EVALUATION OF RECURRENT NODAL DISEASE AFTER DEFINITIVE RADIATION THERAPY FOR NASOPHARYNGEAL CARCINOMA: DIAGNOSTIC VALUE OF FINE-NEEDLE ASPIRATION CYTOLOGY AND CT SCAN

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Abstract: Background. Recurrent nodal disease in patients with nasopharyngeal carcinoma (NPC) after definitive radiotherapy poses a difficult clinical problem. This cohort of patients poses a diagnostic challenge to the head and neck surgeon because evaluation of the post-irradiated neck, both clinically and radiologically, is known to be difficult, and it is not uncommon for neck dissection specimen in suspected recurrent nodal disease to contain no viable tumor cells. Currently, there is no well-accepted method for the preoperative determination of the presence of malignancy in these nodal diseases.

Methods. Over a 7-year period in a tertiary hospital, we systematically reviewed the clinical charts of 42 patients with NPC who were diagnosed with suspected recurrent nodal disease, after radical definitive radiotherapy. Fine-needle aspiration cytology (FNAC) was performed on clinically palpable nodes and results were correlated with final histopathologic results. Findings on CT scan were also correlated with final histopathologic specimens.

Results. The specificity and sensitivity of FNAC was 75.0% and 75.0%, respectively. The positive and negative predictive value of FNAC was 93.8% and 37.5%, respectively. CT scan had a positive predictive value of 78.6%. The negative predictive value for multilevel involvement on CT scan was 20%.

Conclusion. Radiological imaging and FNAC are useful diagnostic modalities in assessing recurrent nodal disease in the post-irradiated neck in patients with NPC. Although routine CT scan criteria for pathologic lymphadenopathy cannot be accurately applied in the post-irradiated neck, it is a useful surveillance tool in the routine follow-up of patients with post-irradiated neck with NPC. Clinicians, however, must understand their limitations when assessing these patients. The possibility of negative neck dissection must be conveyed to the patients.

Keywords: nasopharyngeal carcinoma; negative neck dissection; recurrent nodal disease; fine-needle aspiration cytology; CT scan

Nasopharyngeal carcinoma (NPC) is endemic in southern China where environmental factors, genetic predisposition, and Epstein-Barr virus infection play an important part in its pathogenesis. In Singapore, it is the most common head and neck cancer, with an incidence of 10.8 per 100,000 per year in males (age-standardized rate) and 3.7 per 100,000 (age-standardized rate) per year in females. The mainstay of treatment is radiotherapy in early disease and concurrent chemotherapy/
radiotherapy in advanced locoregional disease. This exquisitely radiosensitive tumor responds very well to radiotherapy. The stage-specific 5-year survival rate after curative radiotherapy is as follows: stage I, 88%; stage II A, 75%; stage II B, 74%; stage III, 60%; stage IV A, 35%; and stage IV B, 28%.²

It is not uncommon for patients to present with recurrent nodal disease after clinical response with no recurrence at the primary site. The incidence of recurrent nodal disease is 7% to 18%.³,⁴ This group of patients poses a clinical dilemma, as it is not uncommon for the nodal disease to contain no viable tumor.⁵–⁷ Moreover, recurrent nodal disease in the neck is notoriously difficult to confirm because in some lymph nodes, only clusters of tumor cells are present.⁵ Salvage surgery has an important role in the treatment of recurrent nodal disease, although some centers advocate reirradiation with external beam or boost radiotherapy, with reported cure rates of 14% to 28%.⁸,⁹ This, however, is associated with treatment-related morbidity, secondary to cumulative radiation-induced injury.

Radical neck dissection is currently an accepted surgical management for residual and recurrent nodal disease in patients with NPC, with well-proven efficacy and safety.⁵–¹¹ While most studies have focused on efficacy and safety of neck dissection in this group of patients, there is currently no well-accepted method for preoperative determination of presence of malignancy. There is also little in the literature documenting the efficacy of fine-needle aspiration cytology (FNAC) and CT scan in assessing this group of patients. More importantly, there have been no studies particularly looking at ways to avoid negative neck dissection in this cohort of patients. We systematically reviewed patients presenting to our institution with this clinical problem and investigated the diagnostic value of FNAC and CT scan in this clinical setting.

