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Multiple lymphatic-venous anastomoses in reducing the risk of lymphedema in melanoma patients undergoing complete lymph node dissection. A retrospective case-control study

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Summary *Background:* Sentinel lymph node biopsy (SLNB) is an indispensable surgical procedure in staging and management of intermediate-to-thick melanomas. Although recent studies have demonstrated that complete lymph node dissection (CLND) does not improve 3-year specific survival, its utility in increasing the disease-free period and the control of local disease remains confirmed. The most frequent complication related to CLND is lymphedema, which may affect up to 20% of patients undergoing CLND. The preventive use of lymphatic-venous micro-anastomoses could avoid this complication.
Materials and methods: We performed a single-institution retrospective case-control study. CLND was proposed to all subjects with positive-SLNB; a preventive procedure involving multiple lymphaticovenular anastomoses (PMA) was performed in a cohort of subjects undergoing

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CLND. Frequency of lymphedema was compared among subjects undergoing and not-undergoing PMA during CLND.

Results: We selected patients affected by melanoma of the trunk and with a minimum follow-up of 3 years, identifying 23 patients who underwent PMA during CLND (PMA group) and 120 subjects who underwent CLND without PMA (control group). The frequency of lymphedema was significantly lower in the PMA group than in the control group (4.3% vs. 24.2%, $p = 0.03$). Patients of the PMA group and the control group showed similar 3-year recurrence-free period (65.2% vs. 62.5%, log-rank test $p = 0.88$) and 3-year overall survival (73.9% vs. 72.5%, log-rank test $p = 0.97$) and frequency of nonsentinel-node metastases (26.7% vs. 30.4%, $p = 0.71$).

Conclusion: PMA appear to represent a useful and safe procedure in reducing the risk of lymphedema in patients with melanoma undergoing CLND.

Background

Cutaneous melanoma (CM) is the most common skin cancer whose incidence is rapidly increasing across the developed world. Survival rates have improved greatly over the last 30 years, with a current 10-year disease specific survival rate of 90%. Mortality is reduced worldwide – patients with regional lymph node metastasis show a 5-year survival rate ranging from 40% to 78% – although it remains elevated in patients with advanced disease.[1] Sentinel lymph node biopsy (SLNB) is the standard procedure for accurate staging in melanoma, also showing a prognostic impact because it identifies patients with nodal metastasis who may theoretically benefit from immediate completion lymph node dissection (CLND). Despite the American and European recommendation[1-3] on completing CLND in all SLN-positive melanoma in relation to thickness and ulceration, its therapeutic and prognostic role is currently debated. In this context, although recent multicenter trials demonstrated that CLND does not produce a survival benefit in terms of melanoma-free survival with regard to observation, its utility in enlargement of disease-free period and control of local disease appears confirmed.[4,5]

Nodal dissection is associated with an extremely low risk of systemic toxicity;[6] nevertheless, this procedure is associated with the risk of both acute and chronic local complications.[7] Lymphedema is the most frequent complication related to CLND, affecting in its frank clinical form up to 20% of patients undergoing CLND.[8] Lymphedema could result in esthetical and functional limitations of affected limbs as well as several other complications (such as erysipelas, warts, and papillomatosis cutis lymphostatica) related to its chronicization.[9] Although the use of therapeutic decompression garments and massages or the performance of microsurgical lymphatico-venous anastomoses or lymph nodes transfers are considered helpful in the management of secondary lymphedema,[10,11] a long-term control of symptoms is obtained only in a low percentage of patients. Therefore, the execution of preventive multiple lymphatic-venous anastomoses (PMA) during lymphadenectomy could be employed as a prevention management strategy for secondary lymphedema.[12,13]

Methods

This research protocol was approved by our local Ethical Committee. Electronic medical records of clinical data of patients with melanoma were collected from a single institution during July 1994 to March 2018. We identified patients with CM of the trunk and a SLNB located in axilla or groin. Patients with stage IV melanoma, affected by other carcinomas, or with prior procedures, which might have compromised lymphatic drainage of the primary site, were excluded.

