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Lymphatic drainage patterns of head and neck cutaneous melanoma: does primary melanoma site correlate with anatomic distribution of pathologically involved lymph nodes?

Petar Suton[1], Ivica Lukšić[2], Danko Müller[3], Mišo Virag[2]

[1] University of Zagreb School of Medicine, Šalata 3, 10000 Zagreb, Croatia

[2] University of Zagreb School of Medicine, Department of Maxillofacial Surgery, University Hospital Dubrava, Ave. Gojko Šušak 6, 10000 Zagreb, Croatia

[3] Department of Pathology, University Hospital Dubrava, Ave. Gojko Šušak 6, 10000 Zagreb, Croatia

Correspondence:

Ivica Lukšić

Department of Maxillofacial Surgery

University Hospital Dubrava

Ave. Gojko Šušak 6

10000 Zagreb

Croatia

Phone: +385 1 290 3067

Fax: +385 1 286 4250

E-mail: luksic@kbd.hr

Abstract

The aim of this study was to analyze patterns of metastatic spread from cutaneous head and neck melanoma which are said to be highly variable. The medical records of 145 patients with pathologically proven metastatic melanoma were reviewed retrospectively. The location of pathologically positive lymph nodes was compared with clinically predicted spread, and patients with metastatic disease in areas outside of predicted drainage patterns were considered aberrant. There were 33 curative and 73 elective neck dissections. Twenty-one of 77 patients undergoing parotidectomy had positive results for metastases. Clinical prediction proved to be correct in 33 of 45 cases (73.3%). Two patients with lateralized melanomas were initially seen with contralateral metastases. Six of 45 patients (13.3%) developed contralateral metastases after neck dissection. Patients with clinical involvement of the parotid gland were at high risk of occult neck disease (40%). Patients undergoing neck dissection for primaries originating in face, forehead, coronal scalp, periauricular area, and upper neck should be considered for parotidectomy. Patients with posterior scalp and posterior neck primaries should be considered for selective neck dissection in conjunction with posterior lymphadenectomy. In patients with coronal scalp and periauricular primaries, a complete neck dissection including parotidectomy is recommended approach.

Keywords: head and neck melanoma, neck dissection, clinical prediction, lymphatic drainage pattern, nodal status

INTRODUCTION

Treatment of melanoma of the head and neck is a complex issue. The behaviour of this malignancy is aggressive, and it has an overall worse prognosis than that of other skin sites[19].

Histological involvement of regional lymph nodes by metastases of malignant melanoma in the head and neck region is a very poor prognostic sign, and it appears to carry an even more ominous prognosis than histological involvement of axillary or inguinal lymph nodes in draining melanomas of the trunk or extremities[32]. Therefore, accurate localization of pathologically involved cervical lymph nodes is crucial in the treatment of these patients.

Some studies have reported that patterns of lymphatic drainage from a given area of skin in patients with melanoma are highly variable from patient to patient and that accurate clinical prediction of lymphatic pathways is not possible[39, 41]. This study is design to determine the accuracy of clinically predicting the distribution of pathologically involved lymph nodes related to primary melanoma site.

MATERIALS AND METHODS

The medical records of patients with primary cutaneous head and neck melanomas, who were referred to the Department of Maxillofacial Surgery of the University Hospital Dubrava, University of Zagreb School of Medicine, from January 1, 1985 to December 31, 2005, were reviewed retrospectively. Patients with primary melanomas of the head and neck who underwent primary surgical treatment were included. The exclusion criteria were as follows: patients who did not undergo primary surgical treatment; patients with primary cutaneous melanoma localized outside of the head and neck region; patients who had been previously excised, had local recurrence, or neck metastasis and patients with external ear melanomas. Among 145 patients with cutaneous head and neck melanomas, 39 patients underwent wide local excision due to their thickness (<1mm), while 106 patients underwent neck dissection.

