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Evaluation of Nodal Response after Intra-arterial Chemoradiation

for Node-Positive Head and Neck Cancer

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Running title: Nodal evaluation after RADPLAT

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INTRODUCTION

Concurrent chemoradiation (CCRT) is the current standard treatment for both advanced unresectable head and neck squamous cell carcinomas (HNSCC) and resectable HNSCC for the purpose of preserving organ functions [1-3]. CCRT has also been shown to be effective for the treatment of nodal metastasis, therefore planned neck dissection (ND) for all node positive (N+) HNSCC patients who undergo CCRT is not considered feasible [4].

It has been showed that superselective intra-arterial infusion of cisplatin and concomitant radiotherapy (RADPLAT) has proved a promising treatment. RADPLAT efficacy of primary sites is high, and RADPLAT followed by planned ND is highly effective for controlling regional disease [5, 6].

The traditional approach of planned ND for all N+ HNSCC patients have been becoming obsolete. However, it is very difficult to evaluate the presence or absence of nodal disease after therapy. Some patients show late failure of disease even if they are regarded as clinical complete response (CR). Therefore, an accurate evaluation of the treatment response after therapy is required, although few studies of nodal evaluation and criteria after CCRT have been reported. The current study therefore aimed to evaluate the accuracy and criteria of nodal response post-RADPLAT, and to determine whether a “wait

and see” policy for N+ HNSCC patients undergoing RADPLAT is acceptable.

PATIENTS AND METHODS

Patients. We retrospectively analyzed 65 patients (59 men and six women) with N+ HNSCC who underwent RADPLAT in Hokkaido University Hospital, Japan between October 1999 and April 2010.

Median age was 59 years (range, 41–74 years; mean, 58.3 years). The follow up length of surviving

patients ranged from six to 127.2 months (median 31.2 months, mean 39.6 months). Primary sites were:

12 paranasal sinus (10 maxillary sinus, two ethmoid sinus), 18 oropharynx, 27 hypopharynx, five larynx,

two oral cavity, and one parotid gland.

(Table 1.)

T and N classification according to the American Joint Committee on Cancer (AJCC) staging system 7th edition 2010 is shown in Table 2. Fifteen patients were diagnosed with N1, 35 with N2b, 13 with N2c, and two with N3.

(Table 2.)

Radiotherapy. The irradiation plan of 2006–2010 was 40 Gy in 20 fractions of 2 Gy over four weeks for the primary site and all nodal areas, immediately followed by a boost of 30 Gy in 15 fractions to the primary cancer and metastatic nodal area over additional three weeks (total dose, 70 Gy). Between 1999–2005, all nodal areas and the primary site were irradiated with 40 Gy in 16 fractions of 2.5 Gy over four weeks, with a boost irradiation of 25 Gy in 10 fractions to the primary tumor and metastatic nodal area over additional 2.5 weeks (total dose, 65 Gy).

Chemotherapy. Chemotherapy comprised 100–120 mg/m² superselective intra-arterial cisplatin administered a median of four times weekly (range, 2–5 times, mean 3.7 times). Simultaneously, sodium thiosulfate was administered intravenously (24 g/body) to provide effective cisplatin neutralization. In cases with large node metastasis, about 10 or 15% of the total cisplatin dose was selectively administered to the metastatic node.

Evaluation of nodal metastasis. Pre-treatment nodal metastasis was evaluated by computed tomography (CT) and/or magnetic resonance imaging (MRI). Nodal response was assessed by CT scan 4-8 weeks after completion of initial therapy. A radiographic complete response (rCR) was recorded in the absence of focal abnormalities and if the maximum diameter of the metastatic node was less than 15 mm. In this

criterion, focal abnormality included lucency, enhancement and calcification. We defined this as “criterion 1” [7]. If residual node metastasis was clear, we performed early salvage ND. For patients assessed as rCR, we practiced a “wait and see” policy. We analyzed sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio, and negative likelihood ratio of CT evaluation, to determine the efficiency of this criterion.

Retrospectively, we applied another criterion using a different nodal size for different levels of the neck. In this criterion, rCR was recorded in the absence of focal abnormalities and if the minimum diameter of metastatic nodes was less than 7 mm in level II and if the minimum diameter of metastatic nodes in the rest of the neck was less than 6 mm. We defined this as “criterion 2” [8]. And we also analyzed the sensitivity, specificity, NPV, PPV, positive likelihood ratio, and negative likelihood ratio of this criterion.

