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research article

Completely resected stage III melanoma controversy - 15 years of national tertiary centre experience

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Background. Two prospective randomized studies analysing cutaneous melanoma (CM) patients with sentinel lymph node (SLN) metastases and rapid development of systemic adjuvant therapy have changed our approach to stage III CM treatment. The aim of this study was to compare results of retrospective survival analysis of stage III CM patients' treatment from Slovenian national CM register to leading international clinical guidelines.

Patients and methods. Since 2000, all Slovenian CM patients with primary tumour ≥ TIb are treated at the Institute of Oncology Ljubljana and data are prospectively collected into a national CM registry. A retrospective analysis of 2426 sentinel lymph node (SLN) biopsies and 789 lymphadenectomies performed until 2015 was conducted using Kaplan-Meier survival curves and log-rank tests.

Results. Positive SLN was found in 519/2426 (21.4%) of patients and completion dissection (CLND) was performed in 455 patients. The 5-year overall survival (OS) of CLND group was 58% *vs.* 47% of metachronous metastases group (MLNM) (p = 0.003). The 5-year OS of patients with lymph node (LN) metastases and unknown primary site (UPM) was 45% *vs.* 21% of patients with synchronous LN metastasis. Patients with SLN tumour burden < 0.3 mm had 5-year OS similar to SLN negative patients (86% *vs.* 85%; p = 0.926). The 5-year OS of patients with burden > 1.0 mm was similar to the MLNM group (49% *vs.* 47%; p = 0.280).

Conclusions. Stage III melanoma patients is a heterogeneous group with significant OS differences. CLND after positive SLNB might still remain a method of treatment for selected patients with stage III.

Key words: cutaneous melanoma; sentinel node biopsy; completion lymph node dissection; overall survival

Introduction

Since Morton has introduced the concept of sentinel lymph node (SLN) biopsy, the procedure had been a central part of cutaneous melanoma (CM) treatment. The information about SLN metastases is considered as one of the most important indicators of recurrence and survival of CM patients.[1,2] Completion lymph nodes dissection (CLND) was offered to patients with positive SLN despite significant morbidity which is only slightly lower in case of CLND compared to therapeutic lymphadenectomy.[3] Common belief was that at least 20% of patients with positive non-SLN would benefit from that kind of treatment.[4]

Despite all attempts to prove otherwise, two prospective randomised studies conducted in recent years have shown that CLND does not improve survival of patients with positive SLN compared to follow up of the nodal basin with ultrasound (US).[5,6]

Although there was no significant improvement of overall survival (OS), the MSLT-2 study did indicate, that immediate CLND offers better regional

control and that non-SLN burden is an independent prognostic indicator for recurrence (hazard ratio [HR]: 1.78; p = 0.005).[5]

In years to follow, studies comparing systemic adjuvant treatment of CM to those receiving placebo after surgical treatment have shown improved regional relapse free survival (RFS) and OS in patients with targeted therapy.[7-9] That knowledge combined with results of MSLT-II and DeCOG led clinicians to belief, that CLND in patients with positive SLN is no longer warranted.[10]

But group of stage III patients is one of the most heterogeneous groups with expected 5-year OS ranging from 30–60% and adjuvant systemic therapy is potentially toxic and costly.[11,12] In case of first reported adjuvant systemic therapy trial, 43% of patients receiving ipilimumab had grade 3 or 4 side effects but in later studies, the percentage has dropped to approximately 14%.[7,8] Toxicity rates have dropped and at the same time 1-year RFS has increased to 70.5% in completely resected stage III CM patients treated with anti-PD-1 agent nivolumab and 75.4% in case of adjuvant pembrolizumab.[13] But one has to keep in mind that individual costs of adjuvant immunotherapy treatment in our country can reach up to 67.000 Euros per year. How to make adjuvant systemic treatment combined with suitable follow up of regional lymph node basin available to all patients are nowadays concerns of many clinicians.

Perhaps additional piece of information is hiding in the SLN burden. Studies in the past have associated SLN burden of > 1 mm with significantly worse outcome and a need for adjuvant systemic treatment. On the other hand different studies were not able to confirm the minimal SLN burden as reproducible factor for excellent survival at all sites. Despite that it seems, that burden of < 0.1 mm is associated with 5-year survival of 83–91%, with non-SLN positivity rates between 0 and 12%.[14]

The aim of our study was to compare survival based on retrospective analyse of stage III CM from national CM base to current understanding of lymph node surgery.

