Normal Tissue Complication Probability Model for Radiation-induced Temporal Lobe Injury after Intensity-modulated Radiation Therapy for Nasopharyngeal Carcinoma

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Purpose: To identify predictors for the development of temporal lobe injury (TLI) after intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma.

Materials and Methods: Data in 351 patients with nasopharyngeal carcinoma treated with IMRT were reviewed retrospectively according to institutional ethics committee approval. Clinical factors associated with TLI were analyzed. Dose-volume histograms for 550 evaluable temporal lobes were analyzed, and the predictive value of therapy-associated and patient-associated factors for the occurrence of TLI was evaluated. Survival curves were depicted by using the Kaplan-Meier method and compared by using the log-rank test. Logistic regression analysis was used for multivariate analyses.

Results: Median follow-up was 76 months (range, 6–100 months). Twenty-nine of 351 patients (8.3%) developed TLI; 21 patients had unilateral TLI, and eight had bilateral TLI. Median latency from IMRT until first TLI was 33 months (range, 12–83 months) among patients with TLI. The actuarial TLI-free survival rates were 94.4% and 91.3% at 3 and 5 years after radiation therapy, respectively. Logistic regression analysis demonstrated that dose delivered to a 1-cm³ volume of the temporal lobe (D₁cm³) was the only independent predictor for TLI. The biologically equivalent tolerance doses at 2 Gy for a 5% and 50% probability of developing TLI were 62.83-Gy equivalents (95% confidence interval: 59.68, 65.97) and 77.58-Gy equivalents (95% confidence interval: 74.85, 80.32), respectively.

Conclusion: D₁cm³ is predictive for radiation-induced TLI, suggesting that delivery of a high dose of radiation to a small volume of the temporal lobe is unsafe. A D₁cm³ of 62.83 Gy by using a correction formula for varying fraction size may be the dose tolerance of the temporal lobe.

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Late temporal lobe necrosis due to radiation therapy is frequently observed and is one of the most important dose-limiting factors in patients with nasopharyngeal carcinoma (NPC), which is primarily treated with radiation therapy. A retrospective study reported by Lee et al indicated that the fractional effect (product of total dose and fractional dose) was the most significant factor associated with temporal lobe necrosis (1). Furthermore, the high frequency of microscopic infiltration into the submucosa and close proximity to the skull base means that the medial temporal lobes are inevitably included in the target volume. Unfortunately, owing to technical limitations, the relationship between temporal lobe injury (TLI) and the actual dose volume of the irradiated temporal lobes by using conventional two-dimensional radiation therapy cannot be readily analyzed.

Intensity-modulated radiation therapy (IMRT) enables detailed analysis of temporal lobe dosimetric parameters on the basis of dose-volume histograms. However, limited data have been published regarding TLI after IMRT in NPC. The purpose of this study was to identify predictive factors for TLI.

### Materials and Methods

**Patient Characteristics**

This study was approved by the institutional ethics committee. A total of 354 patients with newly diagnosed, nonmetastatic, histologically confirmed NPC were treated with IMRT at our center from November 2004 to December 2006. Of the 354 patients, three patients with other malignancies or cerebral infarction that required treatment were excluded. The study group therefore contained a total of 351 patients. The patient characteristics are shown in Table 1.

**Clinical Staging**

All patients completed pretreatment evaluations, including a complete physical examination, hematologic and biochemistry profiles, nasopharyngeal fiberoptic endoscopy, magnetic resonance (MR) imaging of the neck and nasopharynx, chest radiography, bone scintigraphy, and abdominal ultrasonography (US). All cases were restaged according to the seventh edition of the American Joint Committee on Cancer staging system.

**Treatment Methods**

Radiation therapy.—Target volumes were delineated according to our institutional treatment protocol, in agreement with International Commission on Radiation Units and Measurements Reports 50 and 62 (2,3). The lower neck and supraclavicular fossae were treated with a single anterior split field by means of conventional radiation therapy. Planning target volumes for the primary gross tumor volume, nodal gross tumor volume, and clinical target volumes 1 and 2 were generated automatically by adding a 3-mm margin after target delineation according to immobilization and localization uncertainties. Inverse planning was performed on the Corvus System (Peachcock; Nomos, Deer Park, Ill) by using Simultaneous Modulated Accelerated Radiation Therapy boost radiation therapy. The prescribed dose was 68 Gy to the planning target volume of the primary gross tumor volume, 60 Gy to the planning target volume of clinical target volume 1 (ie, high-risk regions), 54 Gy to the planning target volume of clinical target volume 2 (ie, low-risk regions), and 60–66 Gy to the planning target volume of nodal gross tumor volume for positive cervical lymph nodes in 30 fractions. The doses for each critical organ were limited, as described in the Radiation Therapy Oncology Group 02-25 protocol (4) (eg, point < 65 Gy and 1% volume < 60 Gy for temporal lobes).

