Axillary Lymph Node Metastases of Melanoma: Management of Third-level Nodes

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Abstract. Aim: To state the limits of axillary lymphadenectomy in patients with metastatic melanoma. Patients and Methods: We performed a prospective study on patients submitted to axillary dissection for stage III melanoma. At surgery, the third-level nodes were separately dissected to be examined by the pathologist. Results: We analyzed 86 patients. In 93%, the third-level nodes were disease-free; none of the patients with previous positive sentinel nodes (SN) showed nodal metastases at level III. Patients (7%) found to have positive level III nodes had undergone therapeutic lymphadenectomy for bulky nodal disease. Conclusion: Our data show that axillary non-sentinel nodes of level III are usually disease-free in cases of previously positive SN, while they can be involved in the presence of bulky disease. A prerequisite allowing sparing of level III nodes after a positive SN biopsy is the meticulous research of all level I and II lymph nodes.

The outcome of patients with melanoma depends on disease stage at diagnosis. About 84% of patients present with localized disease at diagnosis, 13% with disease extended to regional lymph nodes, and 3% with distant metastatic disease (1, 2). The prognosis is excellent for patients with early stages of the disease but rapidly worsens with the advance of the same. Lymph nodal involvement is a paramount prognostic factor, since it halves the rate of overall survival (3, 4). According to several major guidelines, patients with clinically positive lymph nodes undergo a so-called therapeutic lymph nodal dissection (TLND) of the involved basin, while in the absence of detected metastases but with ≥pT1b primary melanoma, a sentinel lymph node (SN) biopsy is usually performed (5-7). In cases of a positive SN finding, the majority of patients are directed to a complete lymph node dissection (CLND) or included in clinical trials (6, 9), since the real therapeutic benefit of a CLND is still under debate (8), we are awaiting the final results of the MSLT-II trial, that is currently underway. However, if the indication to perform nodal dissection for metastatic melanoma is quite clear, the issue of the extent of lymphadenectomy within nodal fields is often debated; this study describes the Authors’ attempt to assess the anatomical limits of an axillary dissection, particularly regarding the need for routinely removing the third-level lymph nodes.

Patients and Methods

We performed a prospective study at two Centers dedicated to the surgery of melanoma, namely the Department of Surgery of Perugia University and General Hospital, and the Institute of Surgical Dermatology, Health and Science City Hospital, University of Turino, both in Italy.

At both centers, the current clinical practice involves performing a complete axillary dissection (including the third-level lymph nodes) with curative intent for patients with stage III melanoma, as recommended by international guidelines (5, 6).

To exclude the presence of distant metastases, all patients underwent a total-body computed tomographic (CT) scan before SN biopsy. All patients with detection of systemic disease at diagnosis and those who were initially treated for axillary recurrences were excluded from the study. Patients presenting with regional clinical nodal disease (without distant metastases) were directed to TLND.

The same surgical teams based in Perugia and Turin always performed the surgical procedures.

A basic step of the study was the separate sampling of level III lymph nodes in the arm pit at the time of surgery: the soft tissue located medially from the internal edge of the pectoralis minor muscle and between the Halsted ligament inferiorly and the clavicle superiorly was
carefully and completely isolated and then separately dissected from the rest of the axillary content to be sent to the pathologist for separate histological assessment, labeled as "level III". This surgical procedure never demanded the dissection of the pectoralis minor muscle to provide a complete emptying of the third level.

We analyzed 86 patients in 24 months (April 2013-March 2015) of both sexes [54 males (62.8%); 32 females (37.2%)] and average age 56.7 years (range=23-90 years) (Table I).

Sixty-seven patients (77.9%) had metastases in a SN; after surgical removal of the primary melanoma and a negative staging workup, these patients had undergone SN biopsy performed with a preoperative lymphoscintigraphy with radio-labeled nanocolloid [0.1 ml of 10 MBq 99mTc albumin; Nanocoll; Nycomed Amersham Sorin S.r.l., Saluggia (VC) Italy] coupled with staining (Blue Patente' Violet Natrium Salz, 0.050 g; Guerbet, Villepinte, France) and surgical biopsy of the lymph node on the same day. None of the SN nodes was collected from the third level.

The remaining 19 cases (22.1%) came to our attention with a clinically suspected nodal involvement, confirmed by fine-needle aspiration (FNA) of the enlarged axillary lymph nodes.

The mean follow-up, considering the time elapsed between the axillary dissection and the last clinical control, was 16.6 months (range=1-23 months).

Our study aimed to open the path to a different surgical procedure, basing this claim on the uninvolvement of the third level nodes in patients without bulky disease.

**Results**

The mean number of lymph nodes removed from all three levels was about 23 (range=11-52), in line with the literature (10, 11) (Table I). The number of lymph nodes found in level III ranged between 1 and 10 (mean of ~3).

In 93% of cases (80 patients), the third-level lymph nodes were metastasis-free; none of the 67 patients with positive SN subjected to CLND had metastases at level III nodes.

Six patients (7%) had metastatic level III nodes; they all had undergone a TLND for clinically-positive nodes. It should be noted that three of these patients with metastases to the third level had come to our attention because of axillary lymph node enlargement, and the primary melanocytic lesion was never found.

Thirty patients (34.8%) had metastases in level I and II lymph nodes. They underwent CLND in 11 cases and TLND in 19. Therefore, in the presence of a metastatic SN, the rate of disease in non-SNs was 16.4%, only confined to level I and II lymph nodes; these data are similar to those of the literature (10-20%) (12-14).