Patients and methods

Data of CM patients treated at the Institute of Oncology Ljubljana (OI) were prospectively collected into clinical melanoma registry. Data of SLN biopsy procedures were collected since January 2000, the year of the SLN biopsy introduction in Slovenia. Complete lymph node dissection data were registered since 2003. In Slovenia all CM surgical procedures (with exclusion of skin biopsy) are performed at the OI. Clinical melanoma registry of the OI serves as a substitute of the national CM database.

Data of 2426 patients with CM (CM ≥ TIb based on confirmed histology) undergoing SLN biopsy at the OI between 2000 and 2015 were analysed. The SLN biopsy procedure was performed according to established recommendations.[15] During described period, gross and microscopic examination of SLN was performed by 4 dedicated pathologists at the institute using SLN protocol that has been adopted by the EORTC as the standard procedure for pathological handling of SLN for CM.[16] The false negative rate (FNR) was defined as false negative/true positive combined with false negative. All patients with positive SLN and performance status ECOG 0–2, who agreed to further surgical treatment, underwent CLND. Altogether there were 455 patients with positive SLN and CLND.

To that number we added the analysis of 149 patients with synchronous primary CM and clinically detected regional lymph node metastasis (SLNM), 121 patients with metachronous primary CM and regional lymph node metastasis (MLNM), and 64 patients with melanoma of unknown primary site (UPM). Synchronous metastases were defined as metastases detected clinically prior to surgery or occurring within 6 months of the initial CM diagnosis. Patients with first recurrence of the disease in the regional lymph node basin later in course of the disease were classified to the MLNM group. UPM was defined as clinically detected and histologically confirmed nodal melanoma metastases with no evidence of primary lesion. Patients with synchronous nodal and in-transit metastases were excluded from the study as were patients with previously excised pigmented skin lesion without proper histological evaluation. Finally, data of 789 patients after complete lymph node dissection divided in four groups (CLND, SLNM, MLNM and UPM) operated between 2003 and 2015 were retrospectively analysed.

The date of study closure was January 15th 2019. Data were summarized as mean ± SD, unless otherwise specified. Chi-square test was used for categorical variables while quantitative variables were compared using Kruskal-Wallis test. Overall survival (OS) time was calculated from the date of the excision of primary lesion (or the date of lymph node dissection in the case of UPM) to the date of death and censored at the closing date for survivors. Survival analyses were performed

TABLE 1. Demographics of sentinel lymph node biopsy (SLNB) group

	Negative SLN No. (%)	Positive SLN No. (%)	Unfound SLN No. (%)	All SLNB No. (%)
Number of patients	1837(75.7)	519 (21.4)	70 (2.9)	2426 (100.0)
Tumour site				
Head	174 (9.5)	34 (6.6)	21 (30.0)	229 (9.4)
Neck	30 (1.6)	6 (1.2)	7 (10.0)	43 (1.8)
Trunk	857 (46.7)	268 (51.6)	30 (42.9)	1155 (47.6)
Limbs	776 (42.2)	211 (40.7)	12 (17.1)	999 (41.2)
Breslow thickness (mm)				
< 1.5	757 (41.2)	67 (12.7)	24 (32.9)	848 (34.8)
1.5–3.5	735 (40.0)	226 (43.5)	26 (37.1)	987 (40.7)
3.5	323 (17.6)	224 (43.2)	20 (28.6)	567 (23.4)
Unknown	20 (1.1)	3 (0.6)	1 (1.4)	24 (1.0)
Ulceration				
Yes	554 (30.2)	234 (45.1)	40 (57.1)	828 (34.1)
No	1054 (57.4)	232 (44.7)	22 (31.4)	1308 (53.9)
Unknown	229 (12.5)	53 (10.2)	8 (11.4)	290 (12.0)
Tumour subtype				
SSM	260 (14.2)	62 (11.9)	9 (12.9)	331 (13.6)
NM	277 (15.1)	129 (24.9)	10 (14.3)	416 (17.1)
LMM	14 (0.8)	1 (0.2)	1 (1.4)	16 (0.7)
ALM	29 (1.6)	10 (1.9)	0 (0.0)	39 (1.6)
Other	105 (5.7)	25 (4.8)	2 (2.9)	132 (5.4)
Unknown	1152 (62.7)	292 (56.3)	48 (68.6)	1492 (61.5)