All patients with suspicious skin lesions underwent an accurate dermoscopic examination followed by an excisional biopsy with 2/5 mm of healthy margins. Lymphatic mapping and SLNB were performed within 90 days in all subjects with a histological diagnosis of melanoma, with a thickness $\geq$0.75 mm and/or associated with adverse prognostic features (regression, ulceration, high mitotic rate, and vertical growth phase). Lymphoscintigraphy was performed using technetium 99 m nanocolloid human serum albumin injected closely around the primary lesion or around the scar of the previous excision, using ultra high-resolution collimators to reduce artifacts.[14-16] Dynamic and static images were acquired using dual-headed digital gamma cameras both immediately after the radiolabeled colloid injection and then after every lymph node visualization. A handheld gamma probe was used during surgery to guide sentinel node detection. Multiple sections of each sentinel node were examined by conventional hematoxylin and eosin staining and by immunohistochemistry staining.[17,18]

CLND was performed in all patients with positive SLNB. Axillary lymphadenectomy involved the 3 lymphatic levels; groin lymphadenectomy was extended to iliac and obturator lymph nodes.[19,20] In a cohort of patients undergoing CLND, PMA were performed during lymphadenectomy as a prevention management strategy for secondary lymphedema. In this cohort, all patients with risk factors for developing lymphedema were selected, including previous radiotherapy, infections, complicated surgical wounds, seroma, obesity, congenital predisposition, traumatism, chronic inflammatory cutaneous disorders, vascular hypertension, presence of arteriovenous shunts, pacemaker

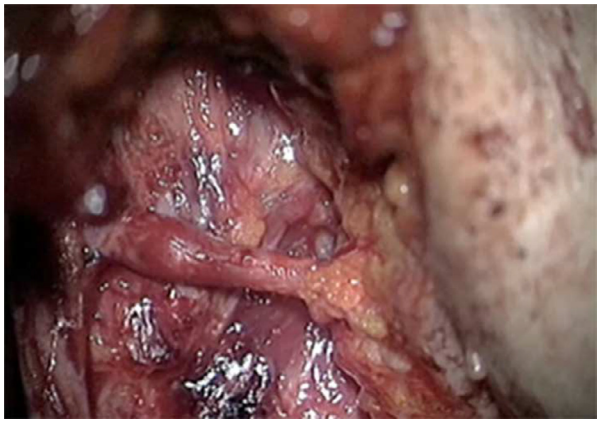

Figure 1 Intraoperative view of the PMA procedure.

implants, familiar anamnesis for chronic edema, orthopedic surgery, venous insufficiency or postphlebitic syndrome, thrombophlebitis, hyperthyroidism, chronic kidney disease, cardiac failure, and malnutrition.

PMA was performed after a preliminary intradermic and deep infiltration of Patent Blue Violet; a "T" shape was then incised on the skin. When possible, PMA for upper limbs were performed in the axillary region using the same surgical access of lymphadenectomy; otherwise, a new incision at the middle third of the arm was made. Similarly, PMA for lower limbs were performed in the inguinal region using the same access of inguinal lymphatic dissection; when this was not feasible, an incision at the middle third of the thigh was made. Lymphatic vessels were identified by Patent Blue Violet dye staining; consequently, under a microscope magnification of 25x, lymphatic vessels coming from the distal part of the limb were identified and isolated. A vein with an adequate caliber was then identified, isolated, ligated in its distal portion, and clamped in its proximal portion. Lymphatic vessels were transfixed with Nylon 11/0 and sutured to the vein with a "Donati" stitch through distally or proximally end-to-end telescopic anastomosis; subsequently, single stitches were affixed between the lymphatic wall and the vein wall. Finally, the initial stitch and the clamp were removed (Figure 1). A written informed consent was obtained from all the patients who underwent PMA.

The histological presence of metastasis both in SLNB and in CLND was categorized as micrometastasis or macrometastasis. Macrometastasis was defined as clinically detectable nodal metastases (macroscopic) confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibited gross extracapsular extension; micrometastasis was defined as clinically occult nodal metastases (microscopic), excluding isolated tumor cells.[21]

All patients underwent a clinical and imaging follow-up (chest X-ray, abdominal and lymphatic ultrasound, and SPECT/CT for difficult areas) every 6 months for the first 5 years and yearly thereafter. During these follow-up visits, calf and/or biceps circumference was measured and water volumetry was performed to detect lymphedema,[22] defined as an increase in the sum of circumferences of the defined points along the limb >= 7% and/or a whole limb volume percentage change of >= 15%.[23,24]

Statistical analysis was performed with *t*-test, Chi-square, and Wilcoxon rank sum test as appropriate. Follow-up time was defined as the time between definitive surgical treatment of the primary melanoma and the last contact with the patient. Survival rates were estimated using the Kaplan–Meier method and multivariate Cox proportional hazards regression models and multivariate Cox proportional hazards regression model. Results were considered statistically significant when $p < 0.05$. All statistical analyses were performed using SAS Software Release 9.4 (SAS Institute, Cary, NC).