All cases were re-classified according to the AJCC melanoma staging system[1]. Primary tumor mitotic rate has been excluded from our survival analysis as potential predictive factor because it was not a factor earlier classifications and data on this are incomplete and unreliable. The harvested lymph nodes were evaluated using serial sectioning with hematoxylin-eosin (H&E) staining while immunohistochemical staining with antibodies for S-100p, HMB-45 and MART-1 were used for patients when H&E did not reveal evidence of metastatic disease since this procedure has 10-30% higher sensitivity for identifying micrometastases compared with conventional H&E staining[9, 17, 24, 42]. The location of pathologically positive lymph nodes was compared with clinically predicted spread, and all patients with metastatic disease in areas outside of predicted drainage patterns (including drainage to contralateral lymph node of neck) were considered aberrant. Follow-up intervals were calculated in months from the date of first treatment at our Department to the date of last follow-up or death.

Statistical methods

In this retrospective, single-institution study, the clinical features, including age, gender, histological type, and localization of the tumours were obtained from clinical records. Patient characteristics were recorded on MS Excel® spreadsheets and analyzed using MedCalc statistical software (Version 11.3.1 © 1993-2010. MedCalc Software bvba, Broekstraat 52, 9030 Mariakerke, Belgium). Fisher's exact test was used to determine the level of significance for categorical variables. The Kaplan-Meier statistical method was used to generate survival curves. Differences in survival were analysed using a log-rank test. Values of $P<0.05$ were considered statistically significant.

RESULTS

Over the 21-year period, 145 patients with head and neck cutaneous melanomas were surgically treated at the Department of Maxillofacial Surgery, University Hospital Dubrava, in Zagreb, Croatia. There were altogether 106 neck dissections, among which 33 were curative and 73 were elective procedures. Radical neck dissections were performed as well as elective and curative treatments (14 vs. 12), while the selective were used almost exclusively as an elective (40 vs. 1). More than two thirds of elective selective neck dissections were supraomohyoid neck dissection (34/40), and the only curative selective dissection was performed for regions 2-5. Modified radical neck dissections were performed more often as elective procedures (12 vs. 7), while extended radical neck dissections were used more often as curative treatments (10 vs. 6). There were 4 bilateral neck dissections (one bilateral modified radical neck dissections, two modified radical neck dissections with contralateral radical neck dissection, and one radical neck dissection with contralateral selective neck dissection). Type of performed neck dissections are summarized in Table 1.

Figure 1 shows Kaplan-Meier survival curves of patients with an ulcerated melanoma compared with patients with a nonulcerated melanoma. Comparation of survival curves has shown significant difference with respect to survival (P=0.048). Age was considered a discontinuous variable and was divided into three arbitrary groups: twenty-nine patients were aged 21 to 40, 33 patients were aged 41 to 60, and 44 patients were above 61 years old. The age groups failed to show any significant difference with respect to survival [(P= 0.624), Figure 2]. Gender was analyzed by log-rank test comparison of survival curves. Cumulative survival at 5 years for entire group was 61.3%. The gender groups differed significantly with respect to survival [(P= 0.042), Figure 3]. Lymph node involvement significantly decreased survival rates (P<0.01). Figure 4 shows comparative melanoma-specific survival among

patients compared to nodal status. Analysis of influence on survival of negative neck compared with nodal disease in the parotid gland and neck and with nodal disease in the parotid lymphatics or neck alone has shown significant difference in survival rates ($P<0.01$). When all node-positive (n=45) and node-negative (n=51) patients were considered as two different groups, the cumulative survival was 44% and 87% at 5 years, respectively ($P< 0.01$).

Extracapsular extension (ECE) of melanomas was identified in 9 of 45 (20%) patients with histological positive nodes. There was no significant difference in survival between patients with ECE compared with patients without ECE ($P=0.956$). Lymph node metastases were found in 84.8% (28 of 33) of curative neck dissections, and occult metastases were identified in 17.8% (13 of 73) of elective neck dissections. In 77 patients, a parotidectomy was carried out in conjunction with a neck dissection. Among the elective procedures, there were 34 superficial and 28 total parotidectomies. The therapeutic procedures comprised 9 superficial and 6 total parotidectomies. Twenty-one patients undergoing parotidectomy as a part of regional lymphadenectomy had involvement of the parotid lymphatics (11 of 15 in therapeutic parotidectomy and 10 of 62 in elective procedures). Among 15 patients with clinical metastatic melanoma of the parotid, 9 patients (60%) had pathological involvement of cervical lymph nodes (6 elective and 3 curative neck dissections). Mean follow up was 56.3 months (range, 0-243). There was one postoperative death involving a 72-year-old man who suffered myocardial infarction and died 6 days after surgical therapy. As adjuvant treatment, the majority of patients received interferon (n=23), followed by chemotherapy (n=18), chemotherapy with radiation (n=3), radiation alone (n=1), and radiation with immunotherapy (n=1) and they were all included in the study group.

