Research Article

The Stage III Melanoma in Cervical Region, Prognostic Impact of The Lymph Node Ratio of The Neck Dissections

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Abstract

Purpose: The lymph node (LN) status is one of the most important prognostic factors of melanoma. The first treatment of LN metastasis is the lymph node dissection (LND). To date the surgical technic for neck metastasis is discussed. The lymph node ratio (LNR) is defined as the number of invaded LNs dividing by the total number of removed LNs. The aim of our study was to evaluate the impact of the LNR and the extent of neck LND on the prognosis.

Methods: We recorded LNDs for neck LN metastasis during 16 years. Selective LND (SLND) was limited to the level with LN metastasis. Extensive LND (ELND) was extended to the adjacent LN level. The LNRs were categorized using cutoff points. Among the 62 included patients, 48 LNRs were available for the survival analysis. Time to event endpoint were defined as the time between the event and the date of the previous recurrence. The cut-off p-value for significant statistic was 0.05.

Results: Breslow thickness < 2mm presented a longer OS (p=0.035) and extracapsular spread presented a shorter OS (p=0.035). Clark levels III and IV presented a longer systemic disease free survival. The OS and the regional control were longer when the LNRs were respectively < 5% and < 10%. ELND improved the regional control, compared to SLND (p=0.02).

Conclusion: The ELND could improve the regional control compared to SLND. The LNR of neck LNDs could be a prognostic factor and should be low as possible to improve the outcomes.

Keywords: Lymph node ratio; Melanoma; Neck metastasis

Introduction

The lymph node status is one of the most important prognostic factors of melanoma patients. The first treatment of lymph node metastasis stays the lymph node dissection [1]. Cutaneous melanoma of the head and neck (CMHN) represents almost 20% of melanoma incidence rate [2]. This localization is associated with a high rate of recurrences compared to other skin sites [3]. About 15 to 20% of patients with clinical N0 head and neck melanoma patients would present node metastasis in the neck. The risk is correlated to the Breslow thickness of the primary melanoma: it is less than 5% for lesions 0.75mm or smaller and ranges from 30 to 50% for lesions larger than 4mm [4]. The identification of sentinel lymph nodes (SLN) in head and neck melanoma often leads to multiple nodes resections in different nonadjacent nodal levels. In case of neck lymph node metastasis, a neck dissection is recommended because the likelihood of additional disease in other lymph nodes is 42 to 66% [5]. The surgical technic for lymph node dissection is well standardized for axillary and groin region [6]. Regarding CMHN the extent of the neck dissection is often discussed: radical neck dissection is the standard procedure but the modified radical neck dissection and the selective neck dissection are becoming more common since adjuvant radiotherapy is frequently advocated [7]. Furthermore a quarter of head and neck melanomas metastasize outside clinically predicted neck levels [8]. The Netherlands Cancer Institute provide for some false negative results but the therapeutic neck dissection should be carefully weight against the overtreatment and the surgical morbidity [8]. In

some other cancer types (colon, lung, gastric, bladder, pancreatic and esophageal cancers) it is clearly demonstrated that the extent of lymph node dissections improve the disease-specific survival [1]. Although lymph node dissection in head and neck metastatic melanoma (stage III) enhances regional disease control, the relationship between extent of dissection and disease-specific survival is unclear [9]. However neither surgery nor radiotherapy has significant impact on overall survival (OS). The lymph node ratio (LNR) is determined by dividing the number of invaded lymph nodes by the total number of removed lymph nodes from a dissection. For melanoma three LNR cutoff values have been used for all regional dissection types but the number of lymph nodes usually excised differs considerably between the site of the dissection (neck, axillary, inguinal with eventually pelvic area) [10]. The first aim of our study is the analyze of the impact of the neck dissection extent and the LNR on the regional disease-control, the occurring of a systemic disease and the OS. The second aim is the study of the relationship between age, sex, histological characteristics of the primitive tumor, the site of the primitive melanoma, the histopathology results of the neck dissection and the regional disease control, the OS and the occurring of a systemic disease.

Materials and Methods

All the patients (n=62) who underwent therapeutic neck dissection for metastatic lymph node(s) of melanoma, between 2000 and 2015, at Jules Bordet Institute were included.

All metastasis were diagnosed by fine-needle aspiration. Patients were staged using head and neck MRI/Computed Tomography (CT) scan and PET-CT/abdominal-chest CT. The patients with distant metastasis and/or whom palliative neck dissection was required, were excluded.