Results

Patients and survival analysis

The database evaluation revealed 656 patients who had been treated with a previous complete local excision and a subsequent SLNB. The clinical and demographic characteristics of the population in study are presented in Table 1. Positive SLBNs were detected in 185 (28.2%) subjects (146 with micrometastatic SLNBs and 39 with macrometastatic SLNBs). CLND was performed in 182 subjects with positive SLNBs. Lymphadenectomy of axilla or groin was performed in 143 patients with melanoma of the trunk, with a follow-up for a minimum time of 3 years. In 23 of them, we performed PMA during CLND, while we included the other 120 in the control group (Table 1). There were no statistically significant differences between the two groups in relation to age, sex, body mass index (BMI), presence of primary tumor ulceration, Breslow thickness, or frequency of macrometastatic SLNBs.

Additional nonsentinel lymph nodes were detected in 32 (26.7%) subjects in the control group and 7 (30.4%) in the PMA group ($p = 0.71$). During the overall follow-up period, 55 (45.8) deaths were recorded in the control group and 9 (39.1) in the PMA group, while 67 (55.8) patients in the control group and 11 (47.8) in the PMA group developed a local, in-transit, regional, or distant recurrence.

At 3 years of follow-up, there were no significant differences in overall survival (73.9% vs. 72.5%; $p = 0.97$ by the log-rank test) and disease-free period (65.2% vs. 62.5%; $p = 0.88$ by the log-rank test) between the control group and PMA group (Figure 2).

The similar prognosis in overall survival (HR 1.139; 95% CI, 0.542–2.296) and disease-free period (HR 1.124; 95% CI, 0.595–2.060) between the two groups was confirmed in a multivariate analysis adjusted for other prognostic factors.

To date, none of the patients included in the PMA group received radiation, while 5 received immunotherapy.

Lymphedema

During a follow-up period of 3 years, patients were evaluated at 6 months, then 12 months, and then once a year. Lymphedema was detected in 29 of 120 (24.2%) subjects in the control group and 1 of 23 (4.3%) patients in the PMA group. Lymphedema was significantly more common in the control group than in the PMA group (Chi-square $p = 0.03$). Lymphedema was less frequent after dissection of axillary

Table 1 Clinical and demographic characteristics of subjects with melanoma-positive SLNB (comparison between PMLA group and control group).

Characteristics	Control group	PMA group	P
Total, n (%)	120	23	/
Gender (M), n (%)	64 (53.3)	12 (52.2)	0.64
Age (y)			
Median	53.3	54.8	0.43
Range	18.9-74.2	18.0-68.9	
Breslow thickness, n (%)			
<1 mm	24 (20.0)	5 (21.7)	0.33
1-2 mm	53 (44.2)	10 (43.5)	
2-4 mm	26 (21.7)	5 (21.7)	
>4 mm	17 (14.2)	3 (13.0)	
Primary lesion ulceration, n (%)	27 (22.5)	5 (21.7)	
Micrometastatic SLNB, n (%)	96 (80.0)	17 (73.9)	0.51
Macrometastatic SLNB, n (%)	24 (20.0)	6 (26.1)	0.51
Duration of surgical procedure (hours)			
Median	0.50	1.75	<0.0001
Range	0.25-1.00	1.32-2.18	
Length of stay (days)			
Median	3	3	0.18
Range	2-9	2-5	

