CRANIAL LOCATION OF LEVEL II LYMPH NODES IN LARYNGEAL CANCER: IMPLICATIONS FOR ELECTIVE NODAL TARGET VOLUME DELINEATION

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Purpose: To analyze the cranial distribution of level II lymph nodes in patients with laryngeal cancer to optimize the elective radiation nodal target volume delineation.

Methods and Materials: The most cranially located metastatic lymph node was delineated in 67 diagnostic CT data sets. The minimum distance from the base of the skull (BOS) to the lymph node was determined.

Results: A total of 98 lymph nodes were delineated including 62 ipsilateral and 36 contralateral lymph nodes. The mean ipsilateral and contralateral distance from the top of the most cranial metastatic lymph node to the BOS was 36 mm (range, 9–120; standard deviation [SD], 17.9) and 35 mm (range, 14–78; SD 15.0), respectively. Only 5% and 12% of the ipsilateral and 3% and 9% of the contralateral metastatic lymph nodes were located within 15 mm and 20 mm below the BOS, respectively. No significant differences were found between patients with only ipsilateral metastatic lymph nodes and patients with bilateral metastatic lymph nodes. Between tumors that do cross the midline and those that do not, no significant difference was found in the distance of the most cranial lymph node to the BOS and the occurrence ipsilateral or contralateral.

Conclusions: Setting the cranial border of the nodal target volume 1.5 cm below the base of the skull covers 95% of the lymph nodes and should be considered in elective nodal irradiation for laryngeal cancer. Bilateral neck irradiation is mandatory, including patients with unilateral laryngeal cancer, when elective irradiation is advised.

INTRODUCTION

Head-and-neck malignancies are relatively rare. With an incidence of 650 patients a year (1:25,000), cancer of the larynx is the second most common form of head-and-neck cancer in The Netherlands. Treatment consists of radiotherapy, surgery, or a combination of both. Primary or postoperative radiotherapy includes the primary tumor or tumor bed and pathologic lymph nodes. Elective nodal treatment is suggested for a risk of subclinical involvement of ≥20% (1, 2).

With the advances in computer technology, radiation treatment planning and delivery have changed extensively recent years. Intensity modulated radiotherapy (IMRT) offers the great opportunity to selectively treat target volumes while minimizing the dose to normal structures. As the parotid glands are positioned near the level II lymph nodes, they are likely to receive a considerable radiation dose. Radiation-induced xerostomia will appear dependent on the dose and volume irradiated (3). Reduction of the dose to the parotid gland has been achieved using IMRT, in combination with lowering the cranial border of level II target border (4–10).

With the advancements of radiotherapy techniques like IMRT, the need for adapted delineation guidelines grew. In recent years much attention has been paid to the development of guidelines, not only based on surgical experience, but also based on imaging (11–18). The cranial border of the level II lymph nodes mentioned in these guidelines varied from boundaries of the transverse process of the atlas (C1), the top of corpus C1, or the bottom of the corpus C1 (13, 16, 19). As there remained a call for standardization of target volume delineation, in 2003 a consensus guideline for delineation of the node levels in the node-negative neck was reached and presented, derived from the Brussels guidelines and Rotterdam guidelines (13, 14, 16). This consensus guideline was dis-

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cussed and agreed with representatives of the major cooperative groups in Europe (DAHANCA, EORTC, GORTEC) and in North America (NCIC, RTOG) (14). According to the consensus guideline, the cranial border of the level II lymph nodes is set at the caudal edge of lateral process of Cl. The question remains whether an anatomic or imaging based guideline is best to use for clinical treatment. It is still unclear whether these boundaries are related to clinical microscopic spread of the malignant cells. Investigating the pattern of macroscopic lymph node spread can reveal possible pathways of microscopic spread. With this knowledge and the possibility of selective irradiation, the elective target volumes might be adjusted and complications like xerostomia possibly reduced. Furthermore the consensus guidelines for target volume delineation in the clinically negative neck were proposed for all head and neck primary sites. However, one may expect that different primary sites may be associated with different patterns of nodal spread. Therefore the consensus guideline should be tailored to specific primary sites. Earlier we presented implications for the cranial border of the level II elective nodal target volume delineation in patients with oropharyngeal or hypopharyngeal cancer. We found that contralateral metastatic lymph nodes were more caudally located than ipsilateral metastatic lymph nodes. And therewith the cranial border of the contralateral elective nodal target volume could be set 20 mm below the base of the skull. Setting the ipsilateral border beneath the base of the skull was not advised (20).

