CANCER DIAGNOSIS & PROGNOSIS
*1*: 165-172 (2021) doi: 10.21873/cdp.10022

# Recurrence of Lymph Node Micrometastases After Radiotherapy for Head and Neck Carcinoma: A Propensity Score-matched Study

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**Abstract.** *Background: The standard irradiation dose to the elective lymph node area (ELNA) in locally patients with advanced head and neck squamous cell carcinoma (LA-HNSCC) to control lymph node micrometastases (LN-MM) has not changed since it was empirically determined in the 1950s. We investigated the optimal irradiation dose for controlling LN-MM in ELNAs. Patients and Methods: The pattern of recurrence of LA-HNSCC was retrospectively evaluated in patients who underwent concurrent chemoradiotherapy with cisplatin or radiation therapy alone. Results: In total, 162 patients were enrolled. The median observation period was 34 months. No recurrence was found in ELNAs. After propensity score matching, a cisplatin dose of ≥200 mg/m$^2$ yielded a significantly higher overall survival rate (p≤0.001) and locoregional control rate (p=0.034) than did a dose of <100 mg/m$^2$. Conclusion: CCRT with a cisplatin dose of ≥200 mg/m$^2$ can reduce the irradiation dose to 40-44 Gy at 2 Gy per fraction to control LN-MM.*



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*Key Words:* Locally advanced head and neck squamous cell carcinoma, radiotherapy, cisplatin, elective lymph node area, patterns of recurrence.



The head and neck are involved in important functions, including breathing, chewing, swallowing, taste, hearing, and facial expression (1). Accordingly, damage to the head and neck region directly affects an individual's quality of life. Thus, for patients with head and neck squamous cell carcinoma (HNSCC), oncologists need to maintain a balance between cure and quality of life (2). Lymph node metastases are common in patients with HNSCC, with lymph node micrometastases (LN-MM) occurring in 12-50% of cN0 cases (3-5). LN-MM are occult neck lymph metastases. The more frequently used diagnostic modalities for HNSCC are computed tomography (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose positron-emission tomography-CT (PET-CT), ultrasonography, ultrasound-guided fine-needle aspiration cytology (US-FNAC), and sentinel node biopsy (6).

Definitive treatment of HNSCC requires the control of clinically false-negative LN-MM. Concurrent chemoradiotherapy (CCRT) or radiation therapy (RT) alone without surgery is recommended for locally advanced disease (LA-HNSCC). The current CCRT strategy for LA-HNSCC requires an irradiation dose of 44-50 Gy at 2 Gy per fraction to the elective lymph node area (ELNA) to control LN-MM (7). Cisplatin has been reported to be superior to cetuximab as the chemotherapeutic agent in CCRT (8-9). At present, high-dose cisplatin is the standard chemotherapeutic strategy in CCRT for LA-HNSCC.

The dose volume of the pharyngeal constrictor muscles, spinal cord, thyroid, salivary glands, mandible, and skin affects the incidence and severity of RT-related side-effects such as swallowing dysfunction, myelitis, hypothyroidism, dry mouth, osteonecrosis, skin hardening, and ulcers. The dose–volume thresholds of late toxicity for these organs are at 40-50 Gy (10-15). Despite novel RT techniques, the irradiation dose to the ELNA has not changed since it was empirically

determined in the 1950s, when the diagnosis of cervical lymph node metastasis relied on palpation and visual inspection (16-17). However, the development of CT, MRI, US-FNAC, and PET-CT has influenced decisions on treatment policy. The combination of these modalities improves the sensitivity of diagnosing lymph node metastasis in ELNAs (18-20). With respect to treatment, lymph node metastases are irradiated with 66-70 Gy at 2 Gy per fraction. Compared to the 1950s, the modern modality has improved the accuracy of diagnosing lymph node metastases. Therefore, the proportion of patients with LN-MM in the ELNA is considered to have decreased. The purpose of this study was to investigate the optimal irradiation dose for LN-MM control in ELNAs.