Chemotherapy.—Of the 351 patients, 102 (29.0%) underwent concomitant chemotherapy, 129 (36.8%) underwent a combination of neoadjuvant and concomitant chemotherapy, and 15 (4.3%) underwent concomitant and adjuvant chemotherapy. Neoadjuvant or adjuvant chemotherapy consisted of cisplatin with 5-fluorouracil.

**Advances in Knowledge**

- Dose delivered to a 1-cm³ volume of the temporal lobe is predictive for radiation-induced temporal lobe injury (TLI) in nasopharyngeal carcinoma (NPC); the biologically equivalent tolerance doses at 2 Gy for a 5% and 50% probability of developing TLI were 62.83-Gy equivalents (95% confidence interval: 59.68, 65.97) and 77.58-Gy equivalents (95% confidence interval: 74.85, 80.32), respectively.
- Delivery of a high dose of radiation to a small volume of the temporal lobe is unsafe.

**Implication for Patient Care**

This study provides valuable insight into the risk factors for TLI and will help to optimize NPC treatment planning to improve tumor control and prevent side effects.
Radiation-induced toxicities were graded according to the Common Terminology Criteria for Adverse Events version 3.0 and the Late Effects of Normal Tissue—Subjective, Objective, Management, Analytic, or LENT-SOMA, scales (5,6).

### Follow-up and Statistical Analysis

Follow-up was calculated from the 1st day of therapy to the day of either death or last examination. After completion of radiation therapy, all patients were followed up every 1–3 months during the first 2 years, every 6 months in years 2–5, and annually thereafter. At each follow-up, disease status and treatment toxicities were assessed by means of head and neck MR imaging, chest radiography, abdominal US, physical examination, and, if indicated, whole-body bone scanning.

Statistical analysis was performed by using the SPSS package version 19.0 (SPSS, Chicago, III). Survival curves were depicted by using the Kaplan-Meier method and compared by using the log-rank test. Logistic regression analysis was used for multivariate analyses. A level of $P < .05$ was considered to indicate a statistically significant difference.

### Dose-Volume Histogram Analysis

For dose-volume histogram analysis, it was assumed that the temporal lobes of each patient responded independently. To enable comparability within this study and within the literature, dose-volume histograms were rescaled for a central late toxicity in normal temporal lobes (1), as:

$$D_2 = D_x \cdot \frac{\alpha/\beta + dx}{\alpha/\beta + 2}.$$  

Here, $D_x$ is the total dose applied with the dose per fraction $x$, denoted as $dx$, and $D_2$ is the isoeffective total dose applied with 2-Gy equivalents per fraction.

Sixteen dose-volume histogram-based variables, including mean doses, were determined. $D_{x\text{av}}$ defines the maximum dose in the remaining volume, excluding the volume value of 0, 0.5, 1, 2, 5, and 10 cm$^3$ with the highest doses in the temporal lobes, respectively.

$V_{2/3}$ indicates the volume receiving more than the minimal dose of 50, 55, 60, 65, 70, 75, 80, 85, and 90-Gy equivalents, respectively. Additionally, one treatment-related variable (concurrent chemotherapy) and patient-related variables (age, patient sex, and T classification) were included as clinical variables.

### Multivariable Analysis for Prediction of TLI

A predictive model was established by using unconditional logistic regression analysis of the TLI rate with a predictive set chosen from the 16 dose-volume histogram-based variables and four clinical variables.

In a preprocessing step, the pairwise correlations between TLI and the 16 dose-volume histogram–based variables and four clinical variables were investigated in 552 temporal lobes by using the Spearman rank correlation coefficient and then by using principal component analysis to identify clusters of variables that provide similar information.