ALM = acral lentiginous melanoma; LMM = lentigo malignant melanoma; NM = nodular melanoma; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SSM = superficial spreading melanoma

by constructing Kaplan-Meier survival curves and compared using log-rank tests. Comparisons between groups of patients undergoing complete lymph node dissection (CLND, MLNM, SLNM and UPM) for each parameter were calculated using $\chi 2$ or nonparametric Kruskal-Wallis analysis as indicated. Statistical analysis was performed using SPSS for Windows, version 22.0. A p-value < 0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board Committee and was conducted in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Results

Between 2000 and 2015, 2426 CM patients had SLN biopsy procedures at the OI. Positive SLN was found in 519 (21.4%) patients, of these 13 (2.5%) had metastatic lymph nodes in two nodal basins. The size of SLN metastasis was recorded (in mm) in 91.7% of cases.

SLN biopsy procedure was unsuccessfully performed in 70 patients (70/2426, 2.9%). Preoperative lymphoscintigraphy failed to detect the SLN in 23/2426 (0.9%) patients. Unsuccessful surgical retrieval was recorded in 47/2426 (1.9%) patients. Lymph node basin with the highest percentage of unsuccessful surgery was neck 24/310 (7.7%), followed by interval lymph nodes 6/115 (5.2%), axilla 13/1238 (1.1%) and groin 4/693 (0.6%).

In 455 patients with positive SLN, CLND was performed. Patients with unsuccessfully retrieved SLN or negative SLN and lymph node recurrence discovered during follow up (88/1837; 4.7%) were considered as false negative (FN). According to that the FNR was 14.5%. In addition, there were 33 patients with only wide local excision who developed nodal recurrence. Since there was no statistically significant difference in OS between the two subgroups of patients (p = 0.373) they were in further analysis merged together as MLNM. Demographics of patients undergoing SLN biopsy are depicted in Table 1.

Demographics of four groups of patients undergoing complete lymph node dissection (CLND, SLNM, MLNM, UPM) are summarized in Table 2.

Median follow-up of patients after lymphadenectomy was 47 months (range 20 days - 198 months). At the time of data cut-off, 60.1% of patients died. The 5-year OS of CLND group was 58%, MLNM 47%, SLNM 21% and UPM 45%, while 10-year OS was as follows: 45% for CLND, 29% for MLNM, 19% for SLNM and 40% for UPM group (Figure 1).

The 5-year OS of MLNM group was significantly worse than survival of CLND group (47% *vs*. 58%; p = 0.003). However, the 5-year OS of CLND group was heterogeneous based on different tumour burden in SLN: < 0.3 mm 86%, 0.3–0.69 mm 72%, 0.7–1.0 mm 61% and > 1.0 mm 49% (Figure 2). Patients with SLN tumour burden < 0.3 mm had the 5-year OS similar to SLN negative group (86% *vs*. 85%; p = 0.926). The 5-year OS of patients with SLN tumour burden > 1.0 mm was comparable to the MLNM group (49% *vs*. 47%; p = 0.280).

The percentage of positive non-SLN differed according to the size of the SLN tumour burden;

3.2% (2/63) of patients with SLN metastasis < 0.3 mm, 7.4% (5/68) of patients with SLN metastasis 0.3–0.69 mm, 11.9% (7/59) of patients with SLN metastasis 0.7–1.0 mm, 23.0% (51/222) of patients with SLN metastasis > 1 mm and 32.6% (14/43) of patients with SLN metastasis of unknown size had positive non-SLN.

Discussion

Data of 2426 patients with CM undergoing SLN biopsy and 789 patients after CLND treated at the Institute of Oncology Ljubljana during 15-year period were retrospectively analysed. The results have shown that 5-year OS of patients with SLN tumour burden < 0.3 mm is comparable to OS of patients with negative SLN (p = 0.926). On the other end of spectrum were patients with SLN tumour burden of > 1 mm with survival comparable to patients with metachronous regional lymph node metastasis (5-year OS 49% *vs*. 47%, p = 0.280). Patients with CLND after positive SLN had significantly improved survival compared to those with dissection after delayed dissection (p = 0.003).

