Regional Control of Head and Neck Melanoma With Selective Neck Dissection

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IMPORTANCE Historically, patients with cervical metastases from melanoma of the head and neck were treated with a radical neck dissection. This study evaluates the efficacy of limiting the extent of lymphadenectomy in this high-risk population.

OBJECTIVES To determine whether limiting the extent of lymphadenectomy for patients with biopsy-proven melanoma has a negative effect on regional control. Our hypothesis was that performing a more limited lymphadenectomy does not have a negative impact on regional control.

DESIGN, SETTING, AND PARTICIPANTS A retrospective, single-cohort study was performed using a prospectively collected database of patients with head and neck melanoma with histopathologically positive lymph nodes after modified radical (MRND) or selective neck dissection (SNDs) performed at a high-volume, academic, tertiary care center.

INTERVENTIONS Lymphadenectomy was performed as clinically indicated.

MAIN OUTCOMES AND MEASURES Primary end points were regional recurrence and regional recurrence free survival. Univariable and multivariable analyses were conducted using multiple patient characteristics.

RESULTS Forty-one patients underwent SND or MRND from 2001 through 2010. The median number of positive nodes was 1 (range, 1-16). Twenty-six patients (63%) received adjuvant radiation and 23 patients (56%) received adjuvant immunotherapy or chemotherapy. The median follow-up time was 17 months (range, 1-116 months). Regional control was achieved in 29 patients (71%). Median regional recurrence-free survival was 21 months (range, 1-116 months). Age (hazard ratio [HR], 1.13; 95% CI, 1.01-1.26), total number of nodes examined (HR, 1.05; 95% CI, 1.01-1.10), and number of sentinel lymph nodes examined (HR, 1.45; 95% CI, 1.01-2.09) were all significantly associated with increased recurrence-free survival. Tumor depth, extracapsular spread, number of nodes positive, prior SLNB, extent of lymphadenectomy, and adjuvant therapy were not significant.

CONCLUSIONS AND RELEVANCE Limiting the extent of lymphadenectomy with frequent use of adjuvant radiation therapy is effective in achieving regional control of head and neck melanoma with cervical metastases.
Cutaneous melanoma was diagnosed in approximately 76,250 individuals in 2013. The mortality rate of melanoma has also increased by approximately 2% per year since the 1960s. Regional lymph node (LN) status remains the most important prognostic factor in predicting recurrence and death from melanoma. Traditionally, a comprehensive regional lymphadenectomy was performed in all patients with clinically positive nodal disease. An elective regional LN dissection was also recommended on intermediate risk lesions, the definition of which has changed over time. While many prospective and retrospective studies have been conducted looking at therapeutic and elective LN dissection, a clear survival benefit has yet to be established. Subsequently, sentinel LN biopsy (SLNB) has become the standard of care for intermediate risks primary lesions with a clinically No neck. Comprehensive lymphadenectomy is therefore only performed in patients with clinically positive disease or a positive SLNB. Even with this increasingly focused strategy, a survival benefit from lymphadenectomy has yet to be established. Therefore, the main utility of a颈 neck dissection is regional control.

The purpose of our study was to determine if performing a more limited, selective neck dissection (SND) had a negative impact on regional recurrence and regional recurrence-free survival. Traditionally, a radical neck dissection was performed for all therapeutic neck dissections. In the 1990s, O'Brien et al. and others began limiting their lymphadenectomies to nodal basins at highest risk for metastasis. Performing SNDs has become a well-adopted strategy to minimize morbidity without sacrificing oncologic outcomes. Our study aimed to examine the effect of dissecting fewer neck levels and compared the regional control of historical studies with a modern cohort that includes sentinel LN biopsies and SNDs. Our hypothesis was that limiting the extent of lymphadenectomies provides similar regional control to the historically published data.

Methods

Oregon Health & Science University (OHSU) institution review board approval was obtained. A retrospective analysis was performed on a cohort of patient data from 2 prospectively collected institutional data sets, The Knight Cancer Institute Cancer Registry and the OHSU Melanoma Database. Included data were from patients with head and neck melanoma who underwent lymphadenectomy for either biopsy-proven LN disease or a positive SLNB. Those with a false-negative SLNB result who subsequently required lymphadenectomy were included in the study. Patients who underwent lymphadenectomy for palpable or radiographically positive disease and had no evidence of disease on final pathologic examination were excluded. Missing variables were added to the database in a retrospective review of the medical record. Patients with less than 1 month of follow-up were excluded. Patients who were followed up at another institution were contacted every 6 months by a member of the tumor registry.

Patient and tumor characteristics included age, sex, tumor site, Breslow thickness, ulceration, neck levels dissected, use of SLNB, incorporation of adjuvant radiation and/or chemotherapy plus follow-up data with time to and location of recurrence. The total number of LNs sampled and number of pathologically positive nodes were also analyzed. For those that underwent SLNB with subsequent lymphadenectomy, the total number of nodes and nodes positive reflects the sum of the SLNB and lymphadenectomy. A dissected neck level was recorded as levels I to VI as classically described, with each side being independent. A parotid dissection was counted as its own “level.” Therefore, a radical neck dissection with a parotidectomy would be considered a level VI operation. Levels on each side of the neck were counted independently.

