Locoregional Control After Intensity-modulated Radiotherapy for Nasopharyngeal Carcinoma with an Anatomy-based Target Definition

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Received May 31, 2013; accepted August 27, 2013

Objective: The objective of the study was to evaluate locoregional control after intensity-modulated radiotherapy for nasopharyngeal cancer using a target definition along with anatomical boundaries.

Methods: Forty patients with biopsy-proven squamous cell or non-keratinizing carcinoma of the nasopharynx who underwent intensity-modulated radiotherapy between April 2006 and November 2009 were reviewed. There were 10 females and 30 males with a median age of 48 years (range, 17–74 years). More than half of the patients had T3/4 (n = 21) and/or N2/3 (n = 24) disease. Intensity-modulated radiotherapy was administered as 70 Gy/33 fractions with or without concomitant chemotherapy. The clinical target volume was contoured along with muscular fascia or periosteum, and the prescribed radiotherapy dose was determined for each anatomical compartment and lymph node level in the head and neck.

Results: One local recurrence was observed at Meckel’s cave on the periphery of the high-risk clinical target volume receiving a total dose of \( \leq 63 \text{ Gy} \). Otherwise, six locoregional failures were observed within irradiated volume receiving 70 Gy. Local and nodal control rates at 3 years were 91 and 89%, respectively. Adverse events were acceptable, and 25 (81%) of 31 patients who were alive without recurrence at 2 years had xerostomia of Grade 1. The overall survival rate at 3 years was 87%.

Conclusions: Target definition along with anatomically defined boundaries was feasible without compromise of the therapeutic ratio. It is worth testing this method further to minimize the unnecessary irradiated volume and to standardize the target definition in intensity-modulated radiotherapy for nasopharyngeal cancer.

Key words: nasopharyngeal cancer – intensity-modulated radiotherapy – anatomical compartment – patterns of spread
INTRODUCTION

Intensity-modulated radiotherapy (IMRT) is one of the most prominent therapeutic advances in the last decade for patients with nasopharyngeal cancer (NPC) with local and nodal control rates exceeding 90% (1–5). In IMRT, meticulous delineation of the clinical target volume (CTV) with special attention to the patterns of spread is extremely important. In general, spread of NPC follows anatomic compartments that are bounded by anatomic barriers (e.g., muscular fascia or periosteum) (6). Recent high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) images have yielded exquisite anatomic information that can clearly depict whether the gross tumor volume (GTV) penetrates these anatomic barriers. Involvement of NPC in one anatomic compartment correlates with contiguous spread to the adjacent compartments (7,8). However, definition of clinical and subclinical target volumes had been largely derived from the experience of two-/three-dimensional radiotherapy, and the method for target delineation by using modern radiographic and fibrescopic images had not been fully addressed. Excellent locoregional tumor control rates had been reported from experienced centers in IMRT to the CTV using GTV plus 5–10 mm uniform expansion with individual modification due to proximity of critical organs (1–4,9). On the other hand, Lee et al. reported that centralized review and feedback for tumor volume contouring (10) were required to diminish major deviation of target specifica-

PATIENTS AND METHODS

PATIENT POPULATION

From April 2006 to November 2009, 41 patients with biopsy-proven squamous cell or non-keratinizing carcinoma of the nasopharynx without evidence of distant organ metastasis underwent IMRT at our institution. All patients underwent CT and MRI of the head and neck as part of the pretreatment evaluation. Diseases were re-staged according to the American Joint Committee on Cancer (AJCC) Staging Manual (seventh edition) (12). One patient died because of an unidentified accident immediately after completion of treatment and excluded from this analysis, and the remaining 40 patients were the subjects of this study.