Then, variables from each principal component analysis cluster were selected on the basis of clinical perspectives and subjected to multivariate analyses to determine significant predictive factors by using a final step-down selection procedure in a logistic regression model.

### Dose Response Analysis

The most predictive dose and volume variables in multivariate analysis were analyzed by using dose and volume response curves, which were generated with the nonlinear regression module of Statistica software (StatSoft, Tulsa, Okla) by using the following logistic dose response model:

$$P(X) = \frac{\beta_0 e^{(\beta_0 + \beta_1)X}}{1 + e^{(\beta_0 + \beta_1)X}},$$

where $X$ is the independent dose or volume variable, respectively. The mode parameters $b_0$ and $b_1$ were determined by using a maximum likelihood-fitting procedure and used to calculate the

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### Table 1

**Characteristics of 351 Patients with NPC**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>267 (76.1)</td>
</tr>
<tr>
<td>Female</td>
<td>84 (23.9)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>252 (71.8)</td>
</tr>
<tr>
<td>≥50</td>
<td>99 (28.2)</td>
</tr>
<tr>
<td>Histologic findings</td>
<td></td>
</tr>
<tr>
<td>WHO type I</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>WHO type II</td>
<td>26 (7.4)</td>
</tr>
<tr>
<td>WHO type III</td>
<td>324 (92.3)</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
</tr>
<tr>
<td>Stage T1</td>
<td>71 (20.2)</td>
</tr>
<tr>
<td>Stage T2</td>
<td>68 (19.4)</td>
</tr>
<tr>
<td>Stage T3</td>
<td>130 (37.0)</td>
</tr>
<tr>
<td>Stage T4</td>
<td>82 (23.4)</td>
</tr>
<tr>
<td>N classification</td>
<td></td>
</tr>
<tr>
<td>Stage N0</td>
<td>79 (22.5)</td>
</tr>
<tr>
<td>Stage N1</td>
<td>162 (46.2)</td>
</tr>
<tr>
<td>Stage N2</td>
<td>77 (21.9)</td>
</tr>
<tr>
<td>Stage N3</td>
<td>33 (9.4)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>37 (10.5)</td>
</tr>
<tr>
<td>Stage II</td>
<td>69 (19.6)</td>
</tr>
<tr>
<td>Stage III</td>
<td>134 (38.2)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>78 (22.2)</td>
</tr>
<tr>
<td>Stage V</td>
<td>33 (9.4)</td>
</tr>
</tbody>
</table>

Note:—Numbers in parentheses are percentages.

WHO = World Health Organization.

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every 3 weeks for two or three cycles. Concurrent chemotherapy consisted of cisplatin weekly or on weeks 1, 4, and 7 of radiation therapy.

### Evaluation of Radiation-induced TLI

The diagnostic criteria for TLI were contrast material enhancement on contrast material–enhanced T1-weighted MR images and corresponding heterogeneous hyperintense cerebral edema on T2-weighted MR images. Differential diagnosis was applied to ensure that the changes were not due to other factors, such as tumor recurrence. All images were reviewed separately by two radiologists (one person with 10 years of experience and another with 8 years of experience), and disagreements were resolved by means of consensus.
Incidence and Latency of TLI

Median follow-up was 76 months (range, 6–100 months). A total of 29 of 351 patients (8.3%) developed TLI; 21 with unilateral TLI and eight with bilateral TLI. Among patients with TLI, the median latency from the end of IMRT until the appearance of TLI was 33 months (range, 12–83 months).

The TLI-free survival rate is shown according to Kaplan-Meier estimation (Fig 1). The TLI-free survival rates were 94.4% and 91.3% at 3 and 5 years, respectively. Scoring of radiation-induced TLI was not observed in stage T1–2 disease. The 5-year actuarial incidence of TLI for stage T3 and T4 disease was 4.7% and 32.8%, respectively (P < .001). The 5-year actuarial incidence of TLI was significantly higher for patients treated with concurrent chemotherapy and radiation therapy compared with those treated with IMRT alone (11.9% vs 2.0%, P = .003).