## Patients and Methods

*Study design and patients*. This retrospective cohort study was approved by The Tohoku University Graduate School of Medicine Ethics Review Committee (Approval number: 2019-1-130; date: May 27, 2019) and by The Miyagi Cancer Center Ethics Review Committee (approval number: 2019-034; date: June 21, 2019). As opt-out, patients were given the opportunity to refuse to be included in this study. The detailed information on this study can be found at the following sites https://www.med.tohoku.ac.jp/public/documents/2019.html and https://www.miyagi-pho.jp/mcc/medical/iinkai/rinri/kadai/index.html (retrieved on October 12, 2020). The study was conducted according to the tenets of the 1975 Declaration of Helsinki as revised in 1983.

We evaluated patients with LA-HNSCC who were treated between January 1, 2008 and December 31, 2017 at Tohoku university hospital or Miyagi Cancer Center, as two high-volume centers in Japan. The patients received RT alone or CCRT with high-dose cisplatin. The inclusion criteria were (i) Age older than 20 years at the start of treatment; (ii) an Eastern Cooperative Oncology Group performance status score of 0-1; (iii) primary malignancy of oropharyngeal, hypopharyngeal, or laryngeal cancer; and (iv) a histological type of squamous cell carcinoma for all primary sites. The exclusion criteria were (i) Double cancer along with LA-HNSCC; (ii) a previous history of malignant disease; (iii) previous history of endoscopic surgery or neoadjuvant or adjuvant chemotherapy for LA-HNSCC prior to CCRT; (iv) distant metastasis; (v) inability to complete treatment; and (vi) enrollment in other clinical trials.

*Diagnosis and human papillomavirus (HPV) status of oropharyngeal cancer.* The patients were diagnosed with cT3-4 or cN1-3 disease, equal to cStage III-IV according to the Seventh Edition of Union for International Cancer Control TNM classification via laryngoscopy, CT, MRI, US-FNAC, and PET-CT (21). For assessment of HPV status of oropharyngeal cancer, US-FNAC pathology results prior to CCRT were reviewed. Cases with unknown HPV status were re-evaluated by restaining if pathological specimens were available at the time of this study. The staining method and positive/negative criteria were based on the discretion of the consulting pathologist.

*Treatment. Radiotherapy:* All patients were fixed with a thermoplastic mask covering the head, neck, and shoulders. The radiation oncologist designated the gross tumor volume (GTV) in the RT planning CT. The primary site was designated as GTVp, and lymph node metastasis in the ELNA was designated as GTVn. The clinical target volume (CTV) covered the pathological spread of the tumor. CTV of the primary site was designated as CTVp. A 1- to 2-cm margin from the GTVp was added to the CTVp, considering the anatomical structure as a barrier to cancer cell invasion. CTV of lymph node metastasis in the ELNA was designated as CTVn. A 0.5- to 1-cm margin from GTVn was added to CTVn considering the anatomical structure as a barrier to cancer cell invasion.

The ELNA was designated as CTVsubclinical. CTVsubclinical included cervical lymph node levels II, III, IVa, IVb, Va, Vb, Vc, and VIIa based on delineation of the neck node levels for head and neck tumors updated in 2013 (22). Levels Ib, VIb, and VIIb were included under CTVsubclinical at the discretion of the attending radiation oncologist. RT was administered in two steps in all cases. CTV in the first half was calculated as CTVinitial=CTVp+CTVn+CTVsubclinical. CTV in the second half was set again by re-imaging with RT planning CT and was defined as CTVboost+CTVp+CTVn.

The planning target volume (PTV) in the first half of RT was calculated as PTVinitial=CTVinitial+0.5-0.7 cm. PTV in the second half was calculated as PTVboost=CTVboost+0.5-0.7 cm. PTVinitial was irradiated with a total dose of 40-44 Gy at 2 Gy per fraction. Subsequently, PTVboost was irradiated with a total dose of 70 Gy at 2 Gy per fraction. For RT alone, irradiation in the second half of RT was performed at a dose of up to 69.5 Gy at 1.5 Gy per fraction with accelerated hyperfractionation at the discretion of the attending radiation oncologist. The indication for RT alone was selected according to the attending physician.

*Chemotherapy:* High-dose cisplatin at a dose of 100 mg/m$^2$ every 3 weeks was used for CCRT. Cisplatin was given to inpatients for up to 3 cycles during RT. Attending physicians adjusted the dose of cisplatin and considered postponing before each course. Cisplatin was not given to inpatients after RT.

