ORIGINAL ARTICLE

Salvage neck surgery in recurrent nodal NPC: Do all patients require a comprehensive neck dissection in the modern MRI era?

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ABSTRACT

Objective: The standard treatment for regional failure in nasopharyngeal carcinoma (NPC) is the radical neck dissection (RND). Our study sought to determine if magnetic resonance imaging (MRI) may accurately predict nodal involvement to allow selected levels of neck dissection to be preserved.

Study Design and Setting: We analysed retrospectively all NPC patients in our centre undergoing neck dissections as salvage therapy for nodal recurrence. Nodal involvement based on the preoperative MRI was assessed and compared with postoperative histopathology.

Methods: This is a retrospective study conducted on patients in our centre with recurrent NPC from February 2002 to February 2017. Patients were identified from the database of the otolaryngology oncology division at our institution. Of these, 28 patients met all our inclusion and exclusion criteria. We calculated sensitivity and specificity as well as average number of nodes per patient.

Results: In our study, we calculated the false negative and false positive rates of preoperative MRI neck by levels. Overall sensitivity of MRI picking up disease by level was 76% and specificity was 86%.

Conclusion: Based on our study, we will be missing a total of 10 (7.1%) diseased neck levels in eight (28.5%) patients. MRI alone, therefore, does not provide enough information to allow safe selective preservation of neck levels in surgical salvage of neck recurrences in NPC.

KEYWORDS:
Nasopharyngeal carcinoma, radical neck dissection, selective neck dissection, magnetic resonance imaging, neck recurrence

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer. It has a high incidence of nodal metastases, with up to 70% of patients presenting with cervical lymphadenopathy.[20] The mainstay of treatment for primary tumours and neck nodal metastases includes radiotherapy (RT) or a combination of RT and chemotherapy. Local recurrence has been reported to be between 10 to 20% of patients following primary curative treatment,[26] while locoregional recurrent nodal metastases has been reported to be 5.8 to 12.9% at 3 years in existing literature[21] Locoregional recurrences are typically salvaged with surgery if resectable. Re-irradiation or chemotherapy can be utilised in unresectable cases. Distant systemic metastases is treated with first line chemotherapy or second line chemotherapy or immunotherapy.[25] Patients who underwent chemotherapy in our centre received a combination of chemotherapy agents such as cisplatin, carboplatin, 5-FU and gemtricitabine.[9]

Locoregional recurrent nodal metastases following primary treatment requires salvage surgery, though the extent of salvage surgery is controversial. Various types of neck dissection are employed. In RND, levels I to V are addressed together with resection of sternocleidomastoid (SCM), internal jugular vein (IJV) as well as accessory nerve. In a modified RND (MRND), levels I to V are addressed with removal of one or more of the more structures (SCM, IJV or accessory nerve). In a selective neck dissection (SND), levels likely to have occult nodal metastases are preferentially dissected. In a super selective neck dissection (SSND), two or fewer contiguous neck levels are dissected as appropriate.[19]

Currently, the widely adopted standard-of-care for neck nodal management is the radical neck dissection (RND). This philosophy was a result of the landmark study by William Wei et al.[5] In this study, Wei examined the extent of nodal disease in 43 RND specimens following NPC recurrence and found that all levels of the neck had the potential to be involved, with level II being the most common (53%) while metastases at levels I or V occurred in only 4% of patients. More than 70% of specimens had a higher number of tumour-bearing lymph nodes than evident on clinical examination and/or preoperative computerised tomography (CT) scans and was frequently complicated by extracapsular spread involving the accessory nerve and the internal jugular vein.[5] Preoperative clinical examination and CT scans were gross underestimates of true nodal involvement. The authors hence concluded that RND is the treatment of choice.

Routine use of RND is, however, associated with significant acute and chronic morbidities.[9,11] As such, some centres have moved towards offering selective neck dissections (SND).

Several previous retrospective studies have reported that SND offers high overall survival and comparable 5-year disease free survival rates[7,32] and can be considered non-inferior to RND.