**MATERIALS AND METHODS**

This is a retrospective chart review of patients with suspected recurrent nodal disease after curative radiotherapy for NPC who presented to the Department of Otolaryngology, Singapore General Hospital, over a 7-year period from April 1, 1995 to April 1, 2002. Forty-four patients were identified, and their clinical, radiological, operative, and histologic records systematically reviewed. Two patients were excluded because of incomplete data. Forty-two patients made up our eventual study population. All patients diagnosed with NPC were treated with standard-course conventional radiotherapy. The typical regimen consists of 70 to 75 Gy to the primary tumor, 66 to 70 Gy to involved lymph nodes, and 50 Gy to the uninvolved neck given in single daily fractions of 1.8 to 2.0 Gy, 5 days per week, over 6 to 7 weeks. All patients required treatment to both sides of the neck. Patients were followed up with both the otolaryngologist and radiotherapist under a standardized protocol. For the initial 5 years, patients had clinical examination, nasoendoscopy, and annual CT scan of postnasal space and neck performed to detect any subclinical tumor recurrence in the postnasal space or for assessment of residual or recurrent nodal disease. All patients with suspected nodal recurrence underwent chest X-ray, ultrasound, or CT scan of the liver or bone scan to exclude metastatic disease.

“Recurrent nodal disease” was defined as reappearance of lymphadenopathy after initial complete regression of nodal disease.¹⁰ Patients with residual nodal disease, defined as persistence of lymph node on clinical examination or CT scan after definitive radiotherapy, were excluded from our study.

We specifically looked at FNAC and CT scan in identifying recurrent nodal disease. All patients with clinically palpable recurrent lymph nodes underwent FNAC by the attending head and neck surgeon. Aspiration of the palpable lymph nodes was performed using a 23-gauge needle mounted on a 10-mL syringe. Gentle suction was applied, and 10 to 15 passes were made in multiple directions. Both air-dried and wet-fixed slides were prepared and checked for adequacy of specimen. The slides were reviewed by attending fellowship-trained pathologists with special interests in head and neck cancer in a multidisciplinary head and neck tumor board. FNAC results were defined as “positive” if malignant cells were seen, “negative” when no malignant cells were seen, and “inconclusive” when atypical cells were seen but inconclusive for malignancy. The result of the FNAC was compared with the final histologic lymph node specimens. We then calculated the sensitivity, specificity, and positive and negative predictive values of this investigation in assessing residual nodal disease.

Similarly, radiological findings on CT scan were correlated with final histopathologic specimens. A positive CT scan for pathologic lymphadenopathy was based on the following criteria: nodal necrosis on CT scan, greatest diameter of lymph...
node >10 mm on CT scan. Diagnostic predictive values were then calculated.

RESULTS

Forty-two patients presented with suspected recurrent nodal disease. All the patients had either type 2a (2 of 42, 4.7%) or 2b (40 of 42, 96%) World Health Organization (WHO) histologic type NPC at primary diagnosis. At initial staging, 10 patients had N0 disease, 13 patients had N1 disease, and 19 patients had N2 disease. All patients had received curative standard-course conventional radiotherapy to the primary site and neck as described.

The demographics of the study population are shown in Table 1. The timing of recurrence was 6 to 240 months (mean 60.7 ± 54.3).

Thirty-seven (88.1%) of the 42 patients had clinically palpable lymphadenopathy, while 5 (11.9%) patients had only radiological evidence of pathologic lymphadenopathy. Of the 37 patients with clinically palpable lymph nodes, 25 (67.6%) patients had a solitary lymph node while the other 12 (32.4%) had multiple lymph nodes on clinical examination.

FNAC was performed on all 37 patients with clinically palpable cervical lymph nodes. Sixteen (43.2%) were positive for malignant cells, 8 (21.6%) were negative and showed follicular hyperplasia, and 13 (35.2%) contained atypical cells and were reported by the pathologist as inconclusive. The FNAC results were correlated with the final histopathologic specimens. All 16 patients with positive FNAC results underwent neck dissection. Fifteen (93.8%) of 16 had tumor cells seen in the lymph node and neck dissection performed at a later date. Three (37.5%) did not have viable tumor cells seen, and no neck dissection was performed. The sensitivity, specificity, and diagnostic predictive values of FNAC were calculated for the 24 patients with definite reading on FNAC report. The sensitivity and specificity of FNAC is 75.0% and 75.0%, respectively, with positive and negative predictive values of 93.8% and 37.5%, respectively. All 13 patients with inconclusive FNAC results with atypical cells seen had neck dissection, 10 (76.9%) had tumor seen in neck dissection specimens, and 3 (23.1%) had negative neck dissection (see Figure 1).