CONTOURING OF THE CLINICAL TARGET VOLUME AROUND THE PRIMARY DISEASE

All patients underwent CT simulation with 3 mm slice thickness after immobilization in the supine position using thermoplastic masks. CT images with and without contrast enhancement were always obtained during simulation, and registration of MRI at the treatment position with planning CT images was routinely used in patients with T3/4 diseases. We considered that head and neck fibrescopy findings were more important than CT/MRI information in the determination of mucosal extent of GTV at the primary site (GTVp). Tumor invasion to adjacent anatomic compartments, such as parapharyngeal, masticator, perivertebral spaces, pterygopalatine fossa, occipital (elivus), temporal (petrous apex) and/or sphenoid bones, was evaluated with CT and MRI. A high-risk CTV was defined as follows: (i) pharyngeal and sinonasal mucosal space within 2 cm from the margin of the mucosal irregularity, unless it was in close proximity to the chisma and optic nerve, (ii) entire ipsilateral parapharyngeal space and/or infratemporal fossa (medial and lateral pterygoid muscles), only when gross tumor invasion to these structures was observed in CT/MRI, (iii) individual cranial bones, pterygopalatine fossa and/or perivertebral space within a volume of GTVp + 1 cm expansion, only when gross tumor invasion to these structures was observed and (iv) Meckel’s cave was included in the high-risk CTV when there was clinical and/or radiographic evidence of tumor penetration through the foramen lacerum and/or foramen ovale. Margins of these high-risk CTVs were defined at the fascia or periosteum of each anatomic compartment.

The intermediate-risk CTV was contoured at the anatomic compartments without gross tumor invasion but abutting to the GTVp as follows: (i) entire parapharyngeal space, (ii) entire medial and lateral pterygoid muscles only when GTVp attached to the inner fascia of these muscles, (iii) entire volume of the sphenoid bone invaded by the tumor and outside of the volume of GTVp +1 cm, (iv) temporal and occipital bone and/or pterygopalatine fossa within GTVp +2 cm and outside of GTVp +1 cm, if tumors invaded these structures and (v) ipsilateral Meckel’s cave when GTVp invaded foramen lacerum and/or masticator space. Schematic figures illustrating the above concept are shown in Figure 1.
(GTVn), which was determined by neck lymph nodes of ≥1 cm in smallest dimension, any equivocal retropharyngeal lymph nodes (15), or which had central necrosis on CT/MRI. In the case of nodal disease that had nodes of ≥3 cm in diameter, or when extracapsular spread was suggested on CT/MRI, the volume within the uniform three-dimensional expansion of gross nodal disease +1 cm was also defined as high-risk CTV. An intermediate-risk CTV was defined as lymph node levels that were adjacent to the high-risk CTV with radiological evidence of extracapsular extension. A low-risk CTV encompassed all Levels II–V and supraclavicular nodes, and retropharyngeal nodal stations above the level of the hyoid bone and that was outside of the high- or intermediate-risk CTV. Level Ib was defined as low-risk CTV when GTVp infiltrated the ipsilateral nasal cavity. All GTVs were contoured according to the physical and radiographic findings before induction chemotherapy for patients who underwent this chemotherapy as described in the next section.
DOSE PRESCRIPTION AND TREATMENT TECHNIQUES

The step-and-shoot technique with a 10 mm-wide multi-leaf collimator was used during this study period. PTV encompassed CTV with a 5 mm margin. Total RT doses to the PTV of high, intermediate and low risks were 70, 60 and 54 Gy, respectively. A simultaneous integrated boost using 33 fractions over 6.5 weeks was used, and the entire PTV was treated with extended-field IMRT. On treatment planning CT, dose distribution in each slice was meticulously evaluated, and the plans were optimized to eliminate hot spots receiving a total RT dose of ≥77 Gy. In principle, the IMRT plan was approved when >95% volume (D95) of the PTV received >95% of the prescribed dose. A part of the PTV within 3 mm beneath the skin surface was eliminated in this evaluation. The total RT dose to the chiasma and at least the unilateral optic nerve was always restricted to <60 Gy because none of the patients had clinical and radiographic signs of optic nerve invasion of the tumor at presentation. Otherwise, the dose constraint to the planning organs at risk volume was determined according to the Radiation Therapy Oncology Group 0225 Study protocol (5).

According to the previous trials (13,14), concomitant followed by adjuvant platinum-based chemotherapy was done in clinically fit patients with Stage III/IV disease. Those who had Stage I/II keratinizing squamous cell carcinoma also received concomitant chemotherapy because of poor expectation of local control in patients with this histology (16). For competent patients with N2/3 disease and/or T4 disease attaching to the optic chiasma, three courses of induction chemotherapy with docetaxel, cisplatin and S-1 were done (17). Dental examinations and placement of a percutaneous gastrostomy tube (PEG) were routinely done before the start of IMRT. Changes in the body contours were monitored at least weekly during the IMRT with megavoltage CT generated by the linac in all patients, with the intention of revising plans according to the estimated changes of dose distribution in the target volume and critical organs. In fact, revisions were made in four patients. IMRT plans were made using Xio version 4.5.0 (Elekta, Stockholm, Sweden) for the first five patients, and Pinnacle 3 (Philips, Amsterdam, the Netherlands) for the rest.