*Recurrence assessment*. Physical examination and nasopharyngeal laryngoscopy were used to evaluate recurrence. Recurrence was recorded only at the first relapse. Local recurrence was evaluated using endoscopic and pathological biopsy results. Recurrence of lymph node metastasis and distant metastasis was determined using CT, PET-CT or MRI evaluated by a radiation oncologist with 4 years of experience and a diagnostic radiologist with more than 10 years' experience in interpreting images of the head and neck region.

In the case of a regional recurrence, the recurrence was contoured on CT and registered with the initial pretreatment RT planning CT. Registration was performed automatically using the Eclipse treatment planning system (Varian Medical Systems Inc., Palo Alto, CA, USA). The exact location of recurrence was determined using the method described by Dawson *et al*. (23). Recurrence was classified as follows: i) In-field, ≥95% of the recurrence volume was within the 95% isodose; ii) marginal, 20-95% of the recurrence volume was within the 95% isodose; or iii) outside, <20% of recurrence volume was within the 95% isodose. Any recurrence outside the PTVinitial was defined as distant metastasis.

*Follow-up*. Patients were evaluated at least once weekly by radiologists or head and neck surgeons during the treatment period. Patients were followed up every 1-2 months in the first year, every 3-4 months in the second year, every 4-6 months in the third to fifth year, and then annually thereafter, if desired. Furthermore, a CT was

Table I. *Patient characteristics (n=162).*

| Characteristic | | Value |
|---|---|---|
| Age, years | Median (IQR) | 65.5 (60-71) |
| Gender, n (%) | Male | 147 (90.7) |
| Measured CCr, n (%) | ≥60 ml/min | 120 (74.0) |
| Tumor site, n (%) | Larynx | 30 (18.5) |
| | Hypopharynx | 52 (32.1) |
| | Oropharynx | 80 (49.4) |
| HPV status of the oropharynx, n (%) | Positive | 42 (52.5†) |
| | Negative | 18 (22.5†) |
| | Unknown | 20 (25.0†) |
| UICC clinical stage, n (%) | III | 47 (29.0) |
| | IVA | 104 (64.2) |
| | IVB | 11 (6.8) |
| cT-Stage, n (%) | T1 | 16 (9.3) |
| | T2 | 57 (35.2) |
| | T3 | 60 (37.0) |
| | T4a | 24 (15.4) |
| | T4b | 5 (3.1) |
| cN-Stage, n (%) | N0 | 25 (15.4) |
| | N1 | 28 (17.3) |
| | N2a | 5 (3.1) |
| | N2b | 58 (35.8) |
| | N2c | 39 (24.1) |
| | N3 | 7 (4.3) |

CCr: Creatinine clearance; HPV: human papillomavirus; IQR: interquartile range; UICC: Union for International Cancer Control 21). †As a percentage of all patients with oropharyngeal cancer.

Table II. *Details of study treatment (n=162).*

| | | Value |
|---|---|---|
| Radiation technique, n (%) | 3DCRT | 103 (63.6) |
| | IMRT | 59 (36.4) |
| Prescribed dose for PTVinitial, n (%) | 44 Gy‡ | 79 (47.8) |
| | 40 Gy‡ | 83 (52.2) |
| Prescribed dose for PTVboost, n (%) | 70 Gy‡ | 156 (96.3) |
| | 69.5 Gy§ | 6 (3.7) |
| Cisplatin dose, n (%) | 300 mg/m$^2$ | 47 (29.0) |
| | ≥200, <300 mg/m$^2$ | 56 (34.6) |
| | ≥100, <200 mg/m$^2$ | 29 (17.9) |
| | >0, <100 mg/m$^2$ | 1 (0.6) |
| | 0 | 29 (17.9) |
| Radiation treatment time, n (%) | ≤56 days | 153 (94.4) |
| | >56 days | 9 (5.6) |
| Follow-up time, months | Median (IQR) | 34 (18-56) |

3DCRT: Three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; PTV: planning target volume; IQR: interquartile range. ‡2 Gy per fraction as conventional fractionation; §1.5 Gy per fraction up to 69.5 Gy from second half as accelerated hyperfractionation.

performed every 3-4 months during the first 2 years of follow-up and every 4-6 months in the third to fifth year of follow-up. Additional diagnostic imaging was performed only when recurrence was suspected.