All 42 patients had CT scan performed and had radiological evidence of pathologic cervical lymphadenopathy. The radiological findings were correlated with the final histopathologic specimens. Nine (21.4%) patients had no viable tumor in lymph node specimens and the rest of the 33 patients (78.6%) had viable tumor cells on permanent histopathologic neck dissection specimen. Of the 42 patients, 17 patients (40.4%) had multiple levels involvement on CT scan and on final neck dissection specimen. The remaining 25 patients had a solitary lymph node on CT scan, of which 16 eventually proved to have multiple-level involvement on final histopathologic neck dissection specimens, while the other 9 had no tumor seen in lymph node specimens. All 5 patients who had radiologically significant but clinically non-palpable node underwent excision biopsy of the lymph node. Three (60%) of the 5 patients who had tumor cells seen in the lymph node had neck dissection performed at a later date. Two (40%) of the 5 patients had no tumor cells seen, and no neck dissection was performed. CT scan positively identified 33 patients with tumor in final histology giving a positive predictive value of 78.6%. In patients in this clinical setting with a solitary lymph node on CT scan, the negative predictive value for CT scan for multiple-level involvement is 20%. Figure 2 showed the correlation between clinical and radiologic findings with eventual histologic findings.

Of the 42 patients who had an operation for suspected recurrent disease, 28 (66.7%) patients had unilateral radical neck dissection, 9 (21.4%) had bilateral synchronous neck dissection (radical on 1 side and modified radical on the other side), while 5 (11.9%) had only excision biopsy. Thirteen patients underwent excision biopsy of the lymph nodes. Eight of the 13 patients who underwent
excision biopsy were positive for nodal disease, and neck dissection was carried out at a later date. Five were negative for metastatic disease, and neck dissection was not performed. Of the 5 patients who had negative excision biopsy, 4 had undergone biopsy for submental lymphadenopathy. There were 4 patients with negative neck dissection. One patient who had positive FNAC and underwent bilateral modified neck dissection had no viable tumor cell in the neck specimen. Three other patients had no tumor cells present in the neck dissection specimen. The negative neck dissection rate for recurrent disease in our study was 10.8% (4 of 37). Figure 3 shows the clinical outcome of these 42 patients, and Figure 4 shows the percentage of patients with levels and frequency of lymph node involvement in recurrent disease. The nodal levels followed the terminology pro-
posed by the American Academy of Otolaryngology and American Society for Head and Neck Surgery.

**DISCUSSION**

Radical neck dissection is documented to be efficacious and safe in treating recurrent nodal disease in NPC after definitive radiotherapy. However, it is not uncommon for neck dissection specimens to contain no viable tumor cells. The incidence of negative neck dissection varies from different series. Ho et al. reported that in that series all patients who underwent radical neck dissection for residual and recurrent disease contained tumor cells, and Wei et al. reported a negative neck dissection rate of 4% to 7% for recurrent nodal disease and 12% for recurrent and residual nodal disease. In our study, the incidence of negative neck dissection on final histologic specimen in patients with recurrent nodal disease after curative radiotherapy for NPC is 10.8% (4 of 37 patients). This finding is important because neck dissection is a huge undertaking with significant morbidity and potential complications. Thus, we undertook this study to determine the efficacy of FNAC and CT scan in identifying preoperative true recurrent nodal disease.

Clinical examination in the post-irradiated neck is extremely difficult because of fibrosis and because deep-seated lymph nodes may not be palpable clinically. In our study population, 5

![Figure 3. Outcome of 42 patients with suspected nodal recurrence.](figure3)

![Figure 4. Percentage of patients with levels of nodal involvement.](figure4)
patients had solitary subclinical lymph node enlargement evident only on CT scan; 3 of these patients eventually proved to have recurrent disease. Of the 25 patients with a solitary lymph node clinically, 5 patients were found to have multiple lymph nodes on CT scan. The study result reiterates the point that clinical examination in the post-irradiated neck is inaccurate, and imaging modalities are needed to assist the clinician in the assessment of this group of patients.

