounding structures, showing that in this group of patients the neck disease was extensive.

Pathologic examination of the entire neck dissection specimen of all 27 patients showed that there were significantly more tumor-bearing lymph nodes than were clinically evident by physical examination before and during surgery. It was not possible to identify all the tumor-bearing nodes before and even during surgery to identify their location. Thus, surgical clearance of the lymph nodes in the entire neck was necessary for eradication of disease. On the other hand, for the one patient who had a 2-cm diameter persistent node, examination of all 109 lymph nodes in his RND specimen revealed no malignant cells. The large upper neck node only showed hyaline fibrosis. It was difficult to determine the presence of malignant cells before surgery in these enlarged lymph nodes that had been irradiated. This confirmed the finding of a previous study9 in which the incidence of negative neck dissection results was 7%. The indication for surgery is based on the clinical condition of the patient and physical findings before surgery. There is a small (1 [4%] of 27) but definite chance of negative RND findings, and this should be made known to the patient before surgery.

The high incidence of extracapsular spread indicated again the extensive nature of the nodal disease in these patients. Frequently, the capsule of the tumor-bearing lymph nodes cannot be identified, and tumor clusters can be seen lying among the muscle and soft tissue. Histologically, in 50% of the specimens, at least 1 lymph node was infiltrating or lying close to the spinal accessory nerve. Because nodes were found most frequently at level II, this finding was expected. The extensive nature of these malignant lymph nodes indicated that RND should be the salvage operation.

The presence of a positive microscopic tumor margin in 13 (50%) of 26 neck dissection specimens reflects the extensive nature of the disease. The area where microscopic tumor cells were detected included the adventitia of the carotid artery, muscles of the floor of the pos-

Table 2. Clinical and Pathological Factors That Affect the Control of Disease in the Neck

<table>
<thead>
<tr>
<th>Factors</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
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<tbody>
<tr>
<td>Sex</td>
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<td>.65</td>
</tr>
<tr>
<td>Age</td>
<td>.54</td>
<td>.17</td>
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<td>Recurrent/persistent node</td>
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<td>.48</td>
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<td>Mobility of node</td>
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<td>.11</td>
</tr>
<tr>
<td>Location and size of node</td>
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<td>.68</td>
</tr>
<tr>
<td>No. of lymph nodes before operation</td>
<td>.69</td>
<td>.35</td>
</tr>
<tr>
<td>No. of lymph nodes at surgery</td>
<td>.02</td>
<td>.06</td>
</tr>
<tr>
<td>No. of lymph nodes in specimen</td>
<td>.005</td>
<td>.02</td>
</tr>
<tr>
<td>Extracapsular specimen</td>
<td>.07</td>
<td>.09</td>
</tr>
<tr>
<td>Lymph nodes close to accessory nerve</td>
<td>.04</td>
<td>.09</td>
</tr>
</tbody>
</table>

terior triangle, and the overlying skin. Resection of the overlying neck skin was possible, whereas surgical clearance of the other structures was difficult. Additional measures such as brachytherapy should be administered to improve the salvage rate. Afterloading brachytherapy was a reasonable alternative.

The placement of hollow nylon tubes at completion of RND was not difficult, as the exact extent of residual tumor could be ascertained with frozen section control. Reconstruction of the cutaneous defect could be satisfactorily achieved with either a deltopectoral flap or a pectoralis major myocutaneous flap. The former was used more frequently because the procedure was straightforward and the surgical field was less extensive. The only disadvantage was that the return of the flap required separate surgery under local anesthesia. The pectoralis major myocutaneous flap, however, besides providing skin coverage also transposed muscle bulk to fill the space created by the RND. The factor that limited its application was that because the skin island had to face outward, 180° twisting of the pectoralis major muscle was necessary before insetting, and this might cause problems. When the reconstructive procedure was performed properly, morbidity was minimal.

Univariate analysis of clinical and pathological factors that affected the control of disease in the neck in the whole group of patients revealed that the number of lymph nodes determined before surgery and at pathologic examination and the proximity of the nodes to the spinal accessory nerve were important. Extracapsular spread of tumor had been identified as an adverse factor for tumor control in the neck.10 It was not found to be a significant factor in this study because although it represented the aggressiveness of the disease, this was better reflected by other factors.

On multivariate analysis, only the number of lymph nodes detected in the specimen was determined to be an independent factor. This factor represented the extensiveness of the disease and overshadowed all other factors detected using univariate analysis. A positive margin was not significant. In 13 patients given brachytherapy after RND, it seems that this additional therapy had contributed to better tumor control in the neck (Table 2).

The overall survival rate in this group of patients was better than when radiotherapy was used alone as sal-
vage. These patients had extensive disease, and the morbidity rate associated with the surgery was acceptable. This improvement might be related to the application of brachytherapy in patients who have advanced disease in the neck.

Brachytherapy or interstitial irradiation is the implantation of radioactive sources within or around tumor residue; it has been in clinical use for more than 60 years. Contemporary brachytherapy is performed frequently with the radionuclides cesium Cs 137, iridium Ir 192, and gold Au 198. Because these brachytherapy sources have a rapid falloff dosage compared with external beam irradiation, they have the advantage of delivering a higher local dose to the tumor than normal tissue. The overall shorter time of treatment for a given dose results in a lower surviving fraction of malignant cells, whereas the lower dose delivered to the normal tissue compared with external beam irradiation allows for more efficient repair of normal tissues.

Brachytherapy for the treatment of patients with extensive neck disease has been reported previously. Iridium wire was frequently used as the brachytherapy source under the circumstances because the physical characteristics of the wire are suitable for afterloading. Because the neck was initially included in the irradiation field, additional brachytherapy may lead to necrosis of the overlying skin, especially when the radiation treatment volume increases. Necrosis of skin is associated with definite morbidity; serious consequences, such as exposure of the carotid artery, might take place. Replacement of the overlying skin during primary surgery with deltopectoral or pectoralis major myocutaneous flaps contributed to the smooth outcome in the present group of patients.

The clinical and pathological features of patients with and without brachytherapy showed that there were significantly larger lymph nodes, with more nodes exhibiting extracapsular extension in the former group. The incidence of positive margins was also significantly higher in the group with brachytherapy. These features suggest that disease was more extensive in the group that received brachytherapy. The 5-year local tumor control rate and the actuarial survival, however, showed no statistical difference between the 2 groups, again suggesting that brachytherapy had improved local control after RND. The survival rate, however, showed some difference favoring the RND alone group, although this had not reached statistical significance. The decision to use brachytherapy in the present study depended on clinical judgment, and these patients probably had more advanced disease. Although adding brachytherapy to surgery could control disease in the neck, there were more failures either at the nasopharynx or at distant sites. This contributes to a lower disease-free survival rate. The difference has not reached statistical significance, but with longer follow-up the difference may become significant.

Patients who experience recurrent or persistent cervical lymph nodes after radiotherapy have extensive disease, as revealed by the pathological study of the neck dissection specimens. Radical neck dissection is mandatory for successful salvage. When the nodes infiltrate or adhere to the surrounding tissue, afterloading brachytherapy with iridium wire in addition to RND might not improve the survival but could provide satisfactory local tumor control.

This study was conducted on a specific group of patients, ie, patients with nasopharyngeal carcinoma who underwent radiotherapy and had persistent or recurrent disease in the neck nodes. The suggested management options are based on the pathological findings in these patients only. The tumor invasion patterns in the metastatic neck nodes in other head and neck cancers need to be evaluated separately.

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