After eliminating patients with histological negative necks (n= 51), patients with nodal metastases from an unknown primary melanoma site (n= 6) and patients with primaries outside the head and neck region with regional metastases (n= 4), 45 patients were eligible for this study. Clinical characteristics of these patients are summarized in Table 2. The study group included 28 men and 17 women with a median age of 49 years (range, 21-75 years).

The mean tumour thickness in the study group was 4.2 mm (range, 1-10 mm). Based on thickness, melanomas were stratified into thin (n=0), intermediate (n=17) and thick (n=28). The number of nodal metastases per patient averaged 3.98 (range, 1-17).

The skin of the head and neck was divided into 6 anatomic subsites (Figure 5). Pathological findings were correlated with primary melanoma site, which was assigned to the one of six anatomic subsites and then compared with clinical prediction. The algorithm for determining drainage was based according to the patterns described by O' Brien et al.[30]. The correlation between clinical prediction based on primary melanoma site and anatomic distribution of nodal metastases is shown in Table 3.

Primary melanomas of the forehead and face were metastasing to the parotid gland or neck levels 1-3 in 12 of 16 cases. One patient with a cheek melanoma developed regional metastases outside of the predicted area (contralateral level 3 lymph nodes) and one patient with upper lip melanoma had regional metastases at level 1 and 4 lymph nodes. A patient with forehead melanoma had positive nodes at level 1 and 5 in the ipsilateral neck. One patient with a melanoma of the face had pathological involvement of an ipsilateral parotid gland and level 2-5 lymph nodes. Primary melanomas of the periauricular area and coronal scalp spread to the parotid region or neck level 1-5 in 15 of 16 cases. One patient with a coronal scalp

malignancy developed ipsilateral pathological involvement of level 1 lymph nodes and contralateral metastatic disease at level 2 lymph nodes. Melanomas of the posterior scalp and posterior neck were metastasing to the occipital lymph nodes or level 2-5 lymph nodes in 2 of 6 patients. Two patients with melanomas of the posterior scalp developed postauricular lymph node involvement. One of these two patients had also metastatic spread to neck levels 2-5, while one patient with the same primary site developed metastatic disease in nuchal lymph nodes. Nuchal lymph node involvement occurred also in patients with a primary melanoma of posteroinferior neck. Melanomas of the superior neck were predicted to spread to level 1-5 lymph nodes, which were found to be true in 3 of 6 cases. Three patients developed metastases in parotid nodes, which were considered an unpredicted lymphatic drainage pattern. One patient with melanoma of the jugular area (anteroinferior neck) developed regional disease in the predicted domain (level 6 lymph node). Two patients with lateralized melanomas were initially seen with contralateral metastatic disease. Six of 45 patients (13.3%) developed drainage to contralateral levels after ipsilateral neck dissection. Level 1 was more commonly involved with anterior primary sites (face, forehead, coronal scalp, periauricular region and upper neck) than posterior sites (posterior scalp and neck), 35.9% vs. 0% respectively. Involvement of level 4 occurred in 15.6% (7 of 45), ranging from 0% for upper neck melanomas to 33.3% for melanomas of posterior scalp and neck. Regional metastatic disease at level 5 occurred in 22.2% (10 of 45), with lowest incidence for upper neck melanomas (0%) and highest for coronal neck and periauricular melanomas (37.5%).

