Regional Control of Melanoma Neck Node Metastasis After Selective Neck Dissection With or Without Adjuvant Radiotherapy

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Objective: To examine the effect of adjuvant radiotherapy on regional control of melanoma neck node metastasis.

Design: A single-institution retrospective study.

Setting: Tertiary care cancer center.

Patients: The study included 64 patients with melanoma neck node metastasis who were treated with neck dissection between 1989 and 2004 in The Netherlands Cancer Institute, Amsterdam. Twenty-four patients were treated with surgery only (15 modified radical neck dissections [MRNDs] and 9 selective neck dissections [SNDs]) (S group), and 40 patients underwent surgery (28 MRNDs and 12 SNDs) and adjuvant radiotherapy (S+RT group).

Results: Prognostic factors, ie, number of nodes, size of nodes, and extracapsular extension, were worse in the S+RT group. With a median follow-up of 2.5 years, the 2-year ipsilateral regional recurrence (RR) rate was 18% in the S+RT group and 46% in the S group. This 28% difference in RR was not statistically significant (P = .16). However, evaluation of the effect of adjuvant RT in multivariate analysis revealed a significant reduction of the RR rate after correction for the number of involved nodes (P = .04). In the S group, SND was associated with a trend toward worse RR rate compared with MRND but was not statistically significant in univariate analysis (P = .08). The type of neck dissection did not influence the RR rate in the S+RT group (P = .60). Three of the 4 RRs occurred outside the dissected volume after SND in the S group.

Conclusions: Based on our findings, we conclude that, compared with extended neck dissection, SND leads to inferior regional control in patients with melanoma neck node metastasis who are not treated with RT, even those with low-risk neck disease. Furthermore, our results suggest that adjuvant RT improves regional control in patients with 2 or more involved nodes.

SND, selective neck dissection; S

Other risk factors were the presence of a large involved node (>3 cm), a tumor spill at time of surgery, and recurrence. Postoperative radiotherapy (RT) should be considered for patients with these characteristics. Combined modality therapy with surgery and RT in high-risk patients consistently lowers the RR rates to 7% to 14% but does not affect overall survival.3 An RR can be a psychological and physical burden, often with limited treatment options. Therefore, preventing an RR can improve quality of life, even if it does not increase long-term survival.

In our study, we reviewed 64 cases of cutaneous melanoma neck node metastasis to analyze the ipsilateral RR rate in low-risk patients after surgery alone and in high-risk patients after surgery and postoperative RT. The influence of the type of neck dissection was evaluated in detail.

### METHODS

Sixty-four patients with newly diagnosed melanoma neck node metastasis who had been treated between 1989 and 2004 in the Netherlands Cancer Institute, Amsterdam, were retrospectively analyzed. The treatment characteristics are summarized in **Table 1**. All patients had pathologically proved melanoma neck node metastasis before a neck dissection was performed either by SN (16%) or by fine-needle aspiration of clinically suspect nodes on palpation or ultrasound (84%). Twenty-four patients were treated with surgery only (S group) and 40 patients underwent combined therapy with surgery and adjuvant RT (S+RT group) of the entire ipsilateral neck.

Surgery consisted of MRND (lymph node levels I-V) or SND (lymph node levels I-III, II-V, or IV-V) depending on the location of the primary tumor. Another consideration was the number of involved neck nodes (eg, MRND was performed in cases involving multiple nodes). Criteria for adjuvant RT were ECE, nodes larger than 3 cm in diameter, or the presence of 2 or more positive nodes (before 1992, ≥ 3 positive nodes; the change in policy was based on our own experience and a publication from the University of Texas M. D. Anderson Cancer Center®). Radiotherapy was delivered in fractions of 6 Gy once a week for 4 to 6 weeks, to a total dose of 24 to 36 Gy. It was started between 3 and 9 weeks after surgery (average, 38 days) and delivered with a 3-dimensional conformal or intensity-modulated RT technique. The primary end point was ipsilateral RR, which was scored as a recurrence on the ipsilateral side of the neck; it was noted whether the recurrence was located inside or outside the surgically treated neck levels. Secondary end points were local control, contralateral regional control, disease-free survival (DFS), and overall survival (OS).