Patients were usually monitored monthly for recurrence in the first year, every couple of months in the second year, every 6 or 12 months thereafter ~~until death or data censoring~~. CT scans were routinely performed once every three months in the first year, every 6 or 12 months thereafter. If lymph node metastases enlarged, patients with resectable neck diseases were referred for dissection.

When there were no tumor cells found in a surgical specimen from ND, a pathological complete response (pCR) was recorded and nodal metastases of these cases were defined as be controlled by RADPLAT alone.

Statistics. The Kaplan-Meier method was applied for nodal control rate using JMP 5.0.1J statistical software (SAS Institute, Cary, NC). Time of interest was duration from the start of treatment to that of regional failure. The log-rank test was used to compare two group control rates, and McNemar's test was used to compare two different criteria.

RESULTS

Forty-four patients (67.7%) did not show nodal recurrence. Two patients (3.1%) died of HNSCC without having undergone ND. Nineteen patients (29.2%) underwent ND at a median of 15.4 weeks (range 6.9–60.4 weeks, mean 18.8 weeks) after the completion of RADPLAT.

The 5-year nodal control rate of overall treatment (including salvage by ND) was 87.1%. The 5-year nodal control rate of RADPLAT alone (not including salvage by ND) was 75.3%. According to N-classification, 5-year nodal control rates of RADPLAT alone were 80% for N1 (n=15), 75.1% for

N2b-c (n=48), and 50% for N3 (n=2).

In the 32 patients who received cisplatin administration only to the primary site, the 5-year nodal control rate of RADPLAT alone was 78.1%; this rate was 72.3% in the 23 patients who received cisplatin administration to both primary and regional sites. There was no significant difference between these two groups ($p=0.74$, log-rank test).

Analysis using Criterion 1. According to criterion 1, 52 patients were considered to be rCR. Ten of these 52 patients underwent ND. Of these, seven patients underwent planned ND, and three patients underwent late salvage ND because of nodal re-enlargement. In two of seven patients undergoing planned ND, surgical specimens revealed residual pathological nodal metastases. In surgical specimens of all three patients undergoing late salvage ND, viable tumor cells were observed. Another patient suffered a re-enlarged metastatic node 28 weeks after initial treatment, but ND was not performed because of inoperable primary site recurrence. These six patients were false negative cases.

Thirteen patients were not considered to be rCR. Of these, four did not undergo ND because of one patient refused surgery and three patients were not indicated ND due to simultaneous unresectable primary disease (one patient) and lung metastases (two patients). However, metastatic node of a patient

who refused ND disappeared thereafter. In the remaining three patients, nodes did not re-enlarge until they died (median 19 months, range 18-22 months, after completion of RADPLAT). These four patients were considered false positive cases. Sensitivity of this criterion was 60%, specificity was 92%, NPV was 88.5%, PPV was 69.2%, positive likelihood ratio was 7.50, and negative likelihood ratio was 0.44.

Analysis using Criterion 2. According to criterion 2, 42 patients were considered to be rCR. Seven patients of these 42 patients underwent ND (five planned ND, and two late salvage ND). In three of these seven patients undergoing ND, surgical specimens revealed pathological nodal metastases. Another patient suffered a re-enlarged metastatic node, but ND was not performed because of primary site recurrence. These four patients were false negative cases.

Twenty-three patients were not considered to be rCR. Of these, 11 did not undergo ND, so. However, nodal re-enlargement was not recognized in all 11 patients. Another patient underwent ND, and pathological findings revealed no viable metastatic cells. These 12 patients were false positive cases. Sensitivity of this criterion was 73.3%, specificity was 76%, NPV was 90.5%, PPV was 47.8%, positive likelihood ratio was 3.06, and negative likelihood ratio was 0.35.

(Table 3. Table 4.)

Table 5 shows the difference between criteria 1 and 2, which was statistically significant by McNemar's test ($p=0.0016$). Ten patients evaluated as rCR by criterion 1 were not using criterion 2.

(Table 5.)