OUTCOME MEASURES AND STATISTICAL CONSIDERATIONS

Patients were monitored at least twice a week during IMRT. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were performed at least twice within 6 months immediately after treatment, and at regular intervals of 6–12 months thereafter. Time-to-event analyses from the start of RT were made using the Kaplan–Meier estimates according to the data fixed on 1 November 2012. Biopsy-proven recurrence of the primary tumor or radiographic evidence of regrowth of neck adenopathy was considered as events for calculating the local and nodal control rates, respectively. Radiographic evidence of development of distant failure was determined as an event for calculating distant failure rates. Patterns of recurrences were classified according to the definition by Chao et al. (18). Patients who died without these events were censored at the time of last follow-up examination. Death from any cause was defined as an event in calculating overall survival. Also, recurrence at any site or death from any cause was used in estimating progression-free survival. Statistical significance was evaluated using the log-rank test. Adverse events were estimated according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0. All patients provided written informed consent. This retrospective analysis was approved by our institutional ethics committee.

RESULTS

PATIENTS

One patient was lost to follow-up at 23 months with radiological evidence of nodal recurrence. The median follow-up period for other surviving patients was 45 months (25–62 months). The characteristics of patients are listed in Table 1. High-risk CTV within the mucosal space was confined within posterior one-third of the nasal cavity in all but one patient, while it was within the pharyngeal mucosal space above the level of inferior border of the second cervical vertebra (C2) in all but two patients. In patients with T4 disease, the entire ipsilateral medial and lateral pterygoid muscles were included in high-risk CTV in three patients, and otherwise, it was confined to the sphenoid and temporal bones, basiocciput, Meckel’s cave, perivertebral, retropharyngeal and sinonasal/pharyngeal mucosal spaces. Concomitant chemotherapy was performed in 38 (95%) patients, and 20 (53%) of these 38 patients also received induction chemotherapy. The overall treatment time of RT ranged from 46 to 57 days (median, 50 days).

TUMOR CONTROL AND SURVIVAL OUTCOMES

There were seven locoregional tumor persistence or recurrences as listed in Table 2. The local and nodal control rates at 3 years were 91% (95% confidence interval, 82–100%) and 89% (79–99%), respectively. The locoregional control rate at 3 years was 83% (71–96%). A review of IMRT dose distributions revealed that six of the seven locoregional failures were ‘in-field’, and one local recurrence at the Meckel’s cave was ‘marginal’ according to the definition by Chao et al. This marginal recurrence occurred in patients who had T3 disease deeply invading the ipsilateral foramen lacerum. Although the site of recurrence was defined as high-risk CTV, the administered total dose was <63 Gy aiming at dose reduction to the adjacent temporal lobe of the brain. Local control rates in patients with T1/2 and T3/4 disease were 95% (95% CI 85–100%) and 90% (77–100%), respectively, at 3 years (P = 0.744). The distant failure rate at 3 years was 24% (8–40%). The Kaplan–Meier estimates of locoregional and
distant failure rates are shown in Figure 2. Progression-free and overall survival rates at 3 years were 61% (45–76%) and 87% (76–98%), respectively (Fig. 3). Locoregional control, distant failure and overall survival rates at 3 years for patients with Stage I–II disease \((n = 21)\) were 81% (95% CI, 64–98%), 17% (0–34%) and 90% (77–100%), respectively, whereas these rates were 89% (74–100%), 27% (8–46%) and 83% (65–100%), respectively, for 19 patients with Stage IV disease. Overall and progression-free survival rates at 3 years for 20 patients who received induction chemotherapy were 89 and 63%, and it was 85 and 59% for the rest, respectively \(\left( P > 0.500 \right)\).