Recurrence and survival were calculated from the time of lymph node dissection. Patients were censored at time of death or last follow-up. Survival curves were constructed using the Kaplan-Meier method. Cox univariate proportional hazards regression analysis was performed to establish factors that were associated with regional control, DFS, and OS. Patient-, tumor-, and treatment-related factors included age, sex, primary location, Breslow thickness, Clark level, histopathologic type, interval between primary tumor and neck node metastasis, type of neck dissection, SN, parotidectomy, RT, number of nodes, nodal diameter, and ECE. The log-rank test was used for comparison between groups; P < .05 was considered significant. To evaluate whether adjuvant RT was a significant predictor of regional control after adjustment for other factors, multivariate analysis was performed. Because of the small population, we added age and known prognostic factors (number of positive nodes, size of positive nodes, and presence of ECE), 1 at a time, to a model with adjuvant RT to see whether the hazard ratio (HR) remained the same (ie, within approximately 10% of its univariate value), indicating that the effect found at univariate analysis is a true effect.
PATIENT, TUMOR, AND TREATMENT CHARACTERISTICS

The patient, tumor, and treatment characteristics are summarized in Table 1. The median follow-up was 2.5 years. All primary tumors were located in the head or neck area, with the occipital region and the cheek being the most common sites in both groups. The mean Breslow thickness was 4.3 mm in the S/H11001 RT group and 3.3 mm in the S group. All patients underwent neck dissection as primary treatment, either MRND (28 of the patients [70%] in the S/H11001 RT group and 15 of the patients [63%] in the S group, respectively) or SND. A posterolateral dissection (levels II-V) and a supraomohyoidal dissection (levels I-III) were almost equally distributed: both were performed in 6 of the patients (15%) in the S/H11001 RT group and 4 of the patients (16%) in the S group. Also, 1 patient in the S group underwent SND of levels IV and V. The prognostic factors were worse in the S/H11001 RT group than in the S group (Table 1). More patients in the S/H11001 RT group had ECE (14 [35%] vs 2 [8%] in the S group), more than 1 positive node (34 [85%] vs 9 [37%] in the S group), and larger nodes (20 [50%] with nodes >1.5 cm vs 7 [29%] in the S group).

IPSILATERAL REGIONAL CONTROL

The 2-year ipsilateral RR rate was 18% in the S/H11001 RT group and 46% in the S group (Figure 1). The 28% difference in regional control in favor of the combined modality group was not statistically significant (P = .16) but was present despite worse prognostic factors in this group.

LOCAL CONTROL, CONTRALATERAL REGIONAL CONTROL, DFS, AND OS

Local recurrence and contralateral RR were not significantly different between the 2 groups (involving 5 and 3 patients, respectively, in the S/H11001 RT group [P = .80] and 4 and 2 patients, respectively, in the S group [P = .80]). Disease-free survival and OS were worse in the combined modality group (the 2-year DFS was 18% in the S/H11001 RT group and 29% in the S group [P = .30, Figure 2]). The combined modality group was associated with a trend toward worse OS but was not statistically significant [the 2-year OS was 26% in the S/H11001 RT group and 58% in the S group [P = .07, Figure 3]].

UNIVARIATE ANALYSIS

The main results of the univariate Cox regression for the end points of ipsilateral RR and failure (local, regional, metastasis, or death) are given in Table 2. Age was the only factor that significantly influenced the risk of RR; the HR was 1.04 (95% confidence interval [CI], 1.01-1.07; P = .02) for each year older. Adding adjuvant RT resulted in an HR of 0.5 for the RR rate, although this effect was not statistically significant (P = .17). The stability of this HR was further investigated in a multivariate analysis.