*Statistical analysis*. Pearson's chi-square test and Fisher's exact test were used to verify the association between recurrence and categorical variables. A t-test was used to compare mean values of the two different groups. The propensity score was matched to adjust for patient background characteristics. Nearest neighbor one-to-one matching was used as the matching method. The caliper coefficient was 0.2. Sex, age, tumor site, HPV status of the oropharynx, creatinine clearance (CCr), T-clinical stage, and N-clinical stage were used as cofactors for calculating the propensity score. CCr was not used as a cofactor when calculating the propensity scores using the cisplatin dose because cisplatin dose is correlated with CCr. Cases with unknown HPV status of the oropharynx were excluded from propensity score matching. Overall survival (OS) and local regional control (LRC) were evaluated using the Kaplan–Meier method and compared using the log-rank test. OS was calculated from the starting date of irradiation until death. LRC was calculated from the starting date of irradiation to local recurrence at the primary site and the ELNA. Statistical significance was set at $p<0.05$. Standard mean differences of ≥0.1 represented meaningful differences in covariates between groups. All statistical analyses were performed using JMP® pro v.14.3.0 (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA.

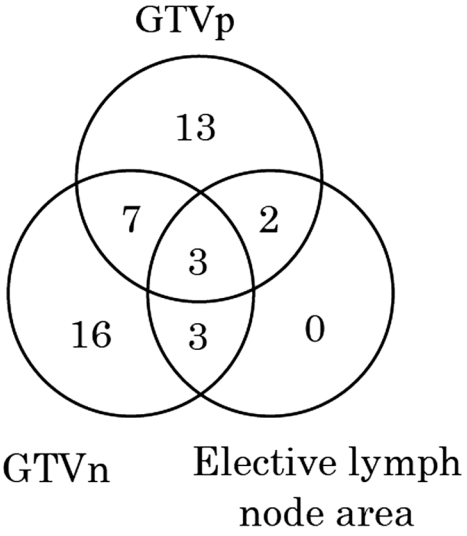


Figure 1. *Recurrence pattern in the local region. No recurrence of lymph node micrometastases in the elective lymph node area was observed. GTVp: Primary gross tumor volume, GTVn: nodal gross tumor volume.*

## Results

*Patient and treatment characteristics*. In total, 162 patients with a median age of 65.5 years (interquartile range=60-71 years) were evaluated. Of them, 30 had laryngeal, 52 hypopharyngeal, and 80 oropharyngeal cancer. The patient characteristics are shown in Table I. With respect to the HPV

Table III. *Cases with recurrence in the elective lymph node area (all male).*

| No. | Age, years | Location of primary | UICC clinical stage, n (%) | RT technique, dose and fractionation for PTVinitial and PTVboost | Total cisplatin, mg/m$^2$ | RTT, days | Initial LNM level | Recurrence pattern |
|---|---|---|---|---|---|---|---|---|
| 1 | 77 | Hypopharynx | cT4bN0 cStage IVb | 3DCRT: PTVinitial: 44 Gy, Cfx PTVboost: 70 Gy, Cfx Field-in-field | 200 | 54 | None | GTVp, VII Right |
| 2 | 66 | Hypopharynx | cT1N2b cStage IVa | 3DCRT: PTVinitial: 44 Gy, Cfx PTVboost: 69.5 Gy AHF Field-in-field | 0 | 48 | II-III Left | GTVp, II Right, Lung |
| 3 | 63 | Larynx | cT2N1 cStage III | 3DCRT: PTVinitial: 40 Gy, Cfx PTVboost: 70 Gy, Cfx | 240 | 63 | II Right | GTVn, IVa Right, |
| 4 | 71 | Oropharynx* | cT2N2b cStage IVa | 3DCRT: PTVinitial: 40 Gy, Cfx PTVboost: 70 Gy, Cfx | 240 | 48 | II Left | GTVp, GTVn, II Left |
| 5 | 73 | Larynx | cT4aN2b cStage IVa | IMRT: PTVinitial: 44 Gy, Cfx PTVboost: 70 Gy, Cfx | 180 | 53 | II Left | GTVn, II Left |
| 6 | 65 | Oropharynx* | cT4aN2c cStage IVa | IMRT: PTVinitial: 40 Gy, Cfx PTVboost: 70 Gy, Cfx | 300 | 50 | II Left, II Right | GTVp, GTVn, II-III Left |
| 7 | 80 | Oropharynx* | cT4aN2c cStage IVa | IMRT: PTVinitial: 40 Gy, Cfx PTVboost: 70 Gy, Cfx | 0 | 50 | II Left, II Right | GTVn, GTVn, VIIb Right |
| 8 | 62 | Hypopharynx | cT3N1 cStage III | IMRT: PTVinitial: 40 Gy, Cfx PTVboost: 70 Gy, Cfx | 300 | 54 | II Right | GTVn, III-IVa Right |