### ADVERSE EVENTS

Grade 3 dermatitis and symptomatic mucositis due to IMRT were observed in 5 (12%) and 25 (63%) patients, respectively. All surviving patients maintained their normalcy of diet and were not PEG dependent at 1 year after completion of IMRT. The median value of mean IMRT doses to the parotid gland on the side receiving lower dose was 33 Gy (19–49 Gy). The mean total IMRT dose to the spared cochlea was <55 Gy in all patients. The type and frequency of late adverse events for 37 patients who were alive at 2 years are listed in Table 3. One patient experienced Grade 3 neck induration at 4 years after IMRT (1 year after completion of salvage chemotherapy for bone metastasis). He died subsequently with radiological evidence of lung metastasis. Of 31 patients who were alive and disease-free at 24 months, hearing loss of Grade 3 was observed in 4 (13%) patients. Twenty-five (81%) of these 31 patients experienced sense of recovery of their mouth dryness and were able to intake a normal solid diet (xerostomia of \(\leq \) Grade 1) at 2 years (Fig. 4). One patient whose T4 disease collapsed at 4 months after completion of IMRT developed a deep ulcer at the parapharyngeal and masticator spaces (Grade 3 pharyngeal necrosis). Osteonecrosis of the ipsilateral mandible and temporal lobe necrosis were observed subsequently. She died of pneumonia without evidence of tumor recurrence at 35 months. Otherwise, no Grade 2 or worse adverse events were observed at the time of last follow-up.

### DISCUSSION

Although excellent locoregional control after IMRT had been reported from certain centers that had abundant experience of two-to-three-dimensional RT for NPC, wide prevalence of these results in the medical community is indispensable. Assuming that inter-observer variation of the target definition is categorized as a systematic error, larger margins would be required to determine the planning target volume than accountable by random errors \(\left( 19 \right)\). Therefore, meticulous target definition based on the detailed estimation of extent of tumor and precise knowledge of patterns of tumor spread is indispensable. Pharyngeal and sinonasal mucosal spaces within GTVp +2 cm margins were determined as high-risk CTV during this study period because of our belief of the aggressive nature of NPC with regard to lymphovascular invasion. However, this should be done with extreme caution. It should be noted that GTVp at the mucosal space was determined by direct fiberscopy findings because GTVp definition based on imaging alone was likely insufficient.
to overestimate the real GTVp (6,20). Correct depiction of this mucosal GTVp for the planning CT is an extremely important process, because any regulation defining a GTV–CTV margin is meaningless without this effort. In our experience, high-risk CTV was confined within posterior one-third of the nasal cavity, and oropharyngeal mucosal space above the level of lower border of C2 with few exceptions. Therefore, the reason must be clearly recorded when high-risk CTV larger than these limits is defined. In other words, adding 2 cm margin to the GTV that was determined with imaging alone should not be done to avoid an unacceptably huge high-risk CTV.

Table 2. Patterns of locoregional failure

<table>
<thead>
<tr>
<th>Patient age/gender</th>
<th>TN classification</th>
<th>Histology</th>
<th>Site of recurrence</th>
<th>Time to event (months)</th>
<th>Salvage treatment</th>
<th>Final status (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49M T2N2</td>
<td>SCC NOS</td>
<td>Local, in-field</td>
<td>0</td>
<td>None</td>
<td>11 DOD</td>
<td></td>
</tr>
<tr>
<td>54M T3N1</td>
<td>Non-kerat. differentiated</td>
<td>Local, in-field</td>
<td>21</td>
<td>Re-RT</td>
<td>45 AWD</td>
<td></td>
</tr>
<tr>
<td>49M T3N1</td>
<td>Non-kerat. differentiated</td>
<td>Local, marginal</td>
<td>36</td>
<td>Re-RT</td>
<td>43 AWD</td>
<td></td>
</tr>
<tr>
<td>53F T2N3a</td>
<td>Non-kerat. undifferentiated</td>
<td>Nodal, in-field</td>
<td>0</td>
<td>None</td>
<td>12 DOD</td>
<td></td>
</tr>
<tr>
<td>34M T1N2</td>
<td>Non-kerat. undifferentiated</td>
<td>Nodal, in-field</td>
<td>10</td>
<td>Re-RT</td>
<td>23 AWD</td>
<td></td>
</tr>
<tr>
<td>47F T2N1</td>
<td>Non-kerat. differentiated</td>
<td>Nodal, in-field</td>
<td>28</td>
<td>Re-RT</td>
<td>54 NED</td>
<td></td>
</tr>
<tr>
<td>45M T4N1</td>
<td>Keratinizing</td>
<td>Nodal, in-field</td>
<td>34</td>
<td>Chemotherapy</td>
<td>38 AWD</td>
<td></td>
</tr>
</tbody>
</table>

M, male; F, female; Non-kerat, non-keratinizing; Re-RT, reirradiation; DOD, died of index cancer; AWD, alive with disease; NED, no evidence of disease; in-field, within irradiated volume receiving 70 Gy/33 fractions; marginal, at the margin of irradiated volume receiving 70 Gy/33 fractions according to the definition by Chao et al. (18).