The influence of the type of neck dissection was evaluated in the 2 groups (S and S/H11001 RT). In the S group, SND
was associated with a trend toward a worse RR rate compared with MRND but was not statistically significant in univariate analysis (P = .08). The type of neck dissection did not influence the RR rate in the S/H11001 RT group (P = .60, Figure 4). In the S group, 4 of 9 patients had an RR after SND and 4 of 15 patients had an RR after MRND. Three of the 4 RRs occurred outside the dissected volume after SND in the S group (Table 3). The 3 patients involved all underwent SND (2 patients, levels I-III; 1 patient, levels IV-V) for a single positive node, and all 3 developed an ipsilateral recurrence at another level. There were no recurrences in level I after SND of levels II through V for a posteriorly located melanoma. In the S/H11001 RT group, 1 of 12 patients had an RR after SND and 5 of 28 patients had an RR after MRND; all RRs occurred inside dissected levels (Table 2).

The DFS and the OS were influenced by the number of positive nodes (OS: HR, 1.19; 95% CI, 1.08-1.31; P = .001). A Breslow thickness extending beyond 4 mm was associated with a trend toward increased failure; however, it did not correlate significantly with OS (HR, 1.6; 95% CI, 0.90-2.90; P = .14).

### MULTIVARIATE ANALYSIS

To evaluate whether adjuvant RT was a predictor for RR after correction for other factors, a multivariate analysis was performed (as mentioned in the “Methods” section, the multivariate analysis was limited because of the small patient group). We included adjuvant RT and 1 other factor at a time. The factors analyzed were age and known prognostic factors for ipsilateral regional control (the number of positive nodes, the size of positive nodes, and the presence of ECE). The HR of 0.5 (the effect of adjuvant RT on the RR rate) found in univariate analysis did not increase after correction for these factors. After correc-

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### Table 2. Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ipsilateral Regional Recurrence (HR [95% CI])</th>
<th>P Value</th>
<th>Failure (Local, Regional, Metastasis, or Death) (HR [95% CI])</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (yes vs no)</td>
<td>0.50 (0.20-1.60)</td>
<td>.17</td>
<td>1.30 (0.70-2.40)</td>
<td>.30</td>
</tr>
<tr>
<td>No. of N+ nodes (N2+ vs N0-1)</td>
<td>1.20 (0.40-3.60)</td>
<td>.24</td>
<td>1.80 (0.95-3.30)</td>
<td>.07</td>
</tr>
<tr>
<td>Size of N+ nodes (&gt;1.5 cm vs ≤1.5 cm)</td>
<td>0.50 (0.10-1.80)</td>
<td>.30</td>
<td>0.70 (0.40-1.30)</td>
<td>.30</td>
</tr>
<tr>
<td>ECE (yes vs no)</td>
<td>0.70 (0.20-2.60)</td>
<td>.60</td>
<td>1.30 (0.70-2.40)</td>
<td>.30</td>
</tr>
<tr>
<td>Age</td>
<td>1.04 (1.01-1.07)</td>
<td>.02</td>
<td>1.01 (1.00-1.02)</td>
<td>.30</td>
</tr>
<tr>
<td>Breslow thickness (≥4 mm vs ≤4 mm)</td>
<td>1.98 (0.69-5.70)</td>
<td>.20</td>
<td>1.70 (0.96-3.00)</td>
<td>.07</td>
</tr>
<tr>
<td>Type of surgery (MRND vs SND)</td>
<td>0.70 (0.20-2.20)</td>
<td>.60</td>
<td>0.60 (0.40-1.10)</td>
<td>.80</td>
</tr>
<tr>
<td><strong>Multivariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy (yes vs no)</td>
<td>0.30 (0.10-0.97)</td>
<td>.04</td>
<td>0.90 (0.40-1.90)</td>
<td>.80</td>
</tr>
<tr>
<td>No. of N+ nodes (N2+ vs N0-1)</td>
<td>2.60 (0.70-9.40)</td>
<td>.15</td>
<td>1.80 (0.90-4.00)</td>
<td>.12</td>
</tr>
<tr>
<td>Radiotherapy (yes vs no)</td>
<td>0.40 (0.20-2.20)</td>
<td>.40</td>
<td>1.50 (0.80-2.90)</td>
<td>.20</td>
</tr>
<tr>
<td>Size of N+ nodes (&gt;1.5 cm vs ≤1.5 cm)</td>
<td>1.06 (0.30-4.10)</td>
<td>.50</td>
<td>0.60 (0.30-1.20)</td>
<td>.17</td>
</tr>
<tr>
<td>ECE (yes vs no)</td>
<td>0.50 (0.20-1.60)</td>
<td>.27</td>
<td>1.30 (0.70-2.50)</td>
<td>.40</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.20-3.70)</td>
<td>.90</td>
<td>1.10 (0.60-2.20)</td>
<td>.70</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ECE, extracapsular extension; HR, hazard ratio; MRND, modified radical neck dissection; SND, selective neck dissection.
tion for 2 or more involved nodes, the resulting HR of 0.3 for ipsilateral RR was significant (95% CI, 0.10-0.97; \( P = .04 \)).