Fig.1 Patient with Oropharyngeal cancer(T4aN2b) undergoing RADPLAT

Fig.2 Patient with Oropharyngeal cancer(T2N2b) undergoing RADPLAT and early salvage ND

Fig.3 Patient with Hypopharyngeal cancer(T4aN2c) undergoing RADPLAT

DISCUSSION

Adequate radiologic evaluation for responses of primary tumor and metastatic regional lymph nodes after CCRT is important. It was reported that MRI measurement of primary lesion 6-8 weeks after RADPLAT was very useful [9]. van den Broek, et al. reported that patients with focal masses <10mm could omit biopsy under general anesthesia. These criteria using MRI are considered to be effective for primary tumor evaluation. However failure of the CCRT to control disease within regional lymph nodes is an indication to perform salvage ND. It is important to find early failure not to miss the chance of surgical salvage. Therefore accurate evaluation during the early post-CCRT period is needed.

A previous study reported that defined rCR using the criterion of no focal abnormality and a maximum diameter of less than 15 mm after radiation therapy (RT), found the NPV to be 94% [7]. Ojiri, et al. applied the same criterion to evaluate nodal response for post-RT patients and reported an NPV accuracy of 96.6–100%; it therefore appeared feasible to decide whether to perform salvage ND using such criteria [10]. When we applied this criterion, the NPV was 88.5%, PPV was 69.2%, and the positive likelihood ratio was 7.50, which is comparable to recent reports.

An ultrasonography (US) study used an alternative criterion of different nodal sizes for different levels of the neck [8]. This suggested that a minimal axial diameter of 7 mm in level II nodes and 6 mm for the rest of the neck represents a reasonable compromise between sensitivity and specificity (sensitivity, 80%; specificity, 59%; NPV, 75%; PPV, 66%). This was deemed suitable for CT, and regarded as useful in the evaluation of nodal response after CCRT and RADPLAT. We applied this criterion after RADPLAT, and achieved an NPV of 90.5%, a PPV of 47.8%, and a positive likelihood ratio of 3.06.

Our study used two criteria to evaluate rCR and, consequently, observed a significant difference between criteria 1 and 2 using McNemar's test ($p=0.0016$), although the NPV of the two

criteria compared favorably. In terms of positive likelihood ratios, criterion 1 had the advantage of reliability over criterion 2 and was much easier to apply. As so few studies of nodal evaluation and criteria after CCRT have been reported, the current investigation might assist in the definition of rCR after CCRT.

Some reports have favored the use of positron emission tomography (PET) and PET-CT in assessing treatment response (giving a NPV between 94-100%) [11-13]. However the appropriate time for PET and PET-CT was under consideration. Yao, et al. recommended PET study was best obtained between 12 and 20 weeks after completion of treatment [12], but it was possible that 12-20 weeks after initial treatment was too late to perform early salvage surgery. However Malone, et al. have indicated that PET-CT done 8 weeks post-treatment has a reliable negative predictive value, which offers an alternative to relying on CT scans alone [13].

(Table 6.)

Using US guided fine needle aspiration cytology, it was reported that specificity was low [14]. However, doppler blood flow and elastography of US were shown to be effective evaluators of nodal response after initial treatment [15], which offered the advantages of convenience and minimal invasion.

Although it will be necessary to reduce disparities in diagnostic levels between testers, the role of US is expected to take on greater importance in the future.

In recent review, it was reported that planned ND after CCRT was not justified [4]. For patients undergoing RADPLAT, that situation was considered to be same. In our study, the 5-year nodal control rate of RADPLAT alone was high (75.3%). Therefore, the benefits of planned ND were considered to be small. Our study also showed that nodal response assessment of CT after initial treatment was feasible (giving a NPV between 88.5–90.5%), so approved a “wait and see” policy for RADPLAT treatment.

CONCLUSIONS

The accuracy of CT evaluation for nodal response post-completion of RADPLAT in the present study was comparable to recent reports, and it appeared feasible to decide whether to perform salvage ND following CT evaluation of nodal response. For those patients evaluated as rCR after RADPLAT, the “wait and see” policy was deemed acceptable. In addition, we recommend applying criterion 1 (less than 15mm maximum diameter and no focal abnormality were defined as rCR) for CT evaluation after completion of RADPLAT.

Conflict of Interest. None.

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FIGURE TITLES AND LEGENDS

Fig.1 Patient with Oropharyngeal cancer(T4aN2b) undergoing RADPLAT

(a)Pre-treatment CT showed metastatic node (30×22mm) in level II

(b)Post-treatment (60days after RADPLAT) CT showed size decreasing node (7×6mm) without focal

abnormality. According to both criteria 1 and 2, this node was defined as rCR. This patient had no nodal

recurrence and survived without disease 14 months after treatment.