The specific levels that were dissected were chosen by removing any clinically positive nodes plus those at greatest risk for occult disease based on the stage and location of the primary. The attending surgeon made this determination. Guidelines used for making this determination were put forth by O’Brien et al. in 1995. For melanomas lying anterior to a coronal plane based through the external auditory canal, the authors suggested parotidectomy plus dissecting levels I to III plus or minus IV. For melanomas posterior to this plane, levels II to V were dissected. For melanoma lying along the plane, levels I to V were dissected, and for lesions lower on the cervical skin, levels III to V. In our patients, occipital nodes were always taken with level V, but level V was sometimes dissected without the occipital nodes. The location of the primary guided this decision. Postauricular nodes were managed in a similar fashion. Three surgeons performed the neck dissections (N.D.G., P.E.A., and J.T.V.). Adjuvant radiation therapy was administered according to National Comprehensive Cancer Network (NCCN) Guidelines. Follow-up protocol varied depending on surgeon and tumor characteristics.

The primary end points were regional recurrence and regional recurrence-free survival (RFS). Data were compared using the Stata software package (StataCorp). Independent-sample t test, χ² tests, and Fisher exact tests were used for univariate analysis. Stepwise multivariable regression analyses were performed with P < .20 being required for inclusion. P < .05 was considered statistically significant.

Results

Patient demographics and tumor characteristics are summarized in Table 1. Forty-one patients underwent therapeutic SND from 2001 through 2010. Men comprised 61% (25 patients) of the study population. The median patient age at the time of diagnosis was 62 (range, 14–83) years. Twenty-six patients (66%) underwent SLNB prior to their lymphadenectomy. Of those, 8 patients (20%) had a false-negative SLNB result. The median (range) number of lymphatic neck levels dissected was 4 (1–7) and positive LNs was 3 (1–16). Thirty-eight lymphadenectomy operations (93%) could be considered SNDs. Nine patients (22%) received adjuvant radiation, 6 patients (15%) received adjuvant immunotherapy or chemotherapy, and 17 patients (41%) received a combination. The median follow-up time was 17 (range, 1–116) months. Regional recurrence occurred in 12 patients (29%) during the study period. Median regional RFS was 21 (range, 1–116) months. Kaplan-Meier curve for regional RFS can be seen
in the Figure. The lymph ratio (number LNs positive to number LNs examined) for patients with regional recurrence was 0.08, yet the ratio in patients without recurrence was 0.13.

Regional recurrences occurred within the previously dissected field in 8 patients (67%), outside the field in 3 patients (25%), and both within and outside of the field in 1 patient (8%). The tumors that recurred outside the previously dissected area were as follows: an auricular primary that recurred with a node next to the thyroid cartilage, an auricular primary lesion that recurred with a contralateral level IILN, and an eyelid primary lesion that recurred in the parotid. In the last patient, the original operation did not include the parotid because the SLNB was positive in level II. The lesion that recurred both within and outside the dissected area was a postauricular primary that recurred in the parotid plus the previously dissected level V. Of the patients who had recurrence within the previous field, 2 were described as subdermal nodules. Table 2 summarizes several other studies attempting to characterize similar data. Regional control rates of therapeutic lymphadenectomy are 17% to 43% in studies from 1984 to 2002; SLNB was not performed in any of these historical controls.

Univariable and multivariable associations between regional recurrence and multiple variables were calculated and listed in Table 3. Age was a significant predictor of regional recurrence (relative risk, 1.08; 95% CI, 1.01-1.15 [P = .02]) in univariable analysis. Tumor depth, extracapsular spread, number of nodes positive, prior SLNB, extent of lymphadenectomy, adjuvant radiotherapy and adjuvant immunotherapy were not significantly associated with overall regional recurrence. Multivariable analysis did not reveal any significant associations. Univariable and multivariable associations between regional RFS and multiple variables were calculated and listed in Table 4. Total number of LNs examined was significantly associated with improved RFS in both univariable (relative risk, 1.03; 95% CI, 1.00-1.07 [P = .05]) and stepwise multivariable (P = .02) analyses; however, the effect was mild, with a hazard ratio of 1.05 (95% CI, 1.01-1.10). While not significant in the univariable analysis, older age (hazard ratio, 1.13; 95% CI, 1.01-1.26 [P = .03]) and number of sentinel LNs examined (hazard ratio, 1.45; 95% CI, 1.01-2.09 [P = .04]) were associated with improved RFS in the multivariable analysis.