Fine-needle aspiration biopsy is routinely performed in our hospital for patients with suspected recurrence or residual nodal disease. However, it may be difficult in determining recurrent nodal disease in this clinical setting due to fibrosis after irradiation. There is no previous study looking at the positive and negative predictive value of FNAC in this clinical setting. It is also important to note that the results of a previous study that reported sensitivity and specificity included patients with suspected residual disease after curative radiotherapy, whereas our study focused on recurrent disease. Our result showed sensitivity and specificity of 75.0% and 75.0%, respectively, and positive and negative predictive values of 93.8% and 37.5%, respectively. Yen et al in their series reported a sensitivity of 83% for FNAC performed on 12 patients. Sensitivity of FNAC in this clinical setting in the literature was reported to be as low as 57%. This is not surprising because FNA is largely operator dependent, and it is often difficult to obtain confirmatory cytology on the post-irradiated neck. Wei et al in their pathologic study showed that tumor cells may only be present in small clusters, which may account for the low negative predictive value of FNAC in our study. The low negative predictive value in our study population has important clinical significance. Our study results suggest that in a patient with suspected recurrent nodal disease with NPC after curative radiotherapy, a negative FNAC should not be dismissed, and further investigation should be obtained to prove the absence of nodal disease. In our study, 8 of the patients with negative FNAC underwent excision biopsy, with 3 patients eventually proven to have only reactive lymph node. The rest (5 of the 8) had tumor cells seen and neck dissection performed subsequently. It is to be noted, however, that some authors do not recommend excision biopsy as a diagnostic procedure because it may increase incidence of flap necrosis in subsequent neck dissection. Although there are no data in the literature to suggest tumor seeding during the excision biopsy in this clinical setting, this is a justified concern. In the 5 patients who subsequently underwent neck dissection, the scar of the lymph node excision biopsy was incorporated in the neck dissection. These patients were followed up for a minimum of 2 years, with no further recurrence. Some authors suggested the use of excision biopsy with intraoperative frozen section. They would proceed with neck dissection if the frozen section showed malignancy. In our study, if atypical cells were seen on the FNAC but reported as indeterminate or inconclusive, there was a high possibility that there would be tumor cells in the final neck specimen. Ten (76.9%) of the 13 patients who had atypical cells seen on FNAC had viable tumor cells in the final neck dissection, and 3 had negative neck dissection. There was a case of false-positive FNA, and the patient underwent bilateral modified neck dissection for submental lymphadenopathy. The neck specimen did not contain any tumor-bearing nodes, and histology showed follicular hyperplasia.

Radiation-induced fibrosis makes the neck stiff, and clinical examination can be difficult. The irradiated neck is not easy to examine, and small, deeply situated lymph nodes may not be detected clinically. Imaging modalities that can assist the clinician include CT scan, MRI, and ultrasound. However, confirming persistent nodal and recurrent nodal metastasis after radiotherapy using radiological means can be difficult due to postirradiation changes. Because of post-irradiation changes, diagnostic criteria in the diagnosis of pathologic lymph nodes such as nodal necrosis or transverse diameter of 10 mm or more on CT scan can be unreliable. At primary diagnosis, the criteria for nodal disease on MRI are low signal intensity on T1-weighted images, low signal intensity focus with rim of enhancing tissue, and high signal intensity on T2-weighted images. High-resolution ultrasound is considered a useful tool, with a sensitivity of 90% in the diagnosis of recurrent nodal disease, and when combined with FNAC, it may give a sensitivity of 95%. However, all these radiological modalities are recognized to be inaccurate in assessing the post-irradiated neck in NPC patients. Ultrasound-guided FNAC was not used in the diagnostic management of this cohort of patients in our institution. Our study showed that although CT scan is able to detect clinically nonpalpable asymptomatic pathologic lymph nodes, it has a positive predictive value of only 78.6%. In post-irradiated NPC patients with suspected recurrent nodal disease with a solitary lymph node on CT scan, it has a
negative predictive value of 20% for multilevel involvement. All 42 patients in our study fulfilled CT criterion for recurrent nodal disease, although only 33 patients had proven nodal disease eventually. Three of 5 patients with no clinically palpable nodes but radiologically diagnosed recurrent disease on routine screening had tumor cells in the neck specimens while 16 (80%) of 20 patients with clinically and radiologically solitary node had multiple nodes involvement on final histology. These findings are not surprising, considering that histopathologic specimens in previous studies had shown that nodal recurrent disease or residual disease can be more extensive than clinically or radiologically suggested.\textsuperscript{7,10–11} Using CT scan as a surveillance tool in diagnosis of recurrent disease has its benefits and limitations. While it is able to detect clinically nonpalpable lymph node recurrence, it may not be able to detect recurrence early. It can often underestimate the true extent of disease and is unable to accurately predict presence or absence of nodal disease.