The purpose of the present study was to investigate the exact position of the most cranial metastatic lymph node in laryngeal cancer. The objective of the study was to specify the cranial border of the elective nodal target volume and therewith optimize the consensus guideline. In this study we restricted our interest to the top edge of level II.

METHODS AND MATERIALS

For this retrospective study, eligibility criteria were patients with primary laryngeal cancer and clinically metastatic lymph nodes, no previous treatment for the laryngeal tumor, and a diagnostic contrast-enhanced computed tomography (CT) of the head-and-neck made at our hospital with maximum slice thickness of 3-mm. The diagnosis of a positive or metastatic lymph node by CT was defined as a lymph node with short-axis diameter greater than 1 cm, any node containing inhomogeneities suggestive of necrosis, extracapsular extension or, if it was pathologically examined, confirmed positive. From all included patients, gender, tumor stage, and ipsilateral, contralateral, or bilateral lymph node metastases were determined. Histologic confirmation of the disease was acquired. Staging accorded to the American Joint Committee on Cancer staging classification of malignant tumors (sixth edition, 2002) (21).

Between January 1995 and September 2004, a total of 152 patients with primary laryngeal cancer and with cervical lymph node metastasis were seen in the joint clinics of head-and-neck surgery and radiotherapy. Of these patients, 95 had CT scanning of the head and neck performed in our hospital. Some of the remaining 57 patients received magnetic resonance imaging (MRI) instead of CT, but most of them were referred to our hospital with CT scanning performed at an outside facility and not available for digital registration in our hospital. In ten cases of the 95 patients, the thickness of the CT slices was more than 3-mm, nine CT scans were taken postoperatively without the digital availability of the diagnostic CT data, and in nine cases there was a synchronic second primary. These cases were not included in the study, which left us with CT data of 67 patients that could be analyzed.

Only the most cranial metastatic lymph node was delineated manually by one clinician and examined by another clinician. One experienced head-and-neck radiologist reviewed some CT images in case of borderline nodes. Nodal masses not distinguishable as discrete nodes were contoured as a single mass. In case of malignant-appearing lymph nodes, the lymph nodes were labeled as metastatic. Delineation was done using in-house developed software as presented before (20, 22). Distances were measured to the caudal border of the base of the skull (BOS), defined as the most caudal and dorsal edge of the foramen magnum. The distance of the top edge of the lymph node to the BOS (zcran) and the distance of the bottom of the lymph node to the BOS (zcaud) were measured. Also the distance between center of the lymph node and the BOS was measured (zcenter) (Table 1). According to the definition a metastatic lymph node is clinically diagnosed with a short-axis diameter >1 cm. When we assume a lymph node to grow from its center, the cranial border of a metastatic lymph node extends at least 5 mm from the center. We calculated the center of the delineated lymph node, and added 5 mm cranially (zcenter + 5 mm). This border was taken as the cranial border of clinically nonmetastatic lymph nodes. The number of cranial lymph nodes included in the nodal target volume when taken this 5 mm margin from the center was calculated.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 10.1 (SPSS Inc., Chicago, IL). Data were analyzed using the paired samples t test, the Pearson correlation, and the independent samples t test. All statistical tests were two-tailed as appropriate, and a criterion of p < 0.05 was accepted for significance.

RESULTS

This report is based upon the retrospective analysis of 67 patients with squamous cell carcinoma of the larynx. Most patients were male (82%) and in 84% of the cases the primary tumor was located in the supraglottic larynx. Patient and tumor characteristics are presented in Table 2. A total of 98 lymph nodes were delineated including 62 ipsilateral and 36 contralateral lymph nodes.

The mean volume of the ipsilateral metastatic lymph nodes was 5.7 cm³ (range, 0.4–42.3 cm³; standard devia-
tion [SD], 8.9) and of the contralateral metastatic lymph nodes 3.0 cm$^3$ (range, 0.3–22.2 cm$^3$; SD 4.8). This difference was statistically significant ($p < 0.001$).