**COMMENT**

If clinically enlarged melanoma neck node metastasis is present, the likelihood of additional disease in the remaining lymph nodes is 42% to 66%, thus indicating the need for treatment. Even in patients with melanoma neck node metastasis that has been diagnosed with an SN, the likelihood of additional disease in the ipsilateral neck is 12% to 42%. Whether a neck dissection in these patients is always indicated is investigated in the second Multicenter Selective Lymphadenectomy Trial.

The efficacy of postoperative RT after nodal surgery for melanoma is still unclear. Several reviews have been published, but they are mainly based on retrospective series owing to a lack of prospective randomized studies. The chance of RRs occurring after surgical treatment of cervical node metastasis is considerable, with percentages ranging from 14% to 57%. With adjuvant RT, the RR rates are lowered to 7% to 14%, without affecting survival. Improved regional control rates are particularly indicated in patients with ECE, multiple involved nodes (>3), and large involved nodes (>3 cm). The complications of adjuvant RT (mainly late fibrosis and edema) are manageable. A prospective randomized trial of observation vs postoperative RT after nodal surgery for melanoma is ongoing to further define the role of postoperative RT (Trans Tasman Radiation Oncology Group and Australian and New Zealand Melanoma Trials Group).

The primary end point in the current retrospective analysis was ipsilateral RR. In agreement with the literature, adding postoperative RT reduced the RR rate, although worse prognostic factors were present in the S+RT group. However, the 28% difference in RR rate after 2 years in favor of the combined modality group was not significant (\( P = .16 \)). Further analysis of the addition of RT on RR in multivariate analysis revealed a significant effect in patients with 2 or more involved nodes (\( P = .04 \)). As expected, OS was worse in the S+RT group.

The extent of neck dissection influenced the RR rate in the S group. Compared with patients who underwent an extended neck dissection, patients treated with SND without RT had inferior regional control, with a substantial risk of recurrence in untreated levels. Regional recurrences outside the levels that were operated on were observed in 3 patients in our study. All 3 patients had low-risk neck disease, with 1 involved lymph node without ECE, at the time of lymph node dissection. In contrast, the extent of surgery had no influence on RR in the S+RT group; in this group, no RRs were found outside the levels that were surgically treated.

One explanation for the inferior regional control after SND without RT is that there is a wide variation in the lymphatic drainage pattern of cutaneous head and neck melanoma. With increased use of SN biopsy, more information becomes available on the lymphatic drainage patterns of head and neck cutaneous melanoma. Detection of SNs is reported to be successful in 75% to 96% of procedures in studies using blue dye and/or radiotracers. In the head and neck area, multiple SNs are frequently found (average, 1-4 reported in the literature). Many patients have SNs that are located in multiple nodal fields, in nonadjacent nodal fields, or in sites not clinically predicted (discordant sites). de Wilt investigated the correlation between preoperative lymphoscintigraphy and metastatic nodal disease sites in 362 patients with cutaneous melanoma of the head and neck. Sentinel nodes were demonstrated in discordant fields in 31.5% of patients (n = 114). Lymph node metastases were found in discordant fields in 13.7% of patients (n = 7) who developed lymph node metastasis; all of the lymph node metastases were ipsilateral.