Additionally, Wei's study was based on clinical examination, with a CT scan performed in selected cases to form an overall clinical impression of the neck levels involvement. The advent, in recent years, of contrast enhanced magnetic resonance imaging (MRI) as the preferred imaging modality with superior soft tissue delineation has enabled more accurate determination of the location of recurrent cancers, relationship to adjacent vital structures and extent of nodal involvement.[13,16]

We therefore sought to determine if modern-day MRI may allow a better assessment of disease, and hence more targeted neck dissections, than clinical exam and/or CT scan alone. This would potentially allow the treating clinician to perform MRI imaged guided selective neck dissections.

MATERIALS AND METHODS
This is a retrospective study conducted on patients in our centre with recurrent NPC from February 2002 to February 2017.

The management of persistent or recurrent nodal disease from NPC at our institution involves preoperative cross-sectional imaging with MRI followed by RND or modified radical neck dissection (MRND). RT and chemotherapy are reserved for selected cases. Because the philosophy has been a comprehensive neck dissection for every patient, this allowed us to compare the final histology with the preoperative MRI, to determine the performance of the MRI scan in delineating the nodes.

Patients were identified from the database of the otolaryngology oncology division at our institution. Between February 2002 and February 2017, 55 patients had suspected nodal recurrence of NPC at our centre. Inclusion criteria were all NPC patients from our institution with (1) residual/recurrent nodal disease after completion of primary RT/CRT, (2) who received a RND or MRND as part of salvage treatment or electively in the presence of local recurrent disease and had a (3) preoperative MRI scan prior to salvage surgery. Of these, 34 patients were excluded for the following reasons (1) 15 had no preoperative MRI and (2) 12 records were not available in our database (Figure 1).

A total of 28 patients with histopathology-proven isolated regional recurrence met all our inclusion and exclusion criteria. This study was approved by our local institutional review board. (NHG DSRB reference: 2018/00184)

Management Protocol
Of the patients undergoing salvage surgery, 11 (39.3%) patients had received RT alone in their initial treatment; 17 (60.7%) patients received both chemotherapy and RT in their initial treatment. All patients in our series underwent only unilateral neck dissection and none received neoadjuvant chemotherapy prior to salvage surgery. As part of workup to evaluate disease extent, all patients with locoregional nodal recurrences included in our study had MRI performed preoperatively. These MRIs were performed at least 3 months following initial treatment to assess for recurrence and within a month prior to salvage surgery.

The MRI protocol consisted of the following sequences: axial T1 weighted, coronal T1 weighted, axial T2 weighted fat sequence spin echo and contrast enhanced axial and coronal spin echoes. Subsequently, the coronal contrast enhanced sequence and axial T2 weighted sequence were later replaced in our institution with an isotropic 3D gradient echo sequence and T2 weighted non-fat saturated sequence respectively. All cases were performed by experienced head and neck surgeons in our department.

Retrospective evaluation of the scans by levels were performed by two senior head and neck radiologists. Both radiologists evaluated all scans independently and any discordance was resolved by mutual discussion and consensus.

All the patients underwent neck dissection of all the five levels. 18 (64.3%) underwent RND while 10 (35.7%) underwent MRND. Lymph node specimens were excised, marked by level, and sent for postoperative histopathological examination.

Number of nodes involved with disease were reported by level and this data was collected retrospectively. Key patient demographics and disease characteristics are summarised in Table I. All patients were staged using the criteria of American Joint Committee on Cancer (AJCC) 8th Edition.

Radiological Criteria
All preoperative MRI scans were read by experienced clinical radiologists in our centre. Each level was analysed for the presence and number of radiologically suspicious nodes using evidence-based criteria. Our criteria to classify lymph nodes seen as suspicious was if the node had any one of the following:
(1) Short axis diameter (retropharyngeal lymph node > 5 mm, level I/II > 11 mm, all other levels >10 mm).[17]
(2) Shape (round or irregular - pathological | ovoid - not pathological).[14]
(3) Margins (irregular or ill-defined - pathological | well-defined - not pathological).[14]
(4) Any extranodal extension (grade 1 and 2) (0 – Tumour confined within the lymph node with no extranodal extension | 1 – Tumour invading beyond the capsule of lymph node, 2 – All tumour tissue with no residual nodal tissue).[22]
(5) Necrosis and clustered[10]

False negative (FN) was defined as a particular level with no suspicious lymph nodes seen on preoperative MRI but metastatic nodes were found on postoperative histopathological analyses. Conversely, false positive (FP) was defined as when suspicious nodes were seen on preoperative MRI but no metastatic nodes were found on histology postoperatively.