Every neck dissection performed during the study was reviewed and classified as follows:

- Selective neck dissection was defined as a procedure limited to the area comprising the pathological lymph node(s).(n=12)

- Extensive neck dissection was defined as a procedure where the dissection was extended to the adjacent free of disease area. (n=36)

- The modified radical neck dissection was defined as the removal of areas I to V without sacrifice of the accessory spinal nerve, internal jugular vein and sternocleidomastoid muscle. The modified radical neck dissections were included in the group of extensive neck dissections.

- The presence of an associated parotidectomy was recorded as separate item (n=16).

We recorded the following data: the age and the gender, the LNR, the extent of the neck dissection, the extracapsular spread, the histological characteristics of the primitive melanoma (Breslow thickness, Clark level, ulceration) and the primitive site. The date of diagnosis of the primitive melanoma, and the

systemic and the loco-regional recurrence(s) were recorded. We recorded the preoperative and adjuvant treatments (radiotherapy, immunotherapy, chemotherapy) and the extent of neck dissection (with or without associated parotidectomy). The LNR was defined by the number of pathological lymph nodes divided by all lymph nodes identified in the neck dissection by the pathologist. Out of the 62 initially included patients, 48 LNRs were available for the survival analysis.

The LNRs were categorized in different groups using 4 cutoff points: 5%, 10% and 25% corresponded to cutoff values in the literature [1]. A cutoff value of 12% was also used it corresponds to the median LNR in our study.

Time to event endpoint (OS, regional control, systemic control) were defined as the time between the event (death, regional recurrence and systemic recurrence respectively) and the date of the previous recurrence. Cox model were used to derive HR and their 95% CI.

Usual statistics (means with standard deviation, median with IQR and proportions) were used to describe characteristics of our population.

The cut-off p-value for significant statistic was 0.05.

Results

Sixty two patients underwent a neck dissection for lymph node metastasis of melanoma. Eleven patients were excluded, 9 for palliative surgery and 2 for neck dissection performed after positives SLNs. Among the 51 remaining patients, there were 12 selective neck dissections and 36 extensive neck dissections. The average age of the 51 patients was 49.4 year's old (SD = 15.7). There were 17 women and 34 men. The average Breslow thickness was 3.1mm (0.15mm to 11mm). Twenty five primitive lesions (49%) were originated from head and neck area. The pathological histology of the primitive lesions were: 20 superficial spreading melanomas (SSM), 10 nodular melanomas, 6 Dubreuilh melanomas and 15 unknown histological diagnosis. We obtained the LNR for 48 patients. Among these patients we registered 9 neck dissections associated with a parotidectomy. The median follow-up (from the first recurrence) was 1.6 years (IQR: 0.76 – 3.13). The average follow-up was 2.5 years (SD = 2.8). The average number of harvested lymph nodes in each neck dissection was 19.3 (SD = 13.1) with an average of 3.65 (SD = 7.5) metastatic lymph nodes. Among elective neck dissections (n = 12), the average number of metastatic lymph nodes was 2.8 (SD = 4.7), the P50 = 1 (min-max: 0-17, IQR: 1-3). Among the extensive neck dissections (n = 36), the average number of metastatic lymph nodes was 3.9 (SD = 8.3), the P50 = 2 (min-max: 0-48, IQR: 1-3). The difference between these groups was not statistically significant. Among the selective neck dissections (n = 12) the average LNR was 0.49 (SD = 0.4), the P50 = 0.50 (min-max: 0-1, IQR: 0.04-0.88). Among the extensive neck dissections (n = 36), the average LNR was 0.18 (SD = 0.22), the P50 = 0.09 (min-max: 0-1, IQR: 0.03-0.23). The difference between these groups was not statistically significant. Twenty patients