The lymphatic drainage pattern in patients with microscopic involved nodes was studied by Pathak et al. They analyzed a group of 169 patients with pathologically proven metastatic melanoma after neck dissection (141 therapeutic neck dissections and 28 elective neck dissections) and correlated the anatomical distribution of involved nodes with the primary melanoma sites. They concluded that head and neck skin melanomas metastasized to clinically predicted nodal groups in 92% of patients.
There is controversy in the literature regarding the extent of lymph node dissection that is needed to control melanoma neck node metastasis. Radical neck dissection is the criterion standard, but MRND and SND are becoming more common. Studies comparing the different types of neck dissections are scarce. Turkula and Woods described a series of 58 patients who underwent neck dissections (34 RNDs, 15 MRNDs, and 17 SNDs) with no significant difference in RR rates (32%, 0%, and 29%, respectively). Grünhagen et al retrospectively analyzed 66 patients who were treated with surgery (20 with MRND and 46 with SND) for melanoma neck node metastasis. They detected a 21% RR rate, without a significant influence of the extent of surgery in Cox regression analysis. On the other hand, in a series of 75 patients who underwent therapeutic neck dissections (32 RNDs, 15 MRNDs, and 28 SNDs), O’Brien et al found RRs in 14%, 0%, and 23% of patients, respectively. They concluded that SNDs were less effective and needed further study. However, the sample sizes were small in these studies, and some of the patients received postoperative RT (22% and 33% in the studies of Grünhagen et al and O’Brien et al, respectively).

After both MRND and SND, regional control is improved in patients who receive postoperative RT compared with patients who are treated with surgery alone. Ballo et al published a large series (160 patients) in which most patients (78%) underwent SND followed by postoperative RT, and the 10-year actuarial regional control rate was 94%. High regional control rates (5-year actuarial regional control, 93%) after local excision of nodal disease followed by RT were also reported in another study at the University of Texas M. D. Anderson Cancer Center. These data suggest that RT can compensate for limited surgery. This statement is supported by our study, in which the extent of surgery did not significantly influence the RR rate in the S+RT group.

There are some limitations to the present study. It was a retrospective study with a relatively short median follow-up (2.5 years). Furthermore, the sample size was small, and prognostic factors were not evenly spread between groups. The 28% difference found for our primary end point (RR) in favor of the combined modality group (S+RT) is clinically significant, especially because the prognostic factors in this group were worse than in the S group. However, this difference did not reach statistical significance (P = .16), likely because of the limited study size/power.

In conclusion, our results suggest that adjuvant RT improves regional control in patients with 2 or more involved nodes. Furthermore, we believe that, compared with extended neck dissection, SND leads to inferior regional control, with a substantial risk of recurrence in untreated levels, in patients treated for skin melanoma neck node metastasis without irradiation. In our institute, we perform neck dissection of levels I through V with or without parotidectomy for anteriorly located melanomas and neck dissection of levels II through V for posteriorly located melanomas. Neck dissections that are more selective should be considered only in combination with adjuvant RT.

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Author Contributions: Dr Hamming-Vrieze had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hamming-Vrieze, Hooft van Huysduylen, and Rasch. Acquisition of data: Hamming-Vrieze and Hooft van Huysduylen. Analysis and interpretation of data: Hamming-Vrieze, Balm, Heemsbergen, and Rasch. Drafting of the manuscript: Hamming-Vrieze, Heemsbergen, and Hooft van Huysduylen. Critical revision of the manuscript for important intellectual content: Balm, Heemsbergen, and Rasch. Statistical analysis: Heemsbergen. Administrative, technical, and material support: Hooft van Huysduylen. Study supervision: Balm and Rasch.

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REFERENCES