Interestingly, all 5 patients who had solitary submental lymphadenopathy either clinically or radiologically did not have any viable tumor cells seen on histologic specimen. Four of the 5 patients had lymph node excision; 1 had false-positive FNAC, and bilateral neck dissection was performed. Submental lymph node is reported to be rarely involved in nodal disease in NPC. None of the 271 NPC patients studied by Sham et al\textsuperscript{16} presented with submental lymphadenopathy at primary diagnosis. However, pathologic study of recurrent nodal disease showed that all 5 levels of lymph nodes can be involved with certain predilection.\textsuperscript{5,11,17} A study by Khoo et al\textsuperscript{11} showed that levels 2 and 3 were most commonly involved, while Yen et al\textsuperscript{11} showed predilection of levels 2 and 4 lymph node involvement in recurrent nodal disease. However, there are no studies done to analyze the incidence of recurrence at the submental triangle (level 1A). Our study also showed that recurrence occurred at multiple levels with predilection at level 2 (50% of patients) and level 3 (40.4% of patients), see Figure 3, and affirmed the use of classical or modified radical neck dissection rather than excision biopsy for treatment of recurrent nodal disease. Unfortunately, in our current study, level 1 lymph node involvement was reported as a whole and not separated into level 1A or 1B. We are thus unable to make a recommendation for management of isolated submental lymphadenopathy in this group of patients. Further prospective studies are needed to investigate nodal recurrence at submental lymph node because if pathologic study did not show presence of recurrence at this level, then excision biopsy of lymph nodes in this group of patients at this site may be an option.

Recurrent nodal disease in postcurative radiotherapy NPC patients poses a diagnostic challenge to the head and neck surgeon. Our study showed clinical evaluation of nodal recurrence in the post-irradiated neck can be difficult, and although a positive FNAC result has good positive predictive value, a negative FNAC result cannot be dismissed. CT scan also has its limitations. Accurate preoperative diagnosis is necessary because it can potentially prevent unnecessary neck dissection in at least 10% of patients. With the advent of positron emission tomography (PET) scan using fluorinated analogue of glucose as a tracer, this modality of imaging maybe helpful in managing this cohort of patients. In fact, PET scan has been found to upstage disease in patients with suspected nodal disease at initial diagnosis and is useful in the detection of recurrence at the primary site and metastases, with positive and negative predictive values of 90% and 91%, respectively.\textsuperscript{18,19} Further study should be performed in the clinical setting of suspected recurrent nodal disease to determine its usefulness.

This retrospective study was conducted with patients with NPC who had curative radiotherapy with suspected recurrent disease in the neck. The findings on CT scan and FNAC and results are thus based on the clinical and pathologic findings in these patients only. The role of FNAC and CT scan in evaluation of post-irradiated neck in other head and neck cancers had to be assessed separately.

On the basis of this retrospective analysis, our recommendations for patients with suspected nodal recurrence after curative radiotherapy include the following: (1) curative radical neck dissection if preoperative FNAC and CT scan are positive for recurrence; (2) if the preoperative FNAC is negative or inconclusive, the patient should have an excision biopsy of the affected node, and frozen section with a view for neck dissection if the frozen section contains malignant cells, even if the CT scan fulfilled criteria for recurrence.

**CONCLUSION**

Recurrent nodal disease in NPC patients after curative radiotherapy is a challenging clinical problem, both diagnostically and therapeutically. Although the safety and efficacy of radical neck
dissection is proven in the treatment of recurrent disease, it is not without morbidity. The clinical and radiological nodal presentation frequently underestimates the actual involvement. Our study showed that while CT scan and FNAC are important in the clinical evaluation of patients with NPC with suspected nodal disease and CT scan for cancer surveillance, they are unable to accurately predict negative neck dissection. The possibility of negative neck dissection should be counseled. PET scan may be helpful in preoperative confirmation of recurrent nodal disease in preventing unnecessary neck dissection in this clinical setting, but further studies need to be performed to assess its efficacy.

REFERENCES