Table I: Summary of patient and disease characteristics

Characteristics	N = 28 (%)
Gender	
Female	4 (14.3%)
Male	24 (85.7%)
Age	
<60	15 (53.6%)
≥60	13 (46.4%)
Primary tumor AJCC VIII stage	
I	0 (0.0%)
II	8 (28.6%)
III	8 (28.6%)
IV	7 (25.0%)
Unknown	5 (17.8%)
Primary tumor treatment	
RT	11 (39.3%)
ChemoRT	17 (60.1%)
Recurrence AJCC VIII stage	
r0	2 (7.1%)
rI	1 (3.6%)
rII	23 (82.1%)
rIII	1 (3.6%)
rIV	1 (3.6%)
Type of surgery	
RND	18 (64.3%)
MRND	10 (35.7%)

Table II: Collective radiological and histopathological analyses of all included specimens

Characteristics	N = 28 (%)
Total number of suspicious lymph nodes on preoperative MRI	
Level I	3
Level II	24
Level III	9
Level IV	2
Level V	7
Total number of tumor-containing lymph nodes on histopathology	
Level I	3
Level II	18
Level III	10
Level IV	6
Level V	4
False negatives	
Level I	3
Level II	0
Level III	2
Level IV	4
Level V	0
False positives	
Level I	3
Level II	6
Level III	2
Level IV	1
Level V	3
Extracapsular spread	
Yes	8 (28.6%)
No	20 (71.4%)

Table III: Patient's with one or more false negative lymph node levels are summarized above with any corresponding extranodal extension noted on postoperative histopathology

Subject number	False negative levels	Extranodal extension
1	1	Yes
3	3	No
17	4	Yes
19	1	No
20	3, 4	Yes
25	4	Yes
27	3, 4	Yes
36	1	No

Table IV: Sensitivity and specificity of preoperative MRI in the detection of recurrent/residual nodal disease of NPC per neck level. Overall sensitivity and specificity were also calculated

N = 28	Sensitivity	Specificity
Level 1	25%	92%
Level 2	100%	40%
Level 3	70%	89%
Level 4	33%	95%
Level 5	100%	88%
Overall	76%	86%

Table V: Overall number of false negatives and positives on modern day preoperative MRI

Total number of levels dissected	140
Overall false negatives	10 (7.1%)
Overall false positives	14 (10%)

Table VI: Mean lymph nodes per patient found in our study with modern-day preoperative MRI compared to Wei et al's landmark study in 1992 using CT and clinical examination. In our study, there is a closer correlation between mean number of suspicious nodes found clinically and that found on histopathology

	Clinically suspicious lymph nodes on clinical exam/CT on histopathology or MRI	Range per patient	Mean per patient	Tumor-containing lymph nodes	Range per patient	Mean per patient	Ratio Difference in detection of nodal recurrence on preoperative scans and postoperative histopathology
Wei et al., 1992[5]	59	0 to 5	1.5	294	0 to 62	7.4	4.6
Current study	105	0 to 10	3.8	91	0 to 5	3.6	0.95

Pathological Analyses
All intraoperative lymph node specimens were sent for postoperative histopathological analyses in 10% neutral buffered formalin for histopathological analyses. These specimens were oriented by the surgeon using orientating sutures demarcating lymph node subgroups (level I to level V) and was sent en-bloc to our histopathology lab for further tissue processing. All the macroscopically negative or equivocal lymph nodes were submitted in totality. Limited representative sections of grossly apparent positive nodes or matted positive nodes were submitted for microscopic documentation of metastasis. Each tissue slice was cut to a thickness of 3 to 4 mm for processing and further paraffin block preparation. Standard 4-micron thick tissue sections were cut on glass slides and stained with haematoxylin and eosin for histology assessment.