Postauricular and nuchal involvement occurred only in cases of posterior scalp and posterior neck melanomas. Clinical prediction proved to be correct in 73.3% of cases. Twelve patients (26.7%) showed lymphatic drainage inconsistent with clinical prediction. Thick melanomas proved to be associated with unpredicted drainage patterns 75% of the time (9 out of 12),

while intermediate melanomas showed aberrant metastatic spread 25% of the time (3 out of 12).

In the follow up period, 29 of the 45 node-positive patients developed recurrence at the mean interval of 15.8 months (from 2 to 86 months). Among 51 node-negative patients 10 developed recurrence at a mean interval of 33.8 months (from 6 to 86 months). From a total of 29 recurrences, the first clinical signs of recurrence were found to be local (n=4; 13.8%), locoregional (n=3; 10.3%), regional (n=10; 34.5%), regional and distant (n=3, 10.3%) and distant metastases (n=9; 31.1%).

DISCUSSION

Management of regional lymphatics among patients with head and neck cutaneous melanoma, especially indications for an elective lymph node dissection (ELND), has been questioned for decades. In the past, randomized controlled trials have been conducted to determine whether ELND in patients with melanoma decreases overall mortality compared with delayed lymphadenectomy at the time of clinical recurrence and no survival advantage has been observed[2, 7, 34, 40]. However, Lens et al.[22] reported through performance of a meta-analysis (1533 participants) that these trials are of questionable validity since they contain significant methodological bias. Furthermore, previous studies involving melanomas from all anatomic sites showed a statistically significant improvement in survival in patient with intermediate thickness melanomas (range, 1-4 mm), which suggests that some subgroups of patients may benefit from ELND[3, 25, 31]. Finally, despite the fact that sentinel lymph node biopsy (SLNB) has been adopted into clinical practice as reliable staging modality, there are lots of arguments against it, such as increased incidence of nodal (regional and in-transit) recurrence in sentinel lymph nodes (SLN) negative patients, possibility of false-negative results, difficult identification of SLN if they are located close to primary site, SLN found in multiple node fields in contrast to melanomas located on extremities which usually drain to only 1 field, SLN in parotid region which are often very small, may be difficult to find, and their removal may put the facial nerve at risk[8, 10, 12, 15, 16, 29, 36, 37]. However, some authors reported that intraparotid SLN biopsy is a reliable, accurate, and safe procedure for staging cutaneous head and neck melanoma[23]. The finding that 1 in 4 patients had aberrant metastatic spread, which was not predicted clinically, is perhaps an indication that some patients may benefit from SLNB and lymphoscintigraphy. In this retrospective study, positron emission tomography (PET) was not used. Although PET's inability to identify microscopic disease suggest that is of limited use in evaluating patients with stage I-II disease, PET can be helpful in managing

patients with stage III melanoma in whom further surgery is contemplated[38]. Furthermore, Iagaru et al.[18] showed that PET has a sensitivity of 89% and a specificity of 88% for melanoma detection during restaging, and therefore should be an integral part in evaluation of patients with high-risk melanoma, prior to selection of the optimal treatment modality.

On the basis of controlled trials and our clinical experience we believe that ELND should not be forgotten treatment modality and that some subgroups of patients may benefit from this procedure.

It is generally agreed that preoperative clinical prediction of potential nodal metastatic sites based on anatomic location of the primary melanoma is difficult because of highly variable lymphatic pathways in the head and neck[39, 41]. In the present study, we have aimed to evaluate patterns of metastatic spread from primary melanoma site and to determine appropriate extent of surgery based on histological evaluation of neck dissection specimens.

This study included patients with positive lymph node pathology detected in the neck, the parotid gland, combined parotid and neck involvement, and metastatic disease outside the parotid region and five main neck levels of lymph nodes. Tumour thickness was the most important factor in determining whether or not to perform an elective neck dissection (END). All patients with histological confirmed cutaneous melanoma thicker than 1mm or thicker than 0.7mm with a Clark level of 4 were considered candidates for END. No strict criteria were used to select the extent of parotid gland surgery; however patients with thick melanomas (>4mm) were more likely to undergo total parotidectomy, no matter if the procedure was performed on an elective or therapeutic basis. The procedure was done in

64.7% (22 out of 34) of those with thick melanomas versus 35.3% (12 out of 34) of those with intermediate thickness melanomas.