In last two decades three prospective randomized studies have addressed the management of regional lymph nodes in CM patients.[2,5,6] The result of the first, MSLT-I, confirmed the critical role of the SLN biopsy although it did not demonstrate the melanoma specific survival (MSS) benefit. Despite that, the results did show that early removal of lymph node metastases in intermediate thickness CM could improve survival. 10-year distant disease free survival was 54.8% in the group with intermediate thickness CM following CLND after positive SLN biopsy and 35.6% in the case of observation and nodal recurrence. According to our analysis 10-year OS was 45% in CLND group compared to the 29% OS of the MLNM group which had the characteristics similar to the true observational group. The survival difference was slightly smaller in our population in comparison to MSLT-1 trial which can be explained by population differences. MSLT-I included 81.6% of patients with intermediate thickness CM with median thickness of 1.8 mm in biopsy group, while median thickness in our population was 3 mm. One third of patients had SLN tumour burden > 1 mm.[2,11] In our population the percentage was 48.8%. The observed differences in survival indicate that the benefit of the CLND is not limited only to patients with intermediate thickness CM.

TABLE 2. Demographics of the four groups with lymph node dissection

	CLND No. (%)	MLNM No. (%)	SLNM No. (%)	UPM No. (%)	p
Number of patients	455 (57.7)	121 (15.3)	149 (18.9)	64 (8.1)	
Age (years)					**0.005**
Mean	56	60	59	58	
Median	56	64	61	61	
Gender					**0.198**
F	206 (45.3)	63 (52.1)	65 (43.6)	23 (36.0)	
M	249 (54.7)	58 (47.9)	84 (56.4)	41 (64.0)	
Primary tumour site					**0.254**
Head	29 (6.4)	16 (13.2)	25 (16.8)	-	
Neck	5 (1.1)	4 (3.3)	2 (1.3)	-	
Trunk	235 (51.6)	48 (39.7)	64 (43.0)	-	
Limbs	186 (40.9)	53 (43.8)	58 (39.0)	-	
Breslow thickness (mm)					**< 0.001**
Mean ± SD	3.9 ± 0.1	3.5 ± 0.3	8.5 ± 0.8	-	
Median	3.0	2.6	6.0	-	
< 1.5	60 (13.2)	28 (23.1)	12 (8.1)	-	
1.5–3.5	202 (44.4)	54 (44.6)	21 (14.1)	-	
> 3.5	190 (41.8)	35 (28.9)	105 (70.5)	-	
Unknown	3 (0.7)	4 (3.3)	11 (7.4)	-	
Clark level					**< 0.001**
II	2 (0.4)	1 (0.8)	1 (0.7)	-	
III	87 (19.1)	32 (26.4)	16 (10.7)	-	
IV	234 (51.4)	50 (41.3)	63 (42.3)	-	
V	41 (9.0)	7 (5.8)	33 (22.1)	-	
Unknown	91 (20.0)	31 (25.6)	36 (24.2)	-	
Ulceration					
Present	197 (43.4)	47 (38.8)	91 (61.1)	-	**< 0.001**
Absent	213 (46.8)	52 (43.0)	18 (12.1)	-	
Unknown	45 (9.9)	22 (18.2)	40 (26.8)	-	
Number of positive nodes					**< 0.001**
Mean ± S.D.	1.6 ± 1.8	3.3 ± 4.0	4.3 ± 5.4	4.5 ± 7.0	
Median	1	2	2	2	
Diameter of the largest lymph node metastases (mm)					**< 0.001**
Mean ± S.D.	3.5 ± 5.7	35.3 ± 30.7	20.8 ± 14.2	46.0 ± 27.2	
Median	1.4	28	16	47	

CLND = completion lymph nodes dissection; MLNM = metachronous lymph node metastasis; SLNM = synchronous lymph node metastasis; UPM = unknown primary site metastases

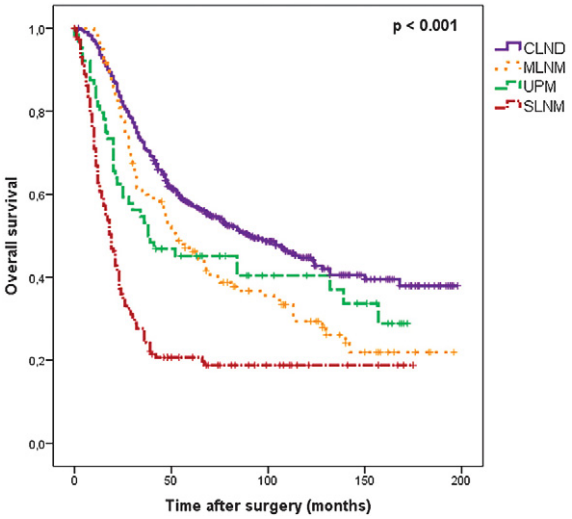

FIGURE 1. Overall survival (OS) of groups with completion lymph nodes dissection (CLND), synchronous lymph node metastasis (SLNM), metachronous lymph node metastasis (MLNM), unknown primary site metastases (UPM).