AHF: Accelerated hyperfractionation; Cfx: conventional fractionation (5 fractions per week with 2 Gy); 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; LNM: lymph node metastasis; PTV: planning target volume; RTT: radiation treatment time; UICC: Union for International Cancer Control (21) *Human papillomavirus-negative. The field-in-field is a method of adding a small amount of dose to the irradiation field that shields the high-dose area in the normal irradiation field to obtain the desired uniform dose.

status of the patients with oropharyngeal cancer, 29 patients had unknown HPV status. Nine pathological specimens of unknown HPV status were re-evaluated, of which five were HPV-positive; 42 patients were HPV-positive, 18 were HPV-negative, and 20 still had an unknown HPV status because no pathological specimens were evaluated. Patients with unknown HPV status were excluded from propensity score matching. For stage, 47, 104, and 11 patients had stage III, IVA, and IVB disease, respectively.

All patients received RT to ELNA of both sides. The details of the treatment are shown in Table II. In total, 103 and 59 patients underwent 3D-CRT and intensity-modulated radiotherapy (IMRT), respectively. Radiation techniques were consistently the same for each patient. The CTVinitial dose was 44 Gy in 79 patients and 40 Gy in 83 patients. Six patients received an irradiation dose of up to 69.5 Gy at 1.5 Gy per fraction with accelerated hyperfractionation in the second half of RT. A total of 103 patients received a total cisplatin dose of ≥200 mg/m$^2$, while 30 patients received a total cisplatin dose of <100 mg/m$^2$. The RT treatment time exceeded 56 days in nine cases. The median observation period was 34 months (interquartile range=18-56 months).

*Recurrence and treatment outcomes*. There were 64 patients who developed recurrence. The locoregional recurrence pattern is shown in Figure 1. Locoregional recurrence occurred in 44 patients. Of the 25 GTVp recurrences, 24 were in-field, and one was marginal. Of the 29 GTVn recurrences, 21 were in-field and eight were marginal. All GTVp and GTVn recurrences included the PTVboost area. There were eight cases with ELNA recurrence, all of which were classified as in-field (Table III). There were no patients with LN-MM recurrence in the ELNA without GTVp and