The metastatic lymph nodes at the ipsilateral side of the tumor had a mean $z_{\text{cran}}$ of 36 mm (SD 18) and at the contralateral side there was a mean $z_{\text{cran}}$ of 35 mm (SD 15) (Fig. 1 and Fig. 2a, Table 3). This difference was not significant ($p = 0.73$). Table 4 shows the percentages of the most cranial metastatic lymph nodes included in the nodal target volume when lowering the cranial border from the BOS in craniocaudal direction. When assuming a lymph node to grow from its center, a margin of 5 mm of radiologic detection is added to the center and the percentages included in the elective nodal target volume are also shown.

No significant difference was observed between the $z_{\text{cran}}$ of patients with only ipsilateral metastatic lymph nodes and the $z_{\text{cran}}$ of patients with metastatic lymph nodes on both sides ($p = 0.19$). In the latter group we investigated whether the location of the contralateral lymph node could be predicted by the location of the ipsilateral lymph node. There was a significant correlation between the $z_{\text{cran}}$ ($p = 0.01$). In other words, the cranial location of the ipsilateral metastatic lymph node can predict the cranial location of the contralateral lymph node.

To determine whether irradiation can be restricted unilateral in case of tumors that do not cross the midline, we investigated the difference in number and location of lymph node metastases between tumors that did cross the midline and those that did not. Nineteen patients had strictly unilateral tumors and of those, 11 patients had only ipsilateral lymph node metastases (58%), 2 patients had only contralateral lymph node metastases (10%), and 6 patients had lymph node metastases on both sides (32%). The 2 patients with only contralateral lymph node metastases had T2 glottic carcinoma. Of the 48 patients with tumors that did cross the midline, 21 patients had only ipsilateral lymph node metastases (44%), 3 patients had only contralateral lymph node metastases (6%), and 24 patients had metastatic lymph nodes on both sides (50%) (Table 5). No significant differences between the distances of the top of the highest metastatic lymph nodes and the base of skull could be found between tumors that did cross the midline and tumors that did not ($p = 0.49$).

Previously we presented the results of the cranial location of metastatic lymph nodes of patients with oropharyngeal or hypopharyngeal cancer (20). When comparing these results with the results found in this study, the distance of the cranial border to the BOS of the metastatic lymph nodes differed from oropharyngeal and hypopharyngeal tumors (Fig. 2a and Fig. 2b). The ipsilateral nodal metastases are located more caudal in patients with laryngeal cancer than in patients with oropharyngeal or hypopharyngeal cancer (mean 36-mm and 26-mm from the BOS, respectively) ($p < 0.005$).


**DISCUSSION**

In this study of 67 patients with advanced laryngeal cancer, we found that more than 50% of the ipsilateral and contralateral cervical metastatic lymph nodes had their cranial edge >3.5 cm below the BOS. There was no statistically significant difference between the cranial border of ipsilateral and contralateral metastatic lymph nodes. No significant difference was found between patients with only ipsilateral metastatic lymph nodes and patients with bilateral metastatic lymph nodes.

The lymphatic drainage in laryngeal cancer occurs along predictable pathways. Level II, III, and IV are most frequently involved in decreasing number (23–26). Transglottic carcinoma cross the laryngeal ventricle and involve both true and false vocal cords. They characteristically spread within the paraglottic space and invade into the laryngeal framework and outside the larynx. Cervical lymph node metastases are common and an incidence of 26–52% has been reported (27). Supraglottic tumors have a higher prevalence of regional metastases compared with cancer of the other laryngeal sites. The supraglottic area is richly supplied by lymphatics that drain into the cervical lymph nodes. An incidence of 40% overall metastatic cervical lymph nodes has been reported and 27–38% of occult metastatic lymph nodes (28, 29). Approximately only 1–8% of all laryngeal tumors are subglottic tumors. Glottic tumors with subglottic extension however are more prevalent, ranging from 11–33%. They spread primarily to the paratracheal lymph nodes. The incidence of lymph node metastases has been reported to be generally less than 10% (30).