Based on the incidence of involvement of parotid lymphatics, anatomic distribution of nodal metastases from levels I through V, and pathological involvement of lymph nodes outside of the five main lymph nodes levels of the neck, the following observations were made. Patients with melanomas of the face, forehead, coronal scalp, periauricular area, and upper neck were at high risk for the involvement of parotid lymphatics, whereas patients with posterior scalp and posterior neck melanomas did not have parotid metastases. These results suggest that parotidectomy should be considered for all head and neck subsites except for posterior primaries and lower neck melanomas. Based on the data from other series, some authors also recommend the use of parotidectomy as part of regional lymphadenectomy for patients with anterior primaries[4, 30, 33]. Finally, other studies reported significant and adverse influence of parotid involvement on survival[5, 6, 27]. Patients with both parotid and neck involvement demonstrated poorer prognosis than patients with neck involvement alone. It is important to be aware that parotid lymphatics are often affected with metastatic spread from upper neck primaries suggesting parotidectomy in conjunction with selective neck dissection. We believe that elective superficial parotidectomy is indicated because the parotid gland was histologically positive for metastatic melanoma in 16.1% of patients with clinically negative physical examinations. This incidence of subclinical disease is much higher than reported in the series by O'Brien et al. (2.4%)[28].

On the other side, patients with posterior scalp and posterior neck primaries had no involvement of the submandibular and submental triangles, or the parotid gland, so it may be justified to perform just a regional lymphadenectomy, excluding dissection of level 1 and any

parotidectomy. Also, patients with upper neck melanomas had no metastatic disease at levels 4 and 5 and therefore it is recommended to exclude lower jugular lymph nodes and posterior triangle when considering surgical options and to rather perform a supraomohyoid dissection. Shah et al.[33] identified similar patterns of metastatic spread from primary melanoma sites. According to results of this study, 5 of 45 patients had drainage in sites outside the parotid gland and five main levels of the neck. These patients demonstrated postauricular, nuchal and paratracheal lymph node involvement. Metastatic disease in postauricular and nuchal lymphatics was associated with posterior scalp and neck primaries. These lymph nodes are not typically dissected in standard neck dissections and spreading to these lymph node groups may be suspected. Previous studies also reported lymphatic drainage to these "discordant" sites from posterior primaries stressing that posterior neck dissection is mandatory and effective procedure to adequately resect the primary lymphatics which provides control of regional metastatic disease[11, 14]. On the other hand, O'Brien et al.[30] reported metastatic spread to postauricular lymph nodes (1 of 18 patients with posterior scalp primaries and 2 of 26 patients with coronal scalp melanomas) but no nuchal or occipital lymph node involvement was seen. Larson et al.[20] stressed that among the sites of origin in the head and neck, melanoma of the scalp and neck carries the highest mortality, with 10-year survival being only 60%. Our recommended operations based on anatomic distribution of regional metastases are summarized in Figure 6.

Also, results of this study show no statistically significant difference in pathologically involved levels between elective lymphadenectomies and therapeutic procedures and a similar distribution of nodal metastases no matter whether neck dissection has been performed based on an elective or therapeutic basis. The incidence of occult lymphatic disease among patients undergoing END was 17.8% (13 of 73 patients), which is consistent with the findings of prior

reports[13, 35]. Parotid lymph nodes were pathologically involved in 27.3% (21 of 77). Eight of 45 patients (17.8%) had involvement of the parotid region only, so cervical lymph nodes are not necessarily the initial site of regional metastases and management of lymph nodes at this site represents a major issue among patients with melanomas originating in head and neck region. Authors from Memorial Sloan-Kettering Cancer Center described different results recommending complete radical neck dissection in therapeutic conditions and more limited surgery in elective procedures[33].