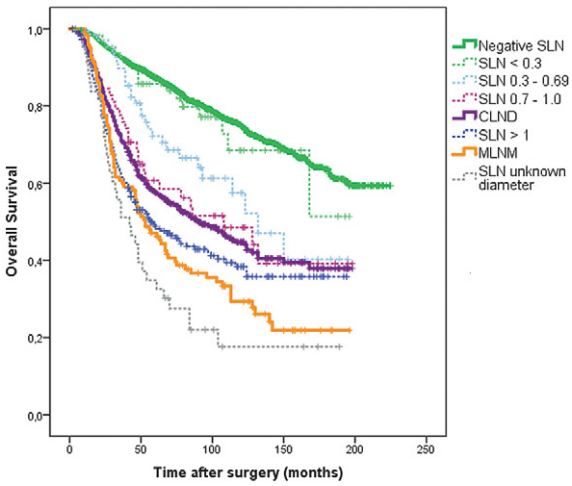

FIGURE 2. Overall survival (OS) according to sentinel lymph node (SLN) tumour burden.

Studies following MSLT-I and addressing the question of improved OS survival after the CLND included small proportion of patients with SLN tumour burden > 1 mm (two thirds of patients in each DeCOG study arm had SLN tumour burden ≤ 1 mm) which would, together with exclusion of patients with head and neck CM and those with extracapsular extension, indicate selection bias during study accrual.[5,6,11] One interesting notion comparing our results to the results of the MSLT-II is, that they have include approximately 6% less patients with ulceration (37.0% of CLND compared to our 43.3%) and 20% less patients with thick melanoma (21.8% MSLT-II *vs*. 41.8%). The percentage of patients with SLN tumour burden > 1 mm was 21.7% in MSLT-II CLND group and 48.8% in our study respectively. The comparison imposes a question whether one can rely on the prospective randomized trials while facing a specific real life population? Differences in our national results indicate that direct implementation of the conclusions of randomised trials may not always be suitable. Results of DeCOG and MSLT-II studies failed to prove the OS survival benefit of the CLND. In case of our cohort the 5-year OS of patients following CLND was improved by 11% compared to the MLNM group (58% *vs*. 47%, p = 0.003) with no signifficant difference in the Breslow thicknes or presence of ulceration between the two groups.

Intriguing relationship between Breslow thickness and nodal burden was observed. In our study the worst OS survival was associated with SLNM group with only 21% alive after 5 years. The group of SLNM patients had substantially thicker CM yet their nodal burden was smaller compared to MLNM group (35.3 ± 30.7 mm MLNM *vs*. 20.8 ± 14.2 mm) indicating different primary tumour biology but also indicating the effect of the delayed lymphadenectomy on the size of the nodal burden. If the timing of lymphadenectomy is a vital part of treatment the concern about possible loss of regional control during observation after SLN biopsy is raised. Many clinicians are aware that unresectable regional disease is a serious clinical problem in CM. At the moment it is not known in how many cases observation and sequential regional relapse would actually cause loss of regional control.[11] But not only regional control, other results could also be influenced by timing, as indicated in the Delgado meta-analysis. They concluded that there appears to be a time-dependent disease specific survival advantage related to early or immediate surgery regardless of the extent of the procedure compared to delayed or none in the case of nodal metastases.[17]