Predictive Factors

Of the 29 patients with TLI, 27 developed TLI within 60 months after IMRT, and two developed TLI at least 60 months after IMRT. The injury-free temporal lobes in those patients followed up for at least 60 months and the four temporal lobes in the two patients who developed TLI at least 60 months after IMRT were regarded as normal. The 249 of 322 patients without TLI were followed up for at least 60 months and underwent MR imaging examinations at least once during the first 60 months of follow-up to exclude TLI. Of the 29 patients with TLI, eight had bilateral TLI, and these 16 injured temporal lobes were included in this study. Of the 21 patients with unilateral TLI, 19 patients developed TLI within 60 months after IMRT; thus, 19 of these 21 injured temporal lobes were included in this study. Fifteen of the 19 patients who developed unilateral TLI within 60 months after IMRT were followed up for at least 60 months; the uninjured temporal lobes in these 15 patients were considered to be normal temporal lobes in the dose analysis. Thus, the incidence of TLI at 5 years was analyzed in 278 patients, including 517 normal temporal lobes and 35 injured temporal lobes.

Dosimetric data were collected for both normal and injured temporal lobes. The sites of TLI coincided with areas of high radiation doses immediately outside the target volume. The maximum radiation dose was located in the contrast-enhanced region on contrast-enhanced T1-weighted MR images in 31 TLI lesions and edematous region on T2-weighted MR images in four TLI lesions. In all 35 injured temporal lobes, the position of the maximum dose was located in the TLI lesions.

In univariate analysis in which the Spearman rank correlation coefficient was used, the dose variables (D\textsubscript{cc}) and volume variable (V\textsubscript{cc}) exhibited statistically significant pairwise correlations (coefficient of 0.6). T classification had a moderate correlation with concurrent chemotherapy and radiation therapy and all dose-volume histogram–based variables. Concurrent chemotherapy and radiation therapy had a moderate correlation with all dose-volume histogram–based variables, except V\textsubscript{cc} and V\textsubscript{cc} > 85. The mean dose did not exhibit uniform pairwise correlations with any variable. Patient age and sex were independent of all other variables. All dose-volume histogram–based variables, except for mean dose, correlated significantly with TLI.

Principal component analysis demonstrated a maximum of four clusters of variables (cluster 1, all D\textsubscript{cc} values and the four lowest V\textsubscript{cc} values; cluster 2, all V\textsubscript{cc} > 85 values; cluster 3, T classification and concurrent chemotherapy and radiation therapy; cluster 4, patient age and sex) that explained more than 83.7% of the variation.

### Table 2

<table>
<thead>
<tr>
<th>Grade</th>
<th>Common Terminology Criteria for Adverse Events Version 3.0 Score</th>
<th>Late Effects of Normal Tissue—Subjective, Objective, Management, Analytic Scales Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1: Graph depicts the Kaplan-Meier estimation of the TLI-free survival rate in 351 patients with NPC after IMRT.
Since the variables within each cluster correlated highly, representative variables were selected from each cluster on the basis of clinical consideration for multivariate regression. $D_{1cc}$ was used to qualify small areas of high dose and indicates steep dose gradients. $V_{D > 80}$ was selected from the TLI volume-effect curve, as it demonstrated the highest loading (0.937) among the $V_{D > y}$ variables. T classification and concurrent chemotherapy and radiation therapy were selected from the third cluster, and patient age and sex were selected from the fourth cluster. In final step-down multivariate logistic regression analysis of these six variables, $D_{1cc}$ was the only independent predictor of TLI (odds ratio, 1.221; 95% confidence interval [CI]: 1.157, 1.289; $P < .001$).

**Dose-Effect Model**

A dose-effect curve was generated for $D_{1cc}$ (Fig 3) and demonstrated an increasing effect probability with increasing dose. The tolerance doses of 5/5 (the tolerance dose for 5% probability to develop TLI within 5 years after IMRT) and 50/5 (the tolerance dose for 50% probability to develop TLI within 5 years after IMRT) were 62.83-Gy equivalents (95% CI: 59.68, 65.97) and 77.58-Gy equivalents (95% CI: 74.85, 80.32), respectively. Further tolerance doses for several probability levels are listed in Table 3.