According to results of this study, patients with recurrence were predominant males (18 vs. 11), had greater average melanoma thickness, higher percentage of 3 or more pathologically involved lymph nodes, higher incidence of extracapsular extension and higher percentage of parotid region drainage. However, none of the covariates tested (for recurrence rates) here were found to be statistically significant. Also, all this variables were compared using survival curves and only male gender differed significantly with respect to survival. On the other hand, some authors identified male gender, primary tumour thickness, type of neck dissection (elective vs. therapeutic), ECE, and number and size of regional metastases, as statistically significant independent negative prognostic factors[21, 26].

In conclusion, cutaneous melanomas of the head and neck metastasized to clinically predict nodal groups in 73.3% of patients in this series. This leaves a significant 26.7% of nodal metastases outside of the arbitrarily defined regions and therefore we believe it would be justifiable to perform more extensive dissection in primaries that have drainage to nodal basins outside of those predicted by the primary site. A similar distribution of nodal metastases was found, no matter if the neck dissection was performed on an elective or therapeutic basis. However, therapeutic dissections revealed aberrant regional metastases

83.3% of the time (10 out of 12), which supports the use of more extensive treatment than clinically indicated in settings of a clinically positive neck.

Also, patients with clinical involvement of the parotid gland were at high risk of occult neck disease (40%) and therefore treatment of a clinically negative neck should be considered in presence of a clinically positive parotid gland to reduce the possibility of failure to detect cervical node involvement and to determine the extent of metastatic spread.

DECLARATIONS

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Ethical Approval: Not required

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CAPTIONS TO ILLUSTRATIONS

FIGURE (1) Survival curves comparing patients with an ulcerated and patients with a nonulcerated melanoma. Solid line = nonulcerated melanoma (n=68), dashed line = ulcerated melanoma (n= 28). Log-rank test, P=0.048.

FIGURE (2) Kaplan-Meier curves showing overall survival of patients of different ages with head and neck cutaneous melanoma. Solid line = ages 21-40, dashed line = ages 41-60, and dotted line = ages 61 and above. Log-rank test, P=0.624.

FIGURE (3) Kaplan-Meier curves showing cumulative melanoma-specific survival for 106 patients and survival of patients separated by gender. Solid line=men (n=56), dashed line=women (n=50). Log-rank test, P=0.042.

FIGURE (4) Kaplan-Meier survival curves of patients compared to nodal status. Solid line = negative neck (n=51), dashed line = positive neck (n=21), dotted line = positive parotid gland (n=8), dot-dashed line = positive both parotid and neck (n=12). Log-rank test, $P<0.01$.

FIGURE (5) Distribution of the primary melanomas with pN+ among defined regions of the skin of the head and neck.

FIGURE (6) Recommended operations based on anatomic distribution of regional metastases.

Table 1

Neck Dissection	Elective ND	Curative ND	TOTAL
ERND	6	10	16
RND	14	12	26
MRND	12	7	19
1. SAN	9	5	
2. SAN + IJV	2	1	
3. SAN + IJV + SCM	1	1	
SND	40	1	41
MRNDBL	0	1	1
MRND + RNDCL	1	1	2
RND + SNDCL 1-3	0	1	1
TOTAL	**73**	**33**	**106**

Abbreviations:

ERND = Extended Radical Neck Dissection

RND = Radical Neck Dissection

MRND = Modified Radical Neck Dissection

SAN = Spinal Accessory Nerve

IJV = Internal Jugular Vein

SCM = Sternocleidomastoid Muscle

SND = Selective Neck Dissection

MRNDBL = Bilateral Modified Radical Neck Dissection

RNDCL = Contralateral Radical Neck Dissection

SNDCL = Contralateral Selective Neck Dissection

Table 2

Sex	No. (%)
Male	28 (62.2)
Female	17 (37.8)
Age	y
Median	49
Range	21-75
Primary melanoma site	No (%)
Face & forhead	16
Coronal scalp & periauricular area	16
Posterior scalp,upper & lower posterior neck	6
Upper neck	6
Lower anterior neck	1
Tumor thickness	mm
Mean	4.2
Range	1-10
Nodal metastases	No
Average	3.98
Range	1-17
Contralateral metastases after treatment	No (%)
	6 (13.3)