Apart from the number of nodes involved by metastatic carcinoma, the greatest dimension of metastatic deposit and the presence or absence of extranodal extension was also documented.

RESULTS
Histopathological Findings
A total of 23 patients had metastatic carcinoma in at least one lymph node level, while five patients had no metastatic carcinoma found in all five levels following RND or MRND. Single level involvement was found in 11 patients, while other 12 patients had multilevel involvement. Nodal recurrences most frequently occurred in levels II and III (n = 8 (28.6%), n = 8 (28.6%) respectively). Eight patients (28.6%)

had extracapsular spread in at least one lymph node seen on postoperative histopathology. Tumour infiltration was found in structures including the perinodal soft tissue, skeletal muscle and vasculature. Interestingly, all levels on preoperative MRI in our study were found to have false negatives, except for levels II and V. Exact distribution of nodal involvement for both preoperative MRI and postoperative histopathology is summarised in Table II.

Comparison Between MRI and Histology (Mean Positive Nodes Detected Per Patient)
In our study, for the 28 patients analysed, a total of 105 radiologically suspicious lymph nodes were detected by MRI with a range of 0 to 10 lymph nodes (mean, 3.8) per patient. In contrast, the number of positive nodes that actually contained tumour on histopathology were 91, with a range of 0 to 5 per patient (mean, 3.6).

False Positives by Level
There were two (6.0%) false positives in level I, six (18.2%) in level II, two (6.0%) in level III, one (3.0%) in level IV and three (9.1%) in level V.

False Negatives by Level
Eight (28.6%) patients had one or more false negatives in one or more neck levels. There were three (10.7%) false negatives in level I, zeo (0%) in level II, three (10.7%) in level III, four (14.3%) in level IV and zero (0%) in level V. Five of these patients also had extranodal extension (Table III).

These figures translate into sensitivities and specificities per level as documented in Table IV. Taking into account all
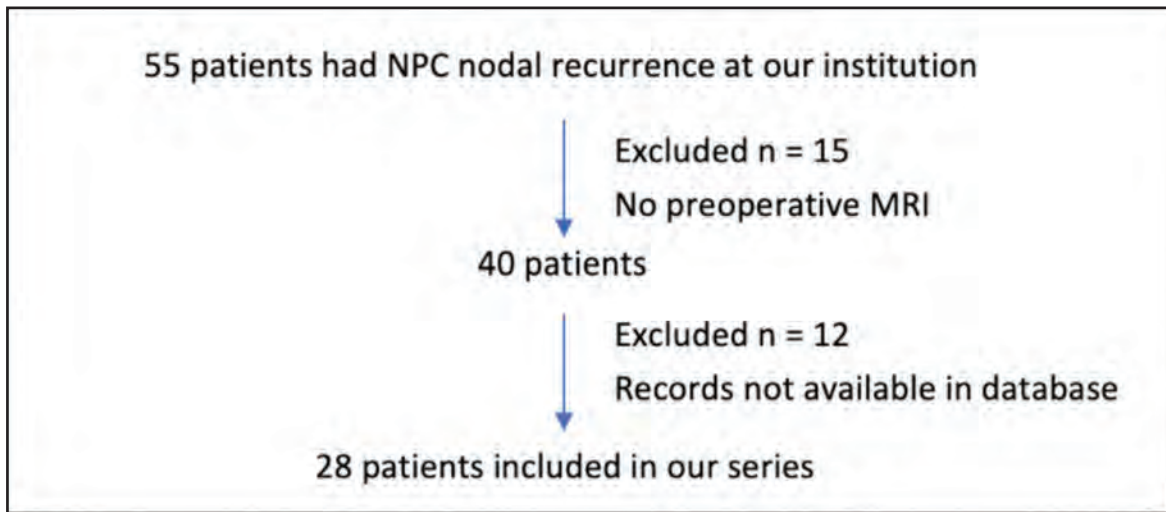
Fig. 1: Exclusion table.

levels, the overall sensitivity and specificity based on all lymph node levels in our series of patients were 76% and 86% respectively. Table V summarises the overall number of false negative and false positives levels out of the 140 levels dissected.