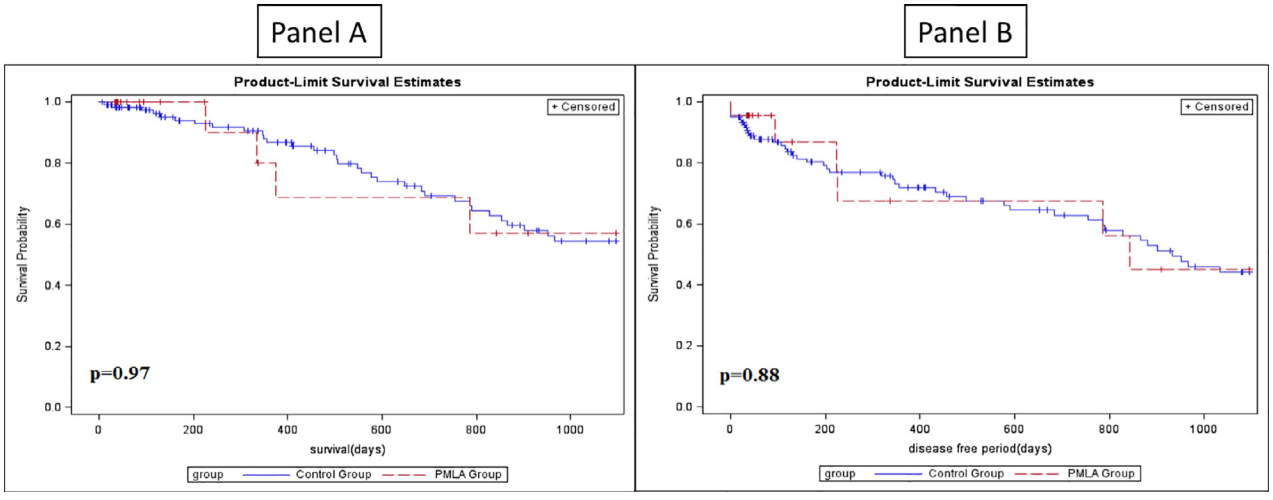

Figure 2 Three years of follow-up; no significant difference in overall survival (Panel A) (73.9% vs. 72.5%; $p = 0.97$ by the log-rank test) and disease-free period (Panel B) (65.2% vs. 62.5%; $p = 0.88$ by the log-rank test) between the PMA group and the control group.

basin than after groin dissection (11.9% vs. 27.4%, Chi-square $p = 0.02$). There were no significant data indicating that the benefit of PMA was limited to either the axillary or the inguinal basin (Table 2).

In addition, BMI, a well-known risk factor for lymphedema, was considered in our analysis. Although the mean BMI in subjects with lymphedema was slightly higher than that in subjects without lymphedema, this difference was not statistically significant (26.4 vs. 25.3, $p = 0.25$). Moreover, a BMI value up to 30 kg/m^2 was used as a criterion to define obesity, identifying 7 (23.3%) obese subjects with lymphedema and 14 (12.4%) in subjects without lymphedema ($p = 0.15$).

A multivariate logistic regression was conducted including risk factors for the development of lymphedema, such as age, sex, obesity, basin site, and execution of PMA. The model identified the execution of PMA procedure as an independent protective factor for lymphedema (OR 0.123, 95% CI 0.015-0.980, $p<0.05$), while the basin site (groin) and obesity showed trends toward an adverse effect on lymphedema risk but without statistical significance (Table 3).

Table 2 Frequency of lymphedema in PMLA group and control group.

CLND site	Frequency of Lymphedema		*P*
	Control group	PMLA group	
Axilla	7/51 (13.7%)	0/8 (0.0%)	/
Groin	22/69 (31.9%)	1/15 (7.7%)	0.05
TOT	29/120 (24.2%)	1/23 (4.3%)	0.03

Table 3 Odds ratio on lymphedema, according to multivariable prognostic factors.

Characteristics	Odds Ratio	95% CI
Age	1.001	0.982
		1.019
Sex (M)	1.503	0.603
		3.743
Obesity (BMI>30 kg/m^2)	1.738	0.588
		5.138
Basin site (groin)	2.542	0.952
		6.787
PMLA	0.123	0.015
		0.980

Surgical procedure, complications, and length of stay

The mean duration of CLND in the control group was 0.51±0.17 h. The execution of PMA during lymphatic dissection increased significantly the duration of surgical procedure; in fact, the mean duration of surgical procedure in the PMA group was 1.75±0.43 h. By Wilcoxon rank sum test, this difference was highly significant ($p<0.0001$). The mean duration of surgical procedures did not show significant difference among patients undergoing axillary or groin dissection both in the control group (0.52±0.18 for axilla and 0.51±0.13 for groin, $p=0.47$) and in the PMA group (1.82±0.41 for axilla and 1.61±0.48 h for groin, $p=0.34$).

Multiple bypasses were performed in all patients included in the PMA group; the average number of lymphatic-venous anastomoses performed was 5.1 ± 2.1.

Regarding complications, wound infections were detected in 10 (8.3%) subjects in the control group and in 2 (8.7%) subjects in the PMA group. There were no PMA-related adverse events.

Length of stay did not vary considerably between the two groups. The mean days of hospitalization in the control group were 3.13±0.81; similarly, the mean length of stay in the PMA group was 3.17±0.72 days ($p=0.82$). The length of stay for patients undergoing axillary or groin dissections did not show significant difference (3.03±1.02 vs. 3.21±0.58 days, $p=0.18$).