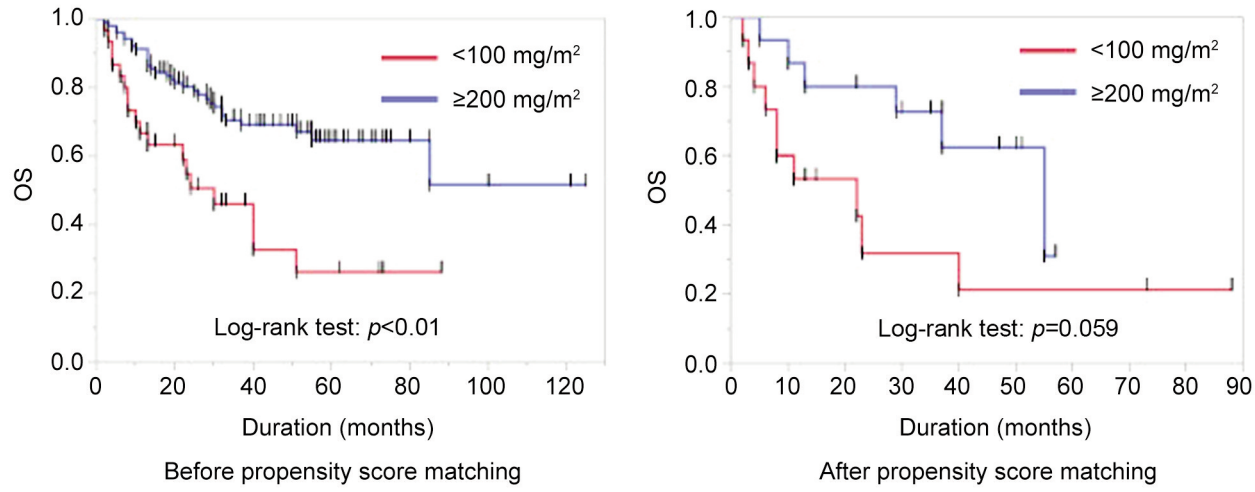


Figure 2. *Overall survival (OS) in patients treated with a cisplatin dose of ≥200 mg/m² or <100 mg/m² before and after propensity score matching. Before matching, the OS of the high-dose cisplatin group was significantly higher than that of the low-dose group. After matching, although the OS of the high-dose cisplatin-treated group was still higher, the difference was no longer significant.*

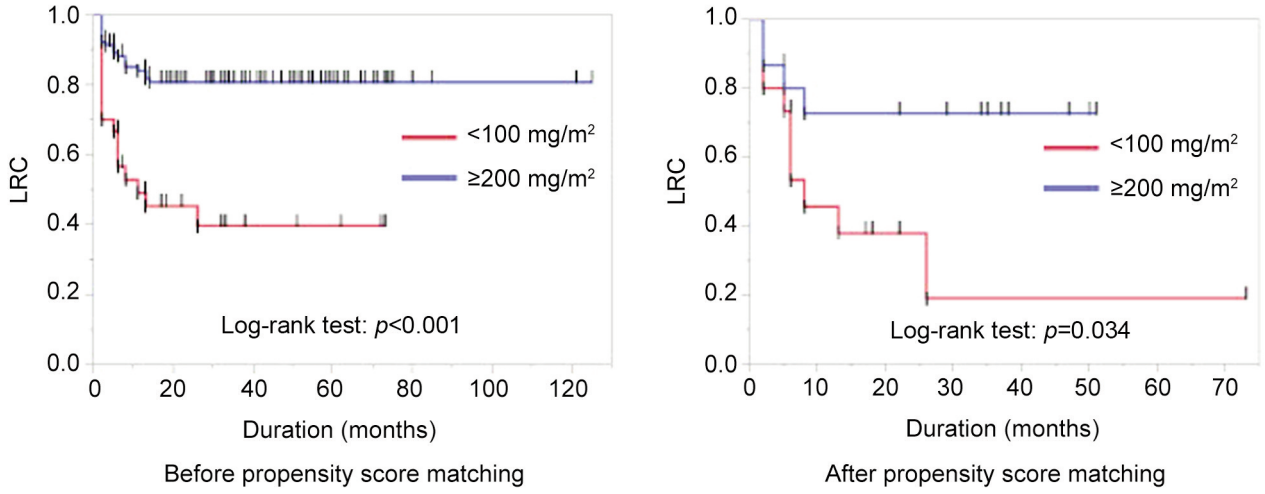


Figure 3. *Locoregional control (LRC) in patients treated with a cisplatin dose of ≥200 mg/m² or <100 mg/m² before and after propensity score matching. Before and after matching, the LRC of the high-dose cisplatin group was significantly higher than that of the low-dose group.*

GTVn recurrences. Distant metastasis was documented in 28 cases.

The area under the curve was 0.923 in calculating the propensity score for a cisplatin dose of ≥200 mg/m² and <100 mg/m² group. The patients' characteristics according to the cisplatin dose group before and after propensity score matching are shown in Table IV. The standardized mean difference decreased overall and 15 patients were matched. The OS and LRC in the groups with cisplatin dose of ≥200 mg/m² and <100 mg/m² before and after propensity score matching are shown in Figures 2 and 3.

Before matching, the OS of the ≥200 mg/m² group was significantly higher than that of the <100 mg/m² group ($p \leq 0.001$). After matching, the OS of the ≥200 mg/m² group was still higher than that of the <100 mg/m² group but the difference was no longer significant ($p=0.059$). Before matching, the LRC of the ≥200 mg/m² group was significantly higher than that of the <100 mg/m² group ($p \leq 0.001$), and a similar finding was obtained after matching ($p=0.034$).