We would, in theory, conserve a total of 95 out of 140 neck levels in our 28 patients if we were to perform selective neck dissections based solely on suspicious lymph node levels on preoperative MRI. This would however result in 10 missed neck levels, affecting eight patients in total (28.6%).

Outcomes
All patients were followed up regularly until discharge or death. Two (7.1%) were lost to follow up. Of the 26 remaining patients, the follow-up interval ranged from 2 months to 14 years and 2 months with a median follow up of 1 year and 7 months. There were four (14.3%) local recurrences and six (21.4%) systemic metastases.

There were also 11 (39.2%) deaths in our series of patients. Two (7.1%) died of systemic metastases and two (7.1%) from local recurrences. Another seven (25%) died of causes not related to recurrent NPC, including cardiac arrests and strokes.

DISCUSSION
In a landmark study, Wei et al. examined a series of whole-neck dissections in 40 patients whose RND specimens contained tumour tissue.[5] The total number of suspicious lymph nodes detected clinically, with or without preoperative CT scan, were 59 with a range of 1 to 5 (mean, 1.5) per patient. The number of lymph nodes that actually contained tumour were 294, with a range of 1 to 62 (mean, 7.4) per patient. In a follow-up study, the authors[9] further found that all neck levels had the potential to be involved with levels II and V being the most common (53%). Extracapsular spread was evident in over 60% of metastatic lymph nodes. These findings reflect the aggressive nature of recurrent NPC in the neck. The authors thus concluded that RND with removal of surrounding sternocleidomastoid, internal jugular vein and spinal accessory nerve is the treatment of choice to achieve curative resection. This conclusion is supported by various other earlier studies.[2,3]

Radical neck dissection, however, is associated with high rates of functional and cosmetic defects. These included postoperative shoulder syndrome in cases of CN XI sacrifice, skin flap necrosis, shoulder syndrome, surgical site infection and delays in wound healing.[11,18] Since the landmark trials almost 20 years ago, more recent studies by Yen et al. and Liu et al. reported similar 5-year survival and neck control rates for patients treated with more limited neck dissections.[7,24,25] Another recently reported large series by Zhang et al[17] analysed 355 patients and recommended selective neck dissection be considered for patients with a single residual node. Other studies have also shown that metastatic lymph nodes appear to be primarily located at levels II and V.[20] With the refinement of surgical techniques and imaging modalities over the last decades, the requirement of a routine RND is under scrutiny.[1,20,24] The concept of sparing unaffected levels has also been applied in the treatment of other head and neck cancers.

Over the past decades, there have been significant advances in imaging with the advent of MRI for evaluating nodal metastases and planning radiotherapy in patients with head and neck cancers. MRI has become the preferred modality of assessment of primary nasopharyngeal cancers because of better contrast resolution and less prominent motion artefacts compared to CT scans.[12] Other authors have also purported that MRI, compared to CT, offers equivalent or superior sensitivity, specificity and accuracy in detecting nodal recurrences and soft tissue extension beyond the nasopharynx (P Olmi et al., 1995).[6]

Our present study is a series of recent (2002 to 2017) recurrent NPC cases treated with neck dissections. All cases underwent preoperative MRI to identify levels with suspicious lymph nodes. Histopathology was subsequently used as a postoperative gold standard to affirm if a neck level was involved. We sought to determine whether we could safely treat NPC neck nodal recurrence with selective neck dissection by demonstrating a high sensitivity of MRI, using histopathology as the gold standard.