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had an extracapsular spread. The median LNR was 0.12 and this number was considered as a threshold in our study. Among these 48 patients, 26 were exclusively treated by surgery, 27 patients (52.9%) received adjuvant radiotherapy and 7 patients have been treated with adjuvant systemic treatment. The median OS was 2.7 years (CI = 95%, 1.6 - 6.6 years) and we recorded 27 deaths during follow-up. The following results are summarized in table 1. The sex and the age (at the diagnosis and at the recurrence) had no impact on the local control, the systemic disease free survival and the OS. Regarding the histological characteristics of the primitive melanoma, the presence of ulceration had no impact on the local control, the systemic control and the OS but the Breslow thickness <2mm was associated to a longer OS. The Clark levels III and IV were associated to a longer systemic disease free survival compared

to the Clark level V. Primary melanoma arising from head and neck were associated with longer systemic disease free survival compared to other primary localizations. We obtained the same results using multivariate analysis for each variable (ulceration, sex, LNR or delay between primitive tumor and recurrence). The OS was shorter when an extracapsular spread was identified by the pathologist. Only the local control was better by extensive lymph node dissection compared to selective neck dissection. The LNR had an impact on the OS when the cut-off was 5%: the OS was longer when the LNR was < 5%. The LNRs lower than 10, 12 and 25% were associated to a better local control but had no impact on the systemic control and the OS. The selective neck dissection was associated to a greater risk of local recurrence compared to the extensive neck dissection, especially with high LNR. The delay

Table 1: Population characteristics, local and systemic control and overall survival.

		Local control (HR)	p	Systemic control (HR)	p	Overall survival (HR)	p
Age at recurrence ≥ 50 years	54.1%(n=26)	1.14 (0.45-2.91)	0.78	0.72 (0.29-1.77)	0.47	1.14 (0.52-2.51)	0.75
Men	66.7% (n=32)	1.64 (0.54-5.00)	0.39	0.99 (0.38-2.64)	0.99	0.54 (0.23-1.26)	0.16
	52.1% (n=25)	0.59 (0.223-1.51)	0.28	0.31 (0.12-0.79)	0.01	4.28 (1.79-10.20)	0.001
Breslow thickness (mm)							
≥ 4	26.8% (n=11)	1	0.84	1		1	
2-4	29.3% (n=12)	1.16 (0.26-5.21)	0.64	0.41 (0.10-1.65)	0.21	0.58 (0.19-1.81)	0.35
< 2	43.9% (n=18)	1.37 (0.36-5.27)		0.41 (0.12-1.35)	0.14	0.31 (0.11-0.92)	0.035
Ulceration	25.0% (n=12)	0.87 (0.31-2.45)	0.79	0.54 (0.18-1.65)	0.28	0.45 (0.15-1.32)	0.15
Adjuvant treatment	47.9% (n=23)	1.63 (0.64-4.15)	0.31			1.60 (0.71-3.57)	0.26
Extracapsular spread	41.7% (n=20)	2.21 (0.87-5.61)	0.1	2.16 (0.87-5.41)	0.1	2.37 (1.06-5.29)	0.035
LNR ≥ 0.05	62.5% (n=30)	2.79 (0.91-2.79)	0.07	1.33 (0.52-3.39)	0.55	2.55 (1.01-6.45)	0.048
LNR ≥ 0.25	35.4% (n=17)	9.52 (3.06-29.4)	< 0.0001	1.23 (0.47-3.26)	0.67	1.49 (0.67-1.49)	0.33
Extensive LN dissection	75.0% (n=36)	3.20 (1.22-8.30)	0.02	1.09 (0.31-3.77)	0.89	0.88 (0.37-2.12)	0.78
Histology other than superficial spreading melanoma	44.1% (n=15)	0.34 (0.09-1.29)	0.11	0.18 (0.04-0.89)	0.035	0.68 (0.24-1.93)	0.47
Delay Primary Tumor -first recurrence < 1 year	52.1% (n=25)	1.95 (0.71-5.30)	0.19			2.56 (1.07-6.12)	0.035
LNR	LN dissection						
≥ 0.12 (n = 24)	Selective	3.0 (1.0-9.0)	0.05	1.22 (0.3-5.8)	0.8	0.85 (0.3-2.5)	0.77
	Extensive	1		1		1	
< 0.12 (n = 24)	Selective	1.4 (0.1-13.0)	0.79	0.72 (0.1-5.8)	0.8	1.38 (0.3-6.5)	0.69
	Extensive	1		1		1	
LNR	LN dissection						
≥ 0.10 (n = 26)	Selective	2.8 (0.98-8.1)	0.054	1.32 (0.3-6.3)	0.72	0.80 (0.3-2.3)	0.66
	Extensive	1		1		1	
< 0.10 (n = 22)	Selective	1.8 (0.2-19.7)	0.6	0.66 (0.08-5.4)	0.7	1.65 (0.3-8.22)	0.54
	Extensive	1		1		1	
LNR	LN dissection						
≥ 0.25 (n = 17)	Selective	1.26 (0.41-3.8)	0.68	1.46 (0.27-8.0)	0.66	0.80 (0.3-2.3)	0.66
	Extensive	1		1		1	
< 0.25 (n = 31)	Selective	1.9 (0.2-18.3)	0.58	0.60 (0.08-4.7)	0.63	0.85 (0.2-3.0)	0.8
	Extensive	1		1		1	
LNR	LN dissection						
≥0.05 (n = 30)	Selective	3.5 (1.2-10.2)	0.02	1.18 (0.26-5.4)	0.83	0.80 (0.3-2.2)	0.63
	Extensive	1		1		1	
< 0.05 (n = 18)	Selective	1.4 (0.1-15.0)	0.77	0.77 (0.09-6.6)	0.81	2.26 (0.4-12.6)	0.35
	Extensive	1		1		1	