Figure 2. Kaplan–Meier estimates of local control (thick solid), nodal control (thin solid) and distant failure rates (dotted line).

Figure 3. Kaplan–Meier estimates of overall (thick) and progression-free (thin line) survival rates.
NPC has a high propensity of parapharyngeal space invasion (8). The parapharyngeal space that was judged as free from tumor invasion was not encompassed within the CTV in this study period. However, no marginal recurrence was observed within the parapharyngeal space in this series of patients. If possibility of tumor invasion could not be completely denied, definition of the high-risk CTV within the parapharyngeal space by expansion of GTVp +1 cm as shown in Figure 1 was thought to be an appropriate option based on the results of previous reports (1,2,4,5,9). In general, most of the patients with NPC had nodal metastasis with radiological signs of extracapsular spread, which required extensive coverage of the ipsilateral parapharyngeal space. Therefore, to determine the entire ipsilateral parapharyngeal space as the high-risk CTV was considered justifiable when the patient had gross tumor invasion to this space on MRI. As noted by Grégoire et al., muscular fascias are strong barriers against muscle infiltration. When the fascia has been disrupted, the whole muscle is at risk (21). Based on this concept, the high-risk CTV encompassed the entire pterygoid muscles in three patients with T4 disease.

Adverse influence of variation in treatment planning was suggested in one patient who experienced marginal recurrence at Meckel’s cave. Consequently, our method should be continuously fine-tuned according to the accumulation of clinical experiences. Otherwise, all locoregional failures were ‘in-field’, which could not be ascribable to inadequacy of our target definition. This single institutional study with a limited number of patients could not demonstrate the appropriateness of our target definition for all patterns of spread. Lin et al. (22) addressed a possibility to reduce IMRT target volume compared with that as defined in two- to three-dimensional radiotherapy era without deterioration of tumor control. Local and nodal control rates exceeded 95% at 3 years and no isolated recurrence was observed at reduced CTV in the posterior maxillary sinus, posterior clivus and/or posterior nasal cavity in 323 NPC patients (75% had T2/3 disease). In our study, three of the seven locoregional recurrences occurred at >2 years post IMRT. Therefore, longer follow-up is required to compare matured results among various definitions of the CTV and chemoradiotherapy procedures.

Table 3. Type and frequency of late adverse events for 37 patients who were alive at 2 years

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Grade 0/1</th>
<th>2</th>
<th>3</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/soft tissue</td>
<td>35</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pharyngeal mucositis/necrosis</td>
<td>36</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>27</td>
<td>7</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Larynx</td>
<td>34</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>33</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>36</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Joint</td>
<td>36</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hearing impaired (at least unilateral)</td>
<td>23</td>
<td>10</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Worst overall</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>27</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>

NA, not assessable because of aggravation of general conditions due to disease recurrence.

*Number of patients who did not experience ≥ Grade 2 late adverse events other than NA items.

Figure 4. Frequency of Grade 0–2 xerostomia at 6, 12 and 18 months (M) after completion of RT and last follow-up visit.

NPC has a high propensity of parapharyngeal space invasion (8). The parapharyngeal space that was judged as free from tumor invasion was not encompassed within the CTV in this study period. However, no marginal recurrence was observed within the parapharyngeal space in this series of patients. If possibility of tumor invasion could not be completely denied, definition of the high-risk CTV within the parapharyngeal space by expansion of GTVp +1 cm as shown in Figure 1 was thought to be an appropriate option based on the results of previous reports (1,2,4,5,9). In general,
study, similar local control rates exceeding 90% at 3 years, which compared favorably with other series, were observed in patients with T1/2 and T3/4 tumors. Therefore, it is conceivable that the significance of our anatomical boundary-based target definition is worth testing further for patients with advanced disease, especially in the new departments intending to implement nasopharynx IMRT into their practice.

CONCLUSION

An anatomical boundary-based definition of the CTV instead of simple three-dimensional expansion of the GTV was feasible without compromising locoregional tumor control and adverse events on the premise that meticulous estimation of extent of the tumor was done with fibrescopic and modern radiographic examinations. This method has a possibility to standardize the target definition as experienced in surgical oncology, and to facilitate reduction of inter-observer variation in multicenter studies. Further study of this procedure is needed in accordance with accumulating experiences and advancing resources in IMRT.

Conflict of interest statement

None declared.

References