

Computed Tomography of Lymph Node Metastasis Before and After Radiation Therapy: Correlations With Residual Tumour

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Abstract. *Background:* Computed tomography (CT) performed after radiation therapy (RT) is used to detect residual lymph node (LN) metastasis. Here, we investigated which LN parameters on pre- and post-RT CT images correlated with residual tumour in patients with head and neck cancer. *Patients and Methods:* We enrolled 23 patients who received RT. A total of 50 LNs were evaluated. Correlations between quantitative and qualitative findings and residual tumours were evaluated. *Results:* The median patient age was 61 years. Thirty-one LNs were histologically confirmed to contain residual tumour. LNs with residual tumour had significantly longer short and long axes on post-RT CT images. A new finding of obscured margins after RT were significantly associated with the presence of residual tumour by univariate and multivariate analyses. *Conclusion:* Comparison of qualitative, LN parameters on pre- and post-RT CT images may improve the detection of residual tumour in patients with suspected residual or recurrent LN metastasis.

Radiation therapy (RT) is often selected for the treatment of head and neck cancer with the goal of preserving function. Salvage neck dissection (ND) can also be considered as standard of care for residual or recurrent neck lymph node (LN) metastasis after RT (1, 2). In a phase III randomised trial of 271 patients, salvage ND was included in the treatment protocol for residual neck LN metastasis detected

during an interim assessment of RT response (3). However, it is extremely difficult to determine using imaging whether a neck LN metastasis after RT has a residual tumour because of oedema and inflammation in the surrounding tissues. One study reported that as many as 87.5% of patients diagnosed with residual tumours after RT by imaging did not have tumours on pathological examination of salvage ND specimens (4). Many previous studies have compared only the reduction in the size of neck LNs after RT, as evaluated by computed tomography (CT), with the histopathological findings of salvage ND specimens (4-7). In the present study, we aimed to investigate which tumour parameters on imaging best correlated with the presence or absence of residual tumour in patients with head and neck cancer. To this end, we evaluated changes in CT findings of neck LN metastases before and after RT, assessing not only the size but also various qualitative parameters, and compared them with the histopathological results of salvage ND specimens.

Patients and Methods

Patients and specimens. A total of 23 patients with biopsy-confirmed head and neck cancer were included in the study. RT was initiated between May 2010 and December 2018, and CT was performed before and after completion of RT. During salvage ND, we removed and examined a total of 50 LNs that were classified as suspicious for residual or recurrent neck metastasis by CT after RT.

This study was retrospective and informed consent was obtained from all patients and the study was performed in accordance with the Declaration of Helsinki.

Evaluation of lymph nodes by CT before and after RT. LNs were evaluated before RT on axial images of contrast-enhanced CT with a slice thickness of ≤ 5 mm using the Synapse Picture Archiving and Communication System viewer (Fuji Medical Systems, Tokyo, Japan). Suspected metastases were defined as the presence of (i) target LNs with a short axis of ≥ 15 mm according to the Response Evaluation Criteria in Solid Tumors (8), (ii) LNs with a long-to-short axis ratio of < 2 according to previous reports (9), or (iii)

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Key Words: Computed tomography, head and neck cancer, histopathology, lymph node metastasis.

presence of internal features such as necrosis, cystic lesion, and extracapsular spread (9-11). The diagnosis was made by experienced radiologists. After RT, size measurements on neck LNs suspicious for residual or recurrent metastasis (*i.e.* short axis, long axis, and long-to-short axis ratio) were evaluated on CT images taken before ND. For LNs with metastasis suspected before RT, the size was measured before and after RT. In addition, the same radiologists diagnosed the presence of changes after RT that were not observed before RT, such as obscuration of the margins, internal necrosis, calcification, and strong contrast enhancement.

Radiation therapy. All patients were treated with three-dimensional conformal RT with 4-MV photon beams. The initial radiation field included not only the gross tumour volume of the primary site but also the involved or regional LN levels. The radiation dose was 2 Gy per fraction per day. A radical radiation dose of 66 Gy was administered to 20 patients. Two patients received a total preoperative radiation dose of 40 Gy. In one patient, the therapeutic strategy was changed to surgery because of insufficient response to RT after a total dose of 26 Gy.

Concurrent chemotherapy regimens. The most common regimen of systemic chemotherapy administered in combination with RT was docetaxel, cisplatin, and 5-fluorouracil in 14 patients (60.9%), followed by cisplatin alone (13.0%), cetuximab alone (13.0%), and a docetaxel-based regimen (13.0%) in three patients each.