Fig.2 Patient with Oropharyngeal cancer(T2N2b) undergoing RADPLAT and early salvage ND

(a)Pre-treatment MRI showed metastatic node (17×16mm) in level II

(b) Post-treatment (40 days after RADPLAT) CT showed size decreasing node (14×14mm) without focal abnormality. According to criterion 1, this node was defined as rCR. According to criterion 2, this node was defined as radiographic N+. Early salvage ND 67 days after RADPLAT revealed pathological N+.

This patient survived without disease 42 months after ND.

Fig.3 Patient with Hypopharyngeal cancer(T4aN2c) undergoing RADPLAT

(a) Pre-treatment CT showed metastatic node (30×17mm) in level II

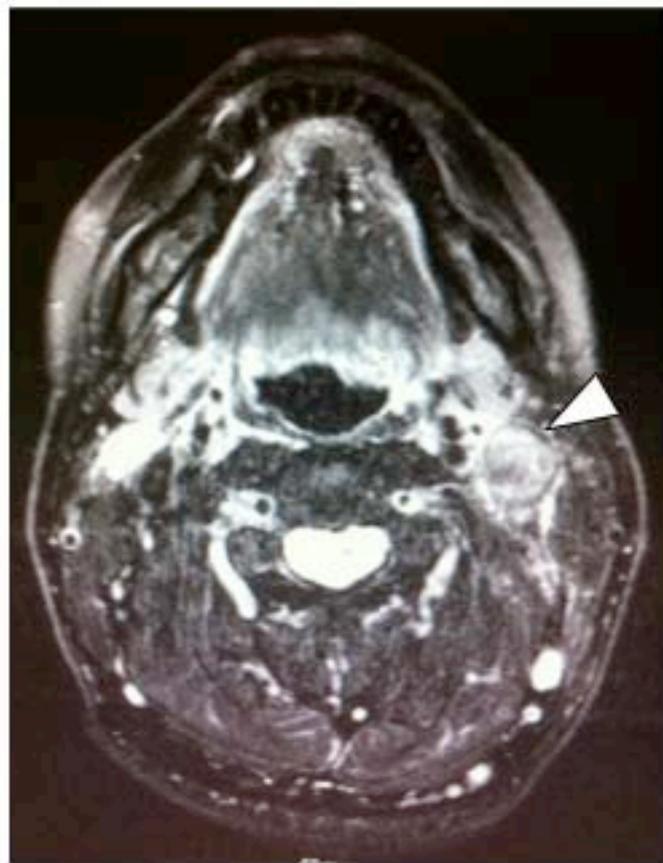
(b) Post-treatment (56 days after RADPLAT) CT showed size decreasing node (20×10mm). According to criteria 1 and 2, this node was defined as radiographic N+. Neck dissection was not performed because of contraindication of general anesthesia. However nodal re-enlargement was not recognized 20 months until he died from lung metastasis . This case was considered to be false positive.



(a)



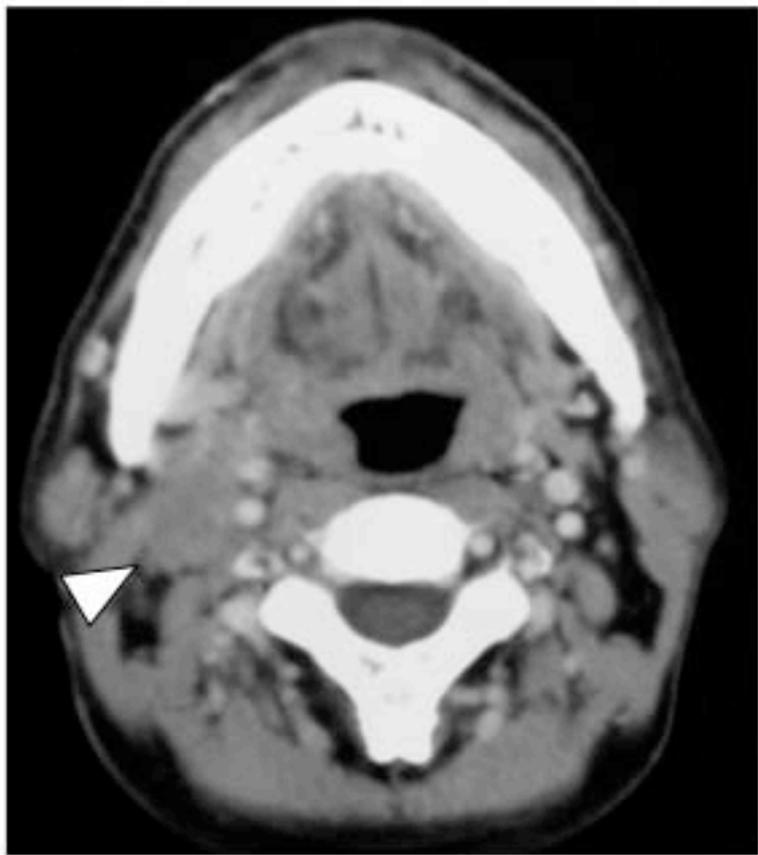
(b)