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between the time of the diagnosis of the primitive tumor and the first recurrence had no impact on the local control. These results were obtained for the delays < 3 years, < 2 years and < 1 year. No relation was found between the age of the primitive tumor diagnosis and the risk of recurrence.

Discussion

The presence of lymph node metastasis is a major prognostic factor in patients with melanoma. The LNR has been described as a prognostic factor for colon, lung, pancreatic and papillary thyroid cancers. No guidelines have been published to determine the extent of the lymph node dissection in metastatic neck lymph nodes of melanoma [9,11-13]. In our study, the local control was better after extensive neck dissection compared to selective neck dissection. The extent of the lymph node dissection had no impact on the free systemic disease survival and the OS. These results are comparable to the results published by Constantine Karakousis et al [6]. Nevertheless in our study the OS was greater only when the LNR was lesser than 5%. Rossi et al. [14] were the first to investigate the impact of the LNR on the survival of patients with melanoma. The 213 included patients were divided in 3 groups according to the LNR: <10%, 10-25% and >25%. This study showed that LNR classification might represent a prognostic factor of survival. These results were confirmed by Spillane et al. [1] in a cohort of 1514 patients. These patients had axillar, groin and neck dissection and were allocated to both AJCC N stage groupings and LNR groupings using thresholds (<10%, 10-25% and >25%). In our study the OS was longer when the LNR was < 5%. This cutoff point was lower compared to other studies, this finding could be related to the worse prognosis of HNCM patients. Furthermore there were some differences between the study of Spillane and our study. Our results concerned only neck dissections and we recorded 36 extensive neck dissections and 12 selective neck dissections among the 48 patients with a LNR. In our cohort, 49% patients (n = 25) had HNCM. In the study published by Spillane [1], 283 neck dissections of at least 4 levels were performed. Among these patients, 79% (n=223) had a HNCM. Our study exhibits a larger proportion of patients with primary lesion located outside the head and neck area, this finding could explain the different LNR thresholds. Testori et al. [10], determined a LNR categorization with the maximal prognostic value. The optimal cut-off point differed for lymph node dissections sites and was 50% for neck dissections. In our study the risk of local recurrence was greater when the LNR was > 10% and the OS was longer when the LNR was <5%. There are significant differences between our study and the study of Testori et al [10] their population counted 262 neck dissections among 2358 included patients. They included lymph node dissections for macro-metastasis (n=1482) and for micro-metastasis (n=876). In this study, the average number of examined lymph nodes in each neck dissection was 22. In our study, it was 19.3 with an average of 3.65 metastatic lymph nodes. The proportion of micro-metastasis among the cervical neck dissections was not specified in the study realized by Testori et al [10]. We did not find any correlation between OS and disease free survival using 50 year's old as a cut-