**Discussion**

The incidence of TLI after IMRT in this study was 8.3%, which is higher than that in most previous reports of patients treated with two-dimensional radiation therapy (1,7,8). Notably, the incidence of TLI increased to 28.0% for stage T4 disease. Therefore, this study indicates that IMRT does not reduce the incidence of TLI compared with two-dimensional radiation therapy. This may be due to larger fractional dose and shorter overall treatment time used in IMRT, as Lawrence et al reported that the brain is especially sensitive to fractions higher than 2 Gy (9), and Lee et al observed that the overall treatment time significantly affected the risk of temporal lobe necrosis (7).
In this study, all cases of TLI occurred in the 29 patients with advanced T-stage disease. These patients had a high prevalence of infiltration into the skull base or intracranial tissue, or their tumors were in close proximity to these structures. Additionally, a portion of temporal lobe was delineated within the target in some patients with advanced T-stage disease. In such cases, regions of temporal lobe may be irradiated with high doses to improve target coverage.

Concurrent chemotherapy and radiation therapy is a standard treatment modality for advanced T-stage disease; however, it seems to significantly increase the incidence of TLI. However, T classification and chemotherapy were not significantly associated with TLI, and $D_{1cc}$ was the only independent predictor of TLI (odds ratio, 1.221; 95% CI: 1.157, 1.289; $P < .001$) in multivariate analysis. It is possible that temporal lobe $D_{1cc}$ is relatively high in some patients with advanced T-stage disease or that it is difficult for cisplatin-based drugs to cross the blood brain barrier effectively in the central nervous system. Since this was a retrospective study, further research is required.

The original estimate of Emami et al for fractionated partial brain radiation therapy suggested a 5% risk at 5 years when one-third of the brain was irradiated to a level of 60 Gy (10). In 2010, the Quantitative Analysis of Normal Tissue Effects in the Clinic, or QUANTEC, study demonstrated that a predicted risk of symptomatic radiation necrosis of 5% and 10% at biologically effective doses of 120 Gy (range, 100–140 Gy) and 150 Gy (range, 140–170 Gy), respectively, corresponded to 72 Gy (range, 60–84 Gy) and 90 Gy (range, 84–102 Gy) in 2-Gy fractions (9). However, in the QUANTEC study, it wasn’t specified which volume limits these constraints were based on, and the conclusions were drawn from heterogeneous data (ie, different target volumes, end points, sample sizes, and brain regions). Schlampp et al analyzed risk factors for temporal lobe reactions after carbon ion radiation therapy in patients with chordoma or chondrosarcoma by using a logistic dose response model (11). Age and $D_{max}$, $v = 1$ cm$^3$ (maximum dose in the remaining temporal lobe volume, excluding the 1-cm$^3$ volume with the highest dose) were the most significant factors in multivariate analysis. The biologically equivalent tolerance doses associated with a 5% probability of temporal lobe reactions were the 68.8 Gy ± 3.3 equivalents. A retrospective study by Su et al demonstrated that the 5-year incidence of TLI for a maximum dose of 64–68 Gy or $D_{1cc}$ of 52–58 Gy was less than 5.0% after IMRT (12). Similarly, a recent retrospective analysis of 20 patients with NPC and unilateral TLI showed that a dose of 69 Gy delivered to $D_{2cc}$ (dose to 0.5 mL of the temporal lobe volume) may be the dose tolerance of the temporal lobe after IMRT (13). In the current study, we reported that the $D_{1cc}$ was the only independent predictor for radiation-induced TLI and estimated that the biologically equivalent tolerance doses at 2 Gy for the 5% and 50% probabilities at 5 years to develop TLI were 62.83-Gy equivalents (95% CI: 59.68, 65.97) and 77.38-Gy equivalents (95% CI: 74.85, 80.32), respectively. A $D_{1cc}$ of 62.83 Gy by using a correction formula for varying fraction size may be the dose tolerance of the temporal lobe.

This study had several limitations. First, our results were not applicable to the condition in which large dose per fraction was delivered to the temporal lobe, such as with stereotactic body radiation therapy. Second, the test set and validation set for the
normal tissue complication probability model were not created because of the small number of patients with TLI after IMRT. We are planning to start a prospective study to verify the model in the near future.

In conclusion, we retrospectively analyzed dose-response relationships for the temporal lobe, with the aim of optimizing IMRT treatment planning for NPC. $D_{1cc}$ was predictive for radiation-induced TLI, suggesting that delivery of high-dose radiation to a small volume of the temporal lobe is unsafe. A $D_{1cc}$ of 62.83 Gy by using a correction formula for varying fraction size may be the dose tolerance of the temporal lobe.

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References