In William Wei's study, for the 40 patients analysed, a total of 59 clinically-suspicious lymph nodes were detected on CT and physical examination preoperatively with a range of 1 to 5 lymph nodes (mean, 1.5) per patient. In contrast the number of lymph nodes that actually contained tumour on histopathology was 294, with a range of 1 to 62 (mean, 7.4). This represents a histology: clinical ratio of 4.6 times difference between the two groups.

In our study, for the 28 patients analysed, a total of 105 radiologically-suspicious lymph nodes were detected by MRI with a range of 0 to 10 lymph nodes (mean, 3.8) per patient. In contrast, the number of positive nodes that actually contained tumour on histopathology was 91, with a range of 0 to 5 per patient (mean, 3.6). This represents a histology: clinical ratio of 0.95 times between the two groups, demonstrating a marked improvement in nodal detection with the routine use of preoperative MRI in the detection of disease from 4.6 times in William Wei's study (Table VI). In fact, with MRI, as opposed to clinical examination and CT in William Wei's study, there were more nodes deemed as suspicious on preoperative assessment compared to those found on final histology.

Despite the superiority of MRI over CT scan, the sensitivity and specificity do not approach 100%. Of note, the use of size itself does not definitely discriminate disease. Nodes larger than 10 mm are conventionally considered abnormal. However, 20% of nodes that exceed 10 mm harbour no metastatic deposits and histologically show only hyperplasia. On the other hand, 23% of nodes that show extracapsular spread measure less than 10 mm.[4] It Is clear that no imaging modality, including MRI, is able to depict all of the micrometastases of small recurrent lymph nodes.[17] Specificity can also be affected by the presence of suppurative nodes that show central areas of low attenuation. Assumptions that these nodes are cancerous are further confounded that such inflammatory nodes can sometimes have irregular and ill-defined margins.[10]

Despite the improved sensitivity of MRI over CT, further analysis showed that the sensitivity of MRI for NPC nodal disease ranged from 25 to 100% by levels and was 76% overall (Table IV). This means that out of the 28 patients (140 neck levels) operated upon, we would be missing 10 (7.1%) diseased lymph node levels in a total of eight patients (28.6% of patients). Hence, based on our study, MRI was not able to allow for an ontologically safe image-guided selective neck dissection.

There are several limitations to this study. First, our study is a retrospective study with a small sample size. Despite the fact that data is examined over a 15-year period, our study was limited by the relative paucity of recurrent nodal metastases in nasopharyngeal cancer in general. Second, the results of this study are based on the definition of what constitutes a radiologically suspicious node, as defined by our paper. It is recognized that different institutions may have different criteria for what constitutes a radiologically suspicious node. However, we envisage that the results of this study should provide a close approximation of the relative sensitivity and specificity of preoperative MRI in the majority of centres. Thirdly, some recent studies have purported improved

metastatic lymph node detection over MRI by using more contemporary imaging modalities such as the 18 flurodeoxyglucose-proton emission tomography CT or MRI (18F PET-CT or MRI) with resultant improved sensitivity of 90% with PET-CT over 77% with MRI alone in detecting nodal recurrence. This can be attributed to the superior ability of PET-CT or MRI to distinguish recurrence NPC from local scar or fibrous tissue following irradiation.[5,26] However, a significant proportion of our patients from earlier years did not undergo routine preoperative PET scans, thus this was not included in our study. PET scans still require a critical volume of disease to pick up tumour, and has its own limitations.

CONCLUSION

Regional neck recurrence after (chemo) radiation of primary nasopharyngeal carcinoma (NPC) can involve all five levels of the neck. Salvage surgery is indicated as first line therapy for such cases. Our study suggests that even with modern-day MRI, we are unable to fully eliminate false negatives to allow safe selective neck dissections. This is of clinical importance as salvage surgery is deemed as a last resort to achieve tumour clearance. Hence, a comprehensive neck dissection should continue to be the first line treatment for recurrent NPC to achieve salvage.

FUNDING INFORMATION

No funding information to declare for this study.

CONFLICTS OF INTEREST

No conflicts of interest to declare for this study.

INSTITUTIONAL REVIEW BOARD (IRB)

This study is approved by Tan Tock Seng Hospital IRB

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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