Discussion

CLND is quite a safe procedure used to control lymphatic metastatic dissemination in patients with melanoma. In the prophylactic lymph node dissection era, there was a high frequency of dissections in patients without lymph nodal disease because of the low frequency of lymphatic involvement in intermediate-thickness melanomas. For this reason, only a minority of patients did benefit from CLND, while all were exposed to complications related to this surgical procedure.[6] The deployment of SLNB allowed identification of patients with lymph nodal disease, reserving the dissection only to the lymphatic basin with positive sentinel nodes.[25] Complications related to SLNB are less common than those associated with CLND; therefore, in the delayed lymphadenectomy era, there was already a reduction in the rate of morbidity in lymphatic surgical management of patients with melanoma.[26]

More recently, various studies have shown that a greater number of lymph nodes excised during dissection were related to a better control of local and general disease.[20,26,27] This evidence has promoted the extension of CLND, including iliac-obturator lymph nodes to groin dissection and level 3 nodes to axillary dissection.[28] Unfortunately, the extension of CLND is associated with a major frequency of acute or chronic local complications.[29] Several modifications of surgical technique have been suggested to reduce risk of complications, including preservation of the saphenous vein and/or the muscular fascia, minimally invasive laparoscopic techniques, and the use of lymph node transfers.[30] Further, the use of postoperative compressions or massages is considered useful in limiting or preventing secondary lymphedema.[31-32] Regardless, recent large multicenter studies have demonstrated an incidence of secondary lymphedema up to 20% in patients with melanoma treated with CLND.[8,33]

Our report shows a similar ratio of lymphedema in the control group, mimicking findings of previous studies in terms of association of lymphedema with groin basin site and obesity. However, the results of the multivariate analysis showed that the only independent factor associated with a significant reduction in lymphedema frequency is the execution of PMA, even when the analysis was corrected by other risk factors. The efficacy of PMA in the prevention of secondary lymphedema was already demonstrated in oncologic patients undergoing axillary and groin dissection;[12,13]our study confirms these results in a case-control balanced analysis on patients with melanoma in which other clinical risk factors have also been considered.

Our data have shown that there are no differences both in overall survival and in recurrence-free periods among subjects of the PMA group and the control group, even when results are corrected for the major clinical and demographic characteristics. These findings demonstrate that PMA do not impact the prognosis of patients with melanoma of the trunk and positive-SLNB in axilla or groin.

Recently, the usefulness of immediate CLND on the prognosis of patients with melanoma with positive SLNB has been debated. In fact, some studies have found a similar 3-year melanoma-specific survival in patients with melanoma-positive SLNB who underwent immediate CLND or delayed CLND after ultrasonography and/or clinical evidence of nodal metastasis.[4,5] Nevertheless, the role of CLND in controlling local disease and increasing disease-free period appears confirmed. These studies conclude suggesting the utility of immediate CLND in regional disease control but not in increasing melanoma-specific survival among patients

with melanoma and sentinel node metastases, underlining the increased risk of complications related to CLND.[5] The execution of PMA during node dissection could ensure an important reduction in the risk of secondary lymphedema in patients undergoing delayed CLND after ultrasonography and/or clinical evidence of nodal metastasis. Moreover, the very low frequency of lymphedema in the PMA group (4.3%) could allow a quite safe execution of immediate CLND in patients with melanoma with a positive SLNB, improving the local control and the recurrence-free period of melanoma.

Finally, our study evidenced an important increase in duration of surgical procedure among patients who underwent PMA during CLND; length of stay, on the other hand, did not show significant difference between the two groups. Although the increased duration of surgical time absorbed major staff and instrumental resources, lengthening the operating room usage time, the decreased incidence of secondary lymphedema in subjects in whom PMA was performed could result in significant savings in costs related to physiotherapeutic or surgical treatments for the care of lymphedema. In fact, the performance of surgical procedures for the treatment of secondary lymphedema (like gastroepiploic lymph node flap transfer) requires longer surgical duration and length of stay than preventive PMA. Moreover, patients treated for secondary lymphedema showed worst outcomes when compared with subjects undergoing preventive PMA. Thus, preventive procedures could ensure lower direct and indirect costs related to secondary lymphedema. The main limitation of our study is its single-institution retrospective design. Further prospective-controlled studies are warranted to confirm our results.

Conclusion

Lymphedema is a common acute and/or chronic complication of CLND. The usefulness of immediate CLND on disease-specific survival in patients with melanoma-positive SLNB is debated, but its utility in the control of local disease is still confirmed. In addition, delayed CLND is strongly recommended in patients with ultrasonography and/or clinical evidence of nodal metastasis. The execution of PMA during lymphadenectomy is a safe procedure that could sensibly reduce frequency of lymphedema both in immediate and in delayed CLND. Its use during immediate CLND could allow a better control of local disease and recurrence-free period, without relevant complications risks associated with this procedure.

Conflict of interest

None.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2019.01.023.

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