(a)



(b)



(a)



(b)

Table 1. Patient Demographics

Characteristic	n
Total	65 (100%)
Gender	
Men	59 (91%)
Women	6 (9%)
Age, years	
Median	59
Range	41-74
Follow up length of surviving patients, months	
Median	31.2
Range	6-127.2
Primary site	
Maxillary sinus	10 (15%)
Ethmoid sinus	2 (3%)
Oropharynx	18 (28%)
Hypopharynx	27 (42%)
Larynx	5 (8%)
Oral cavity	2 (3%)
Parotid gland	1 (1%)

Table 2. Distribution by T and N Classification

	No. of Patients					
	N1	N2a	N2b	N2c	N3	Total
T2	2	0	6	0	0	8
T3	6	0	15	1	1	23
T4a	6	0	11	8	0	25
T4b	1	0	3	4	1	9
Total	15	0	35	13	2	65

Table 3. Results of Criteria 1 (a) and 2 (b) for nodal evaluation

(a)

	rN+	rN-	Total
pN+ or regional recurrence +	9	6	15
pN- or regional recurrence -	4	46	50
Total	13	52	65

(b)

	rN+	rN-	Total
pN+ or regional recurrence +	11	4	15
pN- or regional recurrence -	12	38	50
Total	23	42	65

Abbreviations: “rN+ or -” was radiographic node positive or negative.

“pN+ or -” was pathological node positive or negative after neck dissection.

“Criterion 1” defined less than 15mm maximum diameter and no focal abnormality as radiographic node negative.

“Criterion 2” defined less than 7mm minimum diameter in level II and less than 6mm minimum diameter in rest of neck ,and no focal abnormality as radiographic node negative.

Table 4. Comparison of accuracy between Criteria 1 and 2

	Criterion 1	Criterion 2
Sensitivity	60%	73.3%
Specificity	92%	76%
Negative Predictive Value	88.5%	90.5%
Positive Predictive Value	69.2%	47.8%
Positive Likelihood Ratio	7.50	3.06
Negative Likelihood Ratio	0.44	0.35

Abbreviations: “Criterion 1” defined less than 15mm maximum diameter and no focal abnormality as radiographic node negative.

“Criterion 2” defined less than 7mm minimum diameter in level II and less than 6mm minimum diameter in rest of neck ,and no focal abnormality as radiographic node negative.

Table 5. Difference between Criteria 1 and 2

		Criterion 1		Total
		rN+	rN-	
Criterion 2	rN+	13	10	23
	rN-	0	42	42
	Total	13	52	65

McNemar's test: p= 0.0016

Abbreviations: "Criterion 1" defined less than 15mm maximum diameter and no focal abnormality as radiographic node negative.

"Criterion 2" defined less than 7mm minimum diameter in level II and less than 6mm minimum diameter in rest of neck ,and no focal abnormality as radiographic node negative as radiographic node negative.

Table 6. Studies assessing the accuracy of various imaging modalities

	Modality	n=	Treatment	Timing	Sensitivity	Specificity	NPV	PPV
van der Putten, et al (2009) [14]	US-FNAC	46	RADPLAT	6-8w	80%	42%	81%	40%
Yao M, et al (2004) [12]	PET	58	IMRT	12-20w	100%	96%	100%	78%
Malone JP, et al (2009) [13]	PET-CT	21	RADPLAT	6-8w	75%	94%	94%	75%
Current study (Criterion 1)	CT	65	RADPLAT	4-8w	60%	92%	88.5%	69.2%

Abbreviations: US-FNAC, ultrasound-guided fine-needle aspiration cytology; PET, positron emission tomography
 CT, computed tomography; IMRT, intensity-modulated radiation treatment
 RADPLAT, superselective intra-arterial infusion of cisplatin and concomitant radiotherapy
 NPV, negative predictive value; PPV, positive predictive value