Before propensity score matching, the OS of the ≥200 mg/m² group was significantly higher than that of the ≥100 and <200 mg/m² groups ($p=0.020$). Similarly, the LRC of

Table IV. *Baseline characteristics of groups treated with cisplatin doses ≥200 mg/m$^2$ and <100 mg/m$^2$.*

| Characteristic | | Before matching, n (%) | | | After matching, n (%) | | |
|---|---|---|---|---|---|---|---|
| | | ≥200 mg/m$^2$ (n=103) | <100 mg/m$^2$ (n=30) | SMD | ≥200 mg/m$^2$ (n=15) | <100 mg/m$^2$ (n=15) | SMD |
| Age | Mean±SD | 62.1 (8.7) | 73.4 (9.1) | 1.27 | 67.7 (7.4) | 68.5 (9.9) | 0.09 |
| Gender | Male | 90 (87.4) | 30 (100) | 0.54 | 15 (100) | 15 (100) | 0.00 |
| Tumor site | Larynx | 24 (23.3) | 3 (10.0) | 0.36 | 1 (6.7) | 1 (6.7) | 0.00 |
| | Hypopharynx | 32 (31.1) | 9 (30.0) | 0.02 | 5 (33.3) | 5 (33.3) | 0.00 |
| | Oropharynx | 47 (45.6) | 18 (60.0) | 0.29 | 9 (60.0) | 9 (60.0) | 0.00 |
| HPV status of the oropharynx | Positive | 31 (30.1) | 6 (20.0) | 0.23 | 4 (26.7) | 4 (26.7) | 0.00 |
| | Negative | 64 (62.1) | 19 (63.3) | 0.02 | 11 (73.3) | 11 (73.3) | 0.00 |
| | Unknown | 8 (7.8) | 5 (16.7) | 0.27 | 0 (0) | 0 (0) | 0.00 |
| UICC clinical stage | III | 28 (27.2) | 11 (36.7) | 0.20 | 5 (33.3) | 5 (33.3) | 0.00 |
| | IVa | 70 (68.0) | 15 (50.0) | 0.37 | 8 (53.3) | 8 (53.3) | 0.00 |
| | IVb | 5 (4.9) | 4 (13.3) | 0.30 | 2 (13.3) | 2 (13.3) | 0.00 |
| cT-Stage | T1 | 8 (7.8) | 5 (16.7) | 0.27 | 3 (20.0) | 2 (13.3) | 0.18 |
| | T2 | 40 (38.8) | 8 (26.7) | 0.26 | 3 (20.0) | 2 (13.3) | 0.18 |
| | T3 | 39 (37.9) | 10 (33.3) | 0.10 | 5 (33.3) | 6 (40.0) | 0.14 |
| | T4a | 14 (13.6) | 5 (16.7) | 0.09 | 3 (20.0) | 3 (20.0) | 0.00 |
| | T4b | 2 (1.9) | 2 (6.7) | 0.24 | 1 (6.7) | 2 (13.3) | 0.21 |
| cN-Stage | N0 | 16 (15.5) | 6 (20.0) | 0.12 | 4 (26.7) | 4 (26.7) | 0.00 |
| | N1 | 15 (14.6) | 7 (23.3) | 0.22 | 3 (20.0) | 3 (20.0) | 0.00 |
| | N2a | 4 (3.9) | 3 (10.0) | 0.24 | 0 (0.0) | 0 (0.0) | 0.00 |
| | N2b | 37 (35.9) | 9 (30.0) | 0.13 | 4 (26.7) | 5 (33.3) | 0.14 |
| | N2c | 28 (27.2) | 5 (16.7) | 0.26 | 3 (20.0) | 2 (13.3) | 0.18 |
| | N3 | 3 (2.9) | 3 (10.0) | 0.29 | 0 (0.0) | 0 (0.0) | 0.00 |

SD: Standard deviation; SMD: standardized mean difference, differences of 0.1 or more represent meaningful differences in covariates between groups; UICC: Union for International Cancer Control (21).

the ≥200 mg/m$^2$ group was also significantly higher than that of the other groups ($p$=0.008) before propensity score matching. However, after propensity score matching, there were no longer any significant differences in OS and LRC in the ≥200 mg/m$^2$ group compared to the other two groups.

The RT technique, prescribed PTVinitial dose, and RT treatment time did not cause significant differences in OS and LRC before and after propensity score matching.