Comparison of lymph nodes by histopathology and imaging. Surgical photographs and histology sections of excised LNs were reviewed by experienced pathologists and compared with CT images. The radiologists and pathologists ensured that the LNs evaluated radiographically and histopathologically were the same.

Statistical analysis. SPSS version 21.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Univariate analysis with the Mann-Whitney *U*-test was performed to evaluate associations between LN size measured on CT images pre- and post-RT and histopathologically confirmed residual tumours after ND. Associations between size reduction (relative to the median) or new changes after RT and histopathologically confirmed residual tumours after ND were evaluated by univariate analysis with Pearson's chi-squared test and by multivariate analysis with simultaneous logistic regression. A *p*-value of less than 0.05 was considered statistically significant.

Results

Clinicopathological characteristics. The characteristics of the 23 patients are summarised in Table I. A total of 21 men and two women were included, and the median age at the start of RT was 61 (range=47 to 72) years. The most common primary tumour site was the oropharynx, followed by the hypopharynx. Primary tumour pathology included squamous cell carcinoma in 21 patients, malignant neoplasm only in one patient, and carcinoma with neuroendocrine differentiation in one patient. Post-RT CT of LNs with suspected residual or recurrent metastasis was performed at a median of 45 (range=1 to 664) days after completion of

Table I. *Clinicopathological characteristics of the patients.*

Variable		Value
Age, years	Median (range)	61 (47-72)
	Male	21 (91.3%)
	Female	2 (8.7%)
Primary tumour site	Nasopharynx	2 (8.7%)
	Oropharynx	9 (39.1%)
	Hypopharynx	7 (30.4%)
	Larynx	2 (8.7%)
	Oral cavity	2 (8.7%)
	Unknown	1 (4.4%)
Chemotherapy regimen	TPF	14 (60.9%)
	Cisplatin only	3 (13.0%)
	Cetuximab only	3 (13.0%)
	Docetaxel-based	3 (13.0%)
New changes in LN after RT*	Median reduction, short axis (range), mm	5.05 (-15.8-15.8)
	Median reduction, long axis (range), mm	5.75 (-17.1-28.3)
	Obscuration of the margins	8 (16.0%)
	Internal necrosis	10 (20.0%)
	Calcification	8 (16.0%)
	Strong contrast enhancement	6 (12.0%)
	Histopathological residual tumour in LN*	Yes
No	31 (62.0%)	

TPF: Docetaxel, cisplatin, and 5-fluorouracil; LN: lymph node; RT: radiation therapy *Percentage of the 50 LNs collected.

RT. Histopathological examination of the 50 ND specimens revealed 19 LNs with residual tumour.

Lymph node size. In the LNs without histopathologically confirmed residual tumour, the median short and long axes on CT images before RT were 15.2 (range=7.1 to 38.1) mm and 19.4 (range=8.6 to 56.6) mm, respectively, with a long-to-short axis ratio of 1.32 (range=1.01 to 1.75). In the same LNs, the median short and long axes on CT images after RT (performed before ND) were 6.5 (range=3.0 to 49.1) mm and 10.0 (range=5.1 to 57.5), respectively, with a long-to-short axis ratio of 1.42 (range=1.01 to 2.65) mm.

In the LNs with histopathologically confirmed residual tumour, the median short and long axes before RT were 10.8 (range=7.6 to 31.1) mm and 14.7 (range=9.0 to 41.6) mm, respectively, with a long-to-short axis ratio of 1.34 (range=1.03 to 1.74). In the same LNs, the median short and long axes after RT (before ND) were 11.6 mm (range=4.4 to 24.8) and 14.6 mm (range=6.0 to 30.0), respectively, with a long-to-short axis ratio of 1.32 (range=1.00 to 1.70). Taking all 50 LNs together, the median size reduction after RT was 5.05 mm (range=-15.8-15.8) for the short axis and 5.75 mm (range=-17.1-28.3) for the long axis (Table I).