Can we reassure our patient that it is safe to leave the possible CM metastases in lymph node basin in cases where SLN biopsy is not followed by CLND? Many would argue that in the case of high risk for disease progression, small tumour burden in lymph node basin makes no change.[6,11] Interestingly that is in contrast to some basic research showing that especially in CM models stem-like tumour cells have been found to reside in the vessels in the vicinity of lymphatic nodes, suggest-

ing that there is a kind of 'lymphovascular' stem cell niche which is not removed without CLND. It is speculated that these stem-like tumour cells might 'hibernate' for a long time span within the lymphovascular niche, and may form new tumours even years after surgical removal of the primary tumour. Similarly, the persistence of metastatic tumour cells in non-SLN subcapsular sinuses might also relate to a tumour cell survival supporting function of lymphatic vessels, which could play a role in premetastatic lymphatic niches as well.[18] On the other hand, lymphatic endothelial cells (LEC) are expressing PD-L1 surface receptors that directly interface with leukocytes and causes dysfunctional T cell activation, so one would speculate that the risk of tumour progression can be minimized with adjuvant immunotherapy. Studies aimed at adjuvant therapy in CM patients did show less relapses compared to placebo group and indicated that adjuvant systemic therapy can lead to sustained and durable survival benefit. However additional validation of this approach with extended follow-up in patients receiving adjuvant systemic therapy for CM is warranted, including correlation with OS data.[19] It is important to note that trials that influenced our understanding of stage III melanoma treatment (MSLT-1, MSLT-2, DeCOG) included patients with completely resected CM and SLN burden > 1 mm.[11]

With results of MSLT-II and underpowered DeCOG trial indicating no benefit from CLND after positive SLN we can expect, that only a small number of patients will be advised to have CLND in the future. It will be up to clinicians to decide, who with stage III disease should receive adjuvant systemic therapy and the decision will be based only on information gathered from SLN biopsy instead on information gathered from CLND available for adjuvant trials. Unfortunately, until new conclusions are available, results from previous adjuvant trials cannot simply be extrapolated to patients who only had SLN biopsy. The information about the non-SLN status might be lacking.[20] Our own results show that 17.4% of patients (79/455) had positive non-SLN and with that possible decision influencing information.

The issue of additional information gained from CLND was addressed by Verver and colleagues. They used a retrospective cohort of SN-positive patients previously collected and described to construct a model of risk stratification based solely on primary CM and SLN biopsy information. Their model is based on presence or absence of the ulceration and SLN burden of > 1 mm or ≤ 1 mm. They concluded that CLND upstaged 19% of patients in the N-category and 5% of patients in AJCC stage 8Th edition (6% AJCC stage upstaging in the 7th edition). The survival analysis showed significant difference between low risk group (absent ulceration and SLN burden ≤ 1 mm) with 5-year MSS of 82.4% and intermediate risk (ulceration present and SLN ≤ 1 mm or ulceration absent and SLN > 1 mm) with survival around 67.6% and substantial gap between intermediate and high risk group (ulceration present and SLN > 1 mm) with 44% 5-year MSS in the later.[20] Verver's model is a significant step to understanding the stage III survival heterogeneity but if tumor burden is an important prognostic indicator, four group prognostication sounds somehow crude. In our analysis we defined groups according to SLN burden. The OS survival analysis done according to the four group stratification caused previously described CLND curve to fan out. The analysis proved that group of patients with SLN burden > 1 mm are high risk patients with 5-year OS of 49%. In fact, their survival did not differ statistically from the MLNM group. On the other side of the spectrum are patients with SLN burden < 0.3 mm with excellent prognosis and 5-year OS of 86% similar to the group with negative SLN. In the middle are those with SLN burden > 0.3 mm and ≤ 1 mm with 60–70% 5-year OS. Additional analysis showed that 9.4% of these patients had metastases in non-SLN. Based on current recommendations those patients would not receive any additional adjuvant treatment. For those CM patents not receiving adjuvant systemic treatment and not being able to undergo regular nodal basin US, surgery remains a treatment option, which should be taken under consideration.

Conclusions

Stage III melanoma patients are extremely heterogeneous group with significant survival differences. Since not all of them can be treated with systemic adjuvant therapy, CLND after positive SLNB may be offered to selected CM patients. Considering adjuvant treatment, CLND provides independent prognostic information that at the moment cannot be replaced satisfactorily by other variables.

Authors' contribution

BP contributed to the conception of the study, drafted the work and interpretated the data. SM

performed data acquisition, analysis and contributed to data interpretation. AP contributed to interpretation of data and substantively revised the manuscript. MH made substantial contributions to the conception and design of the work and added critical remarks to the revised version. JZ contributed to the conception, interpretation of data and substantively revised the manuscript.

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