## Discussion

Studies on the optimal radiation dose to ELNAs are limited. This study found that increasing the cisplatin dose improved the LRC and OS. Only the ELNA did not develop recurrence. The irradiation dose to the ELNA was 40-44 Gy at 2 Gy per fraction, and the biological effective dose with an $\alpha/\beta$ of 10 (BED10) was 48-52.8 Gy. The median observation period was 34 months. To our best knowledge, this is the first observational study to clarify the recurrence pattern of LA-HNSCC after CCRT, and after RT alone.

The 2018 National Comprehensive Cancer Network guideline recommends an RT dose of 44-50 Gy at 2 Gy per fraction and a BED10 of 52.8-60 Gy dose to the ELNA (7). Bosch *et al*. reported that irradiation at 57.77 Gy at BED10 with RT alone did not control LN-MM. They used 50.32 Gy irradiation with 1.48 Gy per fraction to the ELNA via RT alone, with a BED10 equivalent of 57.77 Gy (24). Among the lymph nodes with a total minor axis and major axis of ≥17 mm in the ELNA, 6.5% developed recurrence in 2 years without recurrence GTV. No recurrence was observed in the ELNA irradiated with a BED10 of ≥72 Gy. Nevens *et al*. reported that a lower dose to the ELNA was not associated with higher regional recurrences. Only one of the 233 patients developed ELNA recurrence without GTV involvement (25). Furthermore, there was no significant difference in OS and disease-free survival between the BED10 48 Gy and BED10 60 Gy groups (13).

Carde *et al*. reported that CCRT with cisplatin had an enhanced antitumor effect due to radiation sensitization (26). Several studies have also reported that OS improves with increasing CDDP dose (27, 28). Geh *et al*. estimated that 100 mg/m$^2$ cisplatin was equivalent to 7.2 Gy (EQD2) at $\alpha/\beta$= 4.9 and to BED10 8.64 Gy (29). Thus, two courses of 100 mg/m$^2$ cisplatin can be administered during irradiation to the ELNA. The prescribed dose corresponds to BED10 65.28-70.8 Gy when irradiated at 40-44 Gy at 2 Gy per fraction.

Importantly, a BED10 of 65.28-70.8 Gy to the ELNA can be used to control LN-MM. However, this does not explain the fact that recurrence in the ELNA alone was not observed in patients who did not receive full-dose cisplatin. Advances in diagnostic modality have improved sensitivity in detecting lymph node metastases and reduced the number of tumors in the ELNA (6). With modern diagnostic modalities, A BED10 of 48-52.8 Gy may be able to control LN-MM.

The limitation of this study was that the RT techniques varied; some patients underwent 3D-CRT, while others underwent IMRT. Thus, the optimal RT dose for controlling LN-MM needs further study because 3D-CRT has inferior dose uniformity compared to IMRT. On the other hand, the advantage of this study is its retrospective nature. While a prospective study might take 5-10 years from patient enrollment to analysis, this retrospective study was able to investigate, in a shorter period, the possibility of controlling LN-MM by irradiation with 40-44 Gy at 2 Gy per fraction to the ELNA. Our findings provide useful scientific evidence for reducing adverse events during CCRT for HNSCC without compromising the therapeutic effect and without the need for developing new equipment, treatment technology, and further personnel. However, because only 29 patients in this study received RT alone, further studies are needed to determine the feasibility of controlling LN-MM via irradiation with 40-44 Gy at 2 Gy per fraction to the ELNA in RT alone.

## Conclusion

CCRT with a cisplatin dose of ≥200 mg/m$^2$ can reduce the irradiation dose to 40-44 Gy at 2 Gy per fraction to control LN-MM compared when the standard dose. Radiation-sensitizing chemotherapy can reduce the irradiation dose required to control tumor in CCRT.

## Conflicts of Interest

There are no conflicts of interest to disclose.

## Authors' Contributions

Suzuki Y, Jingu K, Ishida E, Murata T and Kubozono M were involved in study design data analysis. Suzuki Y and Jingu K were involved in data interpretation. All authors revised the article, commented on drafts of the article, approved the final article and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Acknowledgements

The Authors gratefully acknowledge the helpful comment and discussion of past and present members of Tohoku University Hospital Radiation Oncology and Head and Neck Cancer Center.

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*Received March 28, 2021*
*Revised April 30, 2021*
*Accepted May 5, 2021*