off, unlike Balch et al [15]. In this study the cut-off was 70 year's old and they included micro-metastasis and macro-metastasis. For Rossi et al [14], the age of the patients with stage III cutaneous melanoma had no impact on the OS. Nevertheless Balch et al [15] reported that age-related survival was different when comparing patients younger and older than 70 year's old. In our study we concluded that the age at the diagnosis of the primitive tumor had no impact neither on the risk of a first or a second recurrence nor on the OS. Concerning the gender, we recorded 34 men and 17 women. This difference could be explained because the site of the primitive melanoma. It has been shown that the anatomic site varies according the sex: 55% melanomas are localized on the trunk in men and 42% on the lower extremities (24% on the lower legs) in women [4]. In our cohort all patients were operated for neck lymph node metastasis and only 49% presented HNCM. The neck lymph node metastasis from lower extremities are not frequent and represent a distant metastatic progression with poor prognosis. Balch et al [15] showed that the Breslow thickness of the primary tumor and the presence of ulceration were the most predictive independent factors for survival in patients with stage III. The patients with ulcerated primary melanoma or thicker than 6mm had a worsened survival. In our study the presence of ulceration had no prognostic impact but a Breslow thickness < 2mm was associated to a longer survival. It is established that HNCM are more aggressive than other primary locations [7,3]. In the present study the head and neck primary melanomas were associated to better outcomes (DFS, OS) compared to other sites. These results could be explained because our study concerned only head and neck node metastasis. Patients with head and neck lymph node metastasis arising from other localizations (trunk, legs, upper limbs) presented a worse prognosis as the disease could be regarded as distant localization whereas it remains regional recurrence for HNCM. The rate of recurrence is higher after a neck dissection for lymph node metastasis of melanoma compared to inguinal and axillary dissection. For these locations the surgical procedure is well standardized but it is not true for neck dissection where the levels of dissection are discussed. Therefore we recorded the LNR to compare the selective neck dissection and the extensive neck dissection to have a prognostic factor. Our results concluded to a better regional control after extensive neck dissection (with dissection of adjacent area) compared to selective neck dissection (limited to the level of the metastasis). HNCM is more likely to exhibit aggressive clinical and pathological characteristics and has an unfavorable prognosis [7,3]. Nevertheless our multivariate analysis shown that head and neck melanoma for each variable (ulceration, sex, lymph node ratio or delay between primary tumor and recurrence) was associated with a longer OS than melanoma of other sites when neck metastasis are present. These results could be explained by two points: we analyzed only neck lymph node metastasis and there were only 49% melanoma originated from head and neck area. The 51% remaining patients presented distant lymph node metastasis and consequently had a poor prognosis. The presence of extracapsular spread, the number of involved lymph nodes and the size of involved lymph nodes (> 3cm) increase the risk of

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regional recurrence [5]. Therefore postoperative radiotherapy could be indicated in each of those conditions [16]. In our study, 52.9 % patients (n=27) among the patients with a known LNR received adjuvant radiotherapy. The cohort in our study was to small to analyze the impact of the radiotherapy on the OS and on the regional control. In the literature [17] short delays between treatment of the primitive tumor and recurrence is associated with poor prognosis and this delay was 12 months. We observed that the delay between the diagnosis of the primitive tumor and the first recurrence had no impact on the local control. The shorter delay was 1 year and our cohort was small therefore that could explain the absence of significant results. We studied a small cohort and the median follow-up was less than 10 years. In the recent years, the indications and the types of adjuvant treatments in metastatic melanoma have considerably evolved (i.e. immunotherapy). Therefore our results concerned mainly the surgical technic and actually could not be generalized for patients with adjuvant immunotherapy. These are the limitations of our study. In our study we analyzed more parameters than other studies about neck dissections in stage III melanoma. It is the first study about the LNR of the neck dissections including the risk of systemic recurrence in melanoma. In comparison to literature, our study analyzed the impact of other different LNR thresholds of neck dissections on OS, local and systemic control. Our study concerned only neck dissections for lymph node macro-metastasis from primitive melanoma originated from different sites including HNCM. All these characteristics constitute the originality of our study.

Conclusion

The number of lymph node metastasis is one of the most prognostic factors in melanoma. Our study concluded that neck lymph node metastasis from HNCM could be associated to a better prognosis than melanoma of other primary sites. This study confirmed that extent of neck dissection could have an impact only on the local control and supported that extent of neck dissections should be based on the biology of the disease. Our study confirmed that LNR of neck dissection might represent a prognostic factor of survival. The LNR should be small to enhance the prognosis and therefore the neck dissection could not be limited to the level of the lymph node metastasis but enlarged to the lymph nodes located in the adjacent neck area. It would be interesting to study a larger cohort during a longer follow-up and including patients with adjuvant immunotherapy to explore the impact of this treatment on the LNR and the extent of the neck dissections in stage III melanoma.

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