Discussion

This retrospective analysis of a prospectively collected database revealed that in patients with melanoma with pathologically positive LNs, limiting the extent of lymphadenectomy is
not associated with worse regional recurrence or regional RFS. The role of regional lymphadenectomy for cutaneous melanoma is changing. Currently, the National Comprehensive Cancer Network (NCCN) recommends offering lymphadenectomy to those with clinically positive disease or patients with a positive SLNB result. The benefit of this strategy is unclear. Prior to the advent of SLNB, several studies failed to show a survival benefit from elective LN dissection. The Mayo Clinic (1978), World Health Organization (1982), and Balch (1996) performed prospective, randomized studies on patients with early-stage melanoma, who were stratified to elective lymphadenectomy vs observation. No survival benefit was established in any trial. In 2006, the Multicenter Selective Lymphadenectomy Trial (MSLT-1) also failed to establish a survival benefit for intermediate-risk patients stratified to observation vs SLNB with immediate lymphadenectomy for positive nodes. The MSLT-2 trial is currently under way and takes this one step further by stratifying patients with a known positive SLNB result into therapeutic lymphadenectomy vs observation. Proposing observation in a patient with a positive SLNB result represents a dramatic shift in ideology from the radical neck dissection historically performed for known node positive disease. While the survival benefit of therapeutic lymphadenectomy is still being elucidated, it remains a standard of care to perform lymphadenectomy on patients with known node positive disease. The extent of this procedure, however, is still being defined. Historically, patients would undergo a radical neck dissection and be subject to its associated morbidity. In 1995, O’Brien et al30 put forth their 175-patient retrospective review, where they suggested performing SNDs in an attempt to minimize surgical morbidity. Their study demonstrated a recurrence rate of 14% for radical neck dissections and 23% for SNDs. Several other studies attempt to characterize similar data and are summarized in Table 2. It appears that regional control of these therapeutic neck dissections is 17% to 43% in the studies from 1984 to 2002.

Our study examines regional control of therapeutic lymphadenectomy in a modern cohort that includes patients with a positive SLNB result in addition to those with a biopsy-proven pathologically enlarged LN. None of the prior studies included SLNB patients, as these studies were performed prior to widespread use of this technology. In our patients, we found a regional control rate of 29%, which is similar to that of historical controls. Our lymphadenectomy operations tended to be limited with a median of 3 levels dissected equal. In addition, dissecting more levels was not associated with improved regional recurrence or RFS. These results suggest that performing a more limited lymphadenectomy can provide similar regional control to the more extensive procedures performed historically.

Similarly, performing a more traditional radical or modified radical neck dissection would not have captured the 33% of recurrences outside of the originally dissected field. Two patients with auricular lesions had recurrence adjacent to the thyroid cartilage and in the contralateral neck. Neither of these sites is typically included in a radical neck dissection. Two other patients with postauricular and eyelid primary lesions had recurrence in the parotid gland. In both cases, the lymphoscintigraphy performed during the SLNB did not indicate the parotid as a primary area of drainage for the lesion, and SLNB is an accurate modality for making this determination. Elective dissection of the parotid in this setting is an area of controversy that requires additional investigation.

The majority of patients (67%) who experienced regional recurrence did so within a previously dissected field. Therefore, performing an operation that removes additional levels is unlikely to provide additional benefit. It is possible, however, that the recurrences were located at the margin of a level.
in which case a more radical operation may have proven useful. In addition, 2 of the regional recurrences were described as subdermal nodules, which may actually represent in-transit metastasis rather than a nodal recurrence. Distinguishing between these 2 entities can be challenging.

Selective neck dissection is based on the concept that when a given level is removed, all of the LNs in that level are extirpated. Whether a more complete lymphadenectomy of a given level would improve regional recurrence is not known. In our study, improved regional RFS was associated with increased number of LNs examined. Increasing the number of LNs examined may be secondary to a more comprehensive lymphadenectomy, but we did not have a standardized protocol for counting LNs. The LN ratio (number of nodes positive to number of nodes examined) has been associated with improved disease-specific survival.18 In our study, the LN ratio of patients with recurrence was paradoxically higher than those without recurrence.

Our armamentarium of adjuvant therapy is growing rapidly.19 New immunotherapeutics used alone and in combination are poised to revolutionize our ability to control melanoma. As lymphadenectomy remains the standard of care for the management of involved nodal basins, our goal is to augment regional control while minimizing morbidity. The role of systemic therapy in regional control is an area of active study.

Our study has several limitations. The small sample size and partial retrospective data collection allow for confounding. The greatest confounder is likely selection bias, since the patients believed to have less aggressive disease were those selected to have less extensive lymphadenectomy procedures. In addition, 63% of patient received adjuvant radiation therapy, which likely augmented our regional control. Patients who underwent adjuvant radiation met the principles of radiation therapy found within the NCCN guidelines.15 Our study also differs by defining the extent of lymphadenectomy as a continuous variable. This decision was made because most of our lymphadenectomy procedures are considered SNDs. If each possible combination of nodal groups were analyzed as its own categorical variable, the sample size for each group would be too small. In addition, we tend to think of nodal drainage as continuous with adjacent groups.

Conclusions

Our study suggests that limiting the extent of lymphadenectomy for head and neck melanoma does not compromise regional control. Given that we offer neck dissections to patients with clinically positive disease and positive sentinel LN biopsy results, it is important that we provide optimal regional control while limiting morbidity. Therefore, performing less extensive lymphadenectomy is a reasonable strategy.

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Study concept and design: Geltzeiler, Monroe, Givi, Andersen, Gross.

Acquisition, analysis, or interpretation of data: All authors.

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REFERENCES