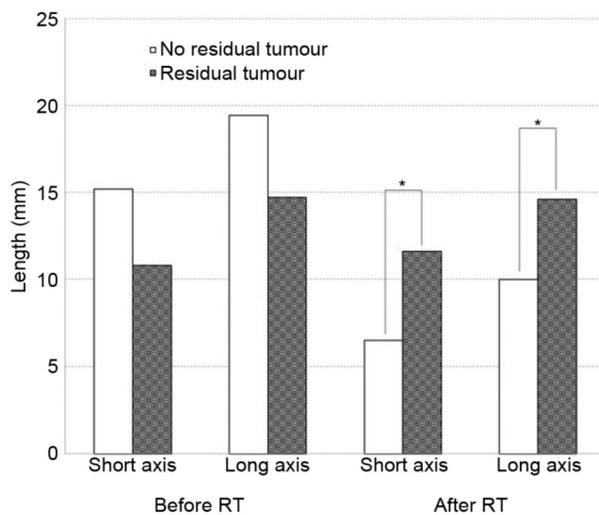


Figure 1. Lymph node size comparison between patients. Lymph node sizes were compared between patients with and without residual tumour before and after radiation therapy (RT). *Significantly different at $p=0.007$ (short axis) and $p=0.022$ (long axis).

The short and long axes of LNs measured after RT were significantly longer for LNs with residual tumour compared with those without residual tumour (Figure 1). However, there were no significant associations between the pre-RT axis lengths or axis ratio and the presence of residual tumours.

New changes in LNs detected after RT. Univariate analysis showed that residual tumours were found significantly more often in LNs with a poor response to RT (*i.e.* <median size reduction for long and short axes) and in those with obscured margins after RT (Table II). However, only the association between residual tumour and obscuration of the margins remained significant by multivariate analysis (Figure 2 and Table II). There were no significant correlations between the other new changes after RT (internal necrosis, calcification, strong contrast enhancement) and the presence of residual tumours.

Discussion

Numerous studies have examined LN metastasis from head and neck cancer by CT, mainly because contrast-enhanced CT is simple and can be performed at most institutions. In recent years, more imaging studies of residual tumours after RT have employed magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography (PET) (12, 13). However, CT is still the standard imaging modality because it requires a shorter scanning time and is less affected by motion artifacts compared with MRI, and CT is less expensive to perform than PET (14).

Table II. Univariate and multivariate analyses of the association between new changes after radiation therapy and histopathologically confirmed residual tumours.

New changes after RT	Univariate analysis	Multivariate analysis		
	<i>p</i> -Value	OR	95% CI	<i>p</i> -Value
Reduction in the short axis <Median vs. ≥median	0.041	0.279	0.029-2.731	0.273
Reduction in the long axis <Median vs. ≥median	0.041	0.710	0.087-5.803	0.749
Obscuration of the margins Yes vs. no	0.019	14.125	1.761-113.296	0.013
Internal necrosis Yes vs. no	0.382	2.304	0.431-12.318	0.329
Calcification Yes vs. no	0.119	1.815	0.269-12.258	0.541
Strong contrast enhancement Yes vs. no	0.123	6.638	0.794-55.466	0.081

CI: Confidence interval; RT: radiation therapy. Bold values indicate statistical significance.

In the present study, we examined the size of LNs both before and after RT. Some studies have suggested that LNs with suspected metastasis have a long axis (>10 mm and the jugulodigastric LN 15 mm) (9), or both short and long axes on pretreatment CT images were significantly greater for LNs with metastasis compared with those without metastasis (15). Other reports indicated that metastasis is more likely to be suspected in essentially spherical LNs (*i.e.* those with a long-to-short axis ratio of <2) (9, 15). In our patients, we detected no correlation between the LN size on CT pre-RT and the presence of residual tumours on ND, whereas both the short and long axes were significantly longer in LNs with residual tumours on the CT post-RT. These results suggest that LN size measurements after RT, rather than before, more accurately reflect the presence or absence of residual tumours on ND. These results have ramifications for patients who will receive RT in the future.

It is extremely difficult to determine whether post-RT tumours are actually residual tumours by imaging because of oedema and inflammation in the surrounding tissues. The sensitivity of CT for the detection of residual tumours after RT has been reported to range from 50% to 86% at primary sites (13, 14, 16). There are few reports on the qualitative evaluation of LN metastasis after RT. Studies evaluating focal lucency, focal enhancement, and other focal abnormalities as indicators of residual tumours have reported positive predictive values for the presence and absence of focal heterogeneity of 36-46% and 29%, respectively (17, 18). These qualitative evaluations were performed only with CT images taken before or after RT.