Before the consensus guideline was reached, several guidelines have been presented for delineation of the nodal target volumes. Most recommended nodal target volumes for the node-negative patient are based on surgical dissection limits and clinical experience (11, 13, 16, 18, 31). A population-based atlas of the normal lymph node anatomy has also been described (32). There is no definitive evidence that demonstrates the superiority of one over the others. The consensus guideline for elective nodal delineation in the node-negative neck is based on anatomic landmarks that are visible on axial CT data (14). In this guideline the cranial border of level II was set at the lateral process of C1 in the node-negative neck. The question remains whether a uniform definition of borders for the head-and-neck is suited for specific head and neck tumors. Earlier we have shown that in patients with oropharyngeal and hypopharyngeal tumors, ipsilateral metastatic lymph nodes reach to the base of skull. Of the contralateral metastatic lymph nodes, 95% were included in the target volume when the cranial border was set at 2 cm from the base of the skull (20). In the present

![Fig. 2. Distribution of the distances between the top of the delineated ipsilateral and contralateral lymph nodes to the base of the skull. A division has been made between tumor groups. Median and quartiles within each category are shown. Figure 2b results adapted from a report presented earlier (20).](image)

<table>
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<th>Value</th>
<th>Side</th>
<th>Minimum (mm)</th>
<th>Maximum (mm)</th>
<th>Mean (mm)</th>
<th>SD</th>
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<td></td>
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<tr>
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<tr>
<td></td>
<td>C</td>
<td>-25</td>
<td>-84</td>
<td>-47</td>
<td>14.9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation; I = ipsilateral; C = contralateral. Values z_cran and z_mean are defined in table 1. Positive values are in cranial direction, negative values are in caudal direction.
midline (unilateral, n = 48) and tumors that did not cross the midline (unilateral, n = 19).

A division has been made between tumors that did cross the midline (bilateral, n = 48) and tumors that did not cross the midline (unilateral, n = 19).
By making two subgroups of patients, one group of patients with tumors that were strictly unilateral and another group of patients with tumors that crossed the midline, we were able to investigate the question. In the group of patients with only unilateral tumors, we saw that in almost half of the patients (42%) contralateral metastatic lymph nodes were visible, and two patients only had contralateral lymph node metastases. This highlights the need for bilateral neck irradiation and confirms today’s policy.

The present study has some limitations. One limitation is the delineation of the metastatic lymph nodes on CT. The Dutch guideline for laryngeal carcinomas recommends CT scan or MRI to be performed for almost all larynx carcinomas (2). CT and MRI have comparable sensitivity and specificity for the detection of lymph node metastases (33, 34). FDG-PET/CT has been proven superior to CT alone for localization of metastatic lymph nodes (35, 36). FDG-PET alone seems not to be superior in the detection of occult lymph node metastases in patients with a palpable negative neck (37). As this is a retrospective study, the first patients included were diagnosed for laryngeal cancer in 1995. At that time MRI or multimodality imaging was not standard at our clinic.

Our study consisted of only patients with advanced stage disease. A translation to the negative neck can be made but the study results are not specific to early stage disease. We delineated the gross tumor volume of the most cranial metastatic lymph node and pose that this gross tumor volume includes the margin of microscopic invasion in case of subclinical disease. That is, the cranial border of the gross tumor volume found in this study could be used as the cranial border of the CTV in elective field radiotherapy. Lymph nodes are considered to be enlarged if they have a short-axis diameter greater than 1 cm. Assuming the lymph node to grow from its center, the cranial edge will be located at higher distance from the BOS than the cranial edge of the clinical metastatic lymph nodes measured in this study. Taking a distance of 1.5 cm below the BOS as the cranial CTV border probably overestimates the number of lymph nodes covered, which keeps us on the safe side. This cranial CTV border does not include margins for patient motion or setup inaccuracy.

CONCLUSIONS

This study provides more evidence for selective nodal target volume delineation. In advanced laryngeal cancer, more than 50% of the cervical metastatic lymph nodes were located >3.5 cm below the caudal border of the base of the skull. This counts for ipsilateral and for contralateral nodes. We found no difference between the location of the most cranial lymph node of patients with an unilateral tumor or patients with a tumor that crosses the midline.

Setting the cranial border of the nodal target volume 1.5 cm from the caudal border of the base of the skull covers 95% of the cranial metastatic lymph nodes and should be considered in elective nodal level II irradiation for laryngeal cancer. When assuming the lymph node to grow from its center, even a further distance from the base of the skull of 2.0 cm can be achieved. Bilateral neck irradiation is mandatory, including patients with unilateral laryngeal cancer, when elective irradiation is advised.

REFERENCES