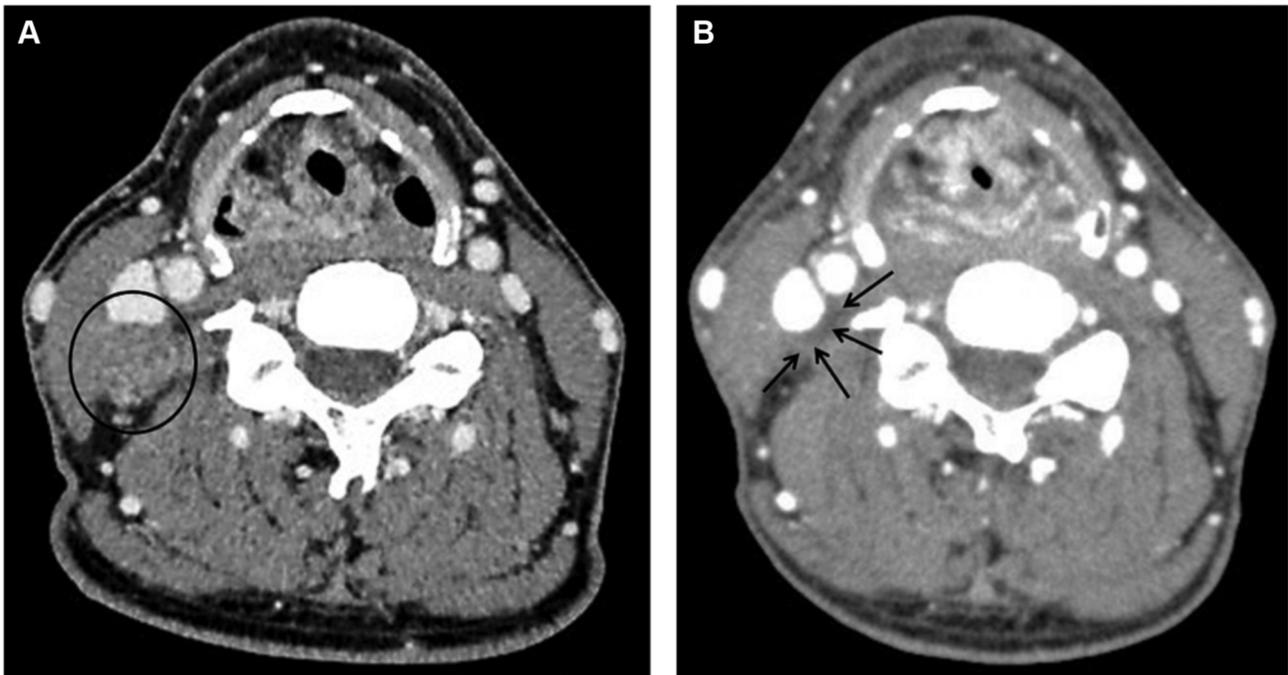


Figure 2. Histopathological residual tumours after salvage neck dissection. Representative contrast-enhanced computed tomographic images before (A) and after (B) radiotherapy, showing obscure margins (arrows) that were not present before radiotherapy.

The present study is the first qualitatively to evaluate new changes, such as obscuration of the margins, observed on CT images after RT but not before RT. In our patients, residual tumours were significantly more common in LNs with obscured margins after RT. Such obscuration may reflect new histopathological extracapsular spread of LN metastasis resistant to RT. While extracapsular spread of LN metastasis is a known factor for poor prognosis (19, 20), residual tumours after RT, like those observed in the present study, may also predict poor prognosis. The diagnosis of extracapsular spread is not always easy to make by CT, and its positive predictive value has been reported to range from 71% to 84% (21). We plan to continue accumulating cases and to conduct a histopathological study to determine the correlation between LNs without residual tumours and the presence of new obscuration of the margins and extracapsular spread after RT. As well as quantitative findings, such as the size, a new finding of obscured margins after post-RT CT images may improve the detection of residual tumour in patients with suspected residual or recurrent LN metastasis.

Conflicts of Interest

Drs. Ishibashi, Maebayashi, Nishimaki and Okada declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

NI collected the patient data and treated the patients and was a major contributor to writing the article. HN reviewed the excised LNs. TM and MO treated the patients. All Authors read and approved the final article.

Acknowledgements

The Authors thank Anne M. O'Rourke, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this article and helping to draft the abstract.

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Received April 17, 2020

Revised May 1, 2020

Accepted May 6, 2020