For the 19 cases presenting with palpable disease, then confirmed by FNA, all 19 patients clearly showed metastases to I and II level lymph nodes and six (31.6%) also to level III (Figure 1); these six patients, given the coarse extension of disease, underwent adjuvant chemotherapy. At 4, 7 and 8 months after surgery, respectively, three patients are alive but with further progression of the disease, two are disease-free at 6 months, while another died after 16 months.

Twenty-one patients with lymph node metastases at level I and II are currently disease-free, one of the TLND group is alive but with distant progression of disease 4 months after surgery, while two patients died, after 13 and 6 months follow-up, respectively–they both had metastases at levels I and II, one of them following a positive SN, the other after TLND.

The 56 patients (65.1% of cases) with positive SN and negative non-SN are currently continuing follow-up without apparent progression of disease.

**Discussion**

When discussing the relationship between surgical control of lymph nodes and general outcome, a main topic is whether nodal metastases can themselves play a significant role in producing distant metastases. If not, nodal dissection would mainly serve for local control of disease and as a prognostic tool (15), since the regional nodal basin is commonly the first site of recurrence and relatively few node-negative
patients develop distant metastases (7). If it were otherwise, lymph node metastases may serve as a source for future distant disease and their removal should impact on overall survival (8, 16).

Since a radical lymphadenectomy is burdened by a discreet morbidity, many authors have attempted to identify factors other than the status of the SN to predict the likelihood of having positive non-SNs in order to identify patients who might avoid lymphadenectomy. The thickness and ulceration of the primary tumor, number of positive SNs, location and size of the disease in the SN (micro/macrometastases), extranodal extension and dendritic cell density (as an index of immunomodulation) have all been correlated with the presence of cancer in non-SNs (17-22).

To date several authors have reported an overall rate of about 15-18% diseased non-SNs in patients treated with CLND after a positive SN biopsy (13, 14, 23); our results are also in accordance with such data (16.4%).

Some studies tried to correlate the SN tumoral burden to the hazard of metastases in non-SNs, considering that in the presence of subcapsular isolated micrometastases, the likelihood of finding positive non-SNs is almost nil; these patients might possibly avoid CLND (12, 24).

Despite numerous studies on the indication for performing CLND for metastatic melanoma in the SN, few articles have been published regarding the ideal extension of axillary dissection, and particularly about the need for routinely removing the third-level lymph nodes. Although guidelines advocate "complete" axillary nodal dissection (6), some consider it most appropriate to spare level III nodes (16, 25-27) as widely adopted for patients with metastatic lymph nodes from breast cancer and our data seem to be consistent with this. A study of Namm et al. analyzed 270 patients with positive SN treated with a level I-II axillary dissection: after a mean follow-up of 44 months, only 5% of patients had an axillary recurrence, with just one case occurring at the level III nodes (25). Another study by Guggenheim et al. included 48 patients who underwent level I and II dissection, associating level III removal in just one case with clinically suspicious lymph nodes: after a mean follow-up of 38.8 months, the local recurrence rate was 4.3% (26). These studies both concluded that level III nodal removal was unnecessary to obtain complete regional control of disease in the event of a positive SN (without clinically appreciable nodes). None of our patients presenting with a positive SN bore disease in level III nodes at the subsequent CLND.

In the literature, the only study aimed at evaluating the frequency of lymph node metastases in axillary level III was conducted by Nessim et al. in patients with stage III melanoma (27). The retrospective study analyzed the data of 117 patients who underwent axillary lymph node dissection of the three levels, showing level III involvement only in two out of 65 patients with SN-positive disease (3%); the rate rose to 18% in case of palpable disease and to 100% in case of bulky disease; these data agree with the literature (28, 29), as do our results. The study concludes that the level III axillary lymph nodes are rarely involved after a positive SN, questioning the need for a routine complete axillary dissection; moreover, patients with palpable or bulky disease developed distant metastases with such rapidity that it suggested the presence of occult metastases at diagnosis.

Complete axillary lymph node dissection may be associated with significant morbidity. The Sunbelt Melanoma Trial stated that the complication rate was significantly lower after SN biopsy (5%) rather than after CLND (23%) after a mean follow-up of 16 months (30, 31). Although no studies have specifically evaluated the consequences of third-level lymph node removal in patients with melanoma, we believe that the advantages of sparing the third level could reside in a possible lower risk for lymphedema of the arm (even if randomized studies are lacking on this subject) and in avoiding a dissection that could possibly be challenging for unskilled surgeons, mostly in cases of bleeding in the uppermost corner of the axilla. On the other hand, in the case of recurrence in level III nodes, a disadvantage could be the difficulty of completing axilla dissection in a second surgery. In fact it is difficult to determine the adequacy of axillary lymph node dissection solely based on anatomical landmarks, and the number of excised lymph nodes is usually considered as a benchmark for successful dissection; since the number of diseased lymph nodes is a powerful independent factor predictive of survival in patients with stage III melanoma (3, 10, 11), the hypothesis that the number of diseased nodes in relation to total number of harvested nodes (the so-called N-ratio) could be an independent prognostic factor (32) was advanced.

**Conclusion**

Third-level axillary non-SNs rarely reveal melanoma metastases after a positive SN biopsy. Since the number of removed nodes is an indicator of surgical appropriateness and a powerful prognostic factor, when a thorough I and II level dissection is granted and an adequate specimen is presented to the pathologist, the level III nodes could possibly be spared.

Furthermore, metastases in the level I and II non-SNs generally lead to a poor prognosis, suggesting that the presence of disease in the level III lymph nodes would not change the prognosis nor the adjuvant treatment approach.

The management of nodal disease in patients with melanoma remains a very active area of research and a source of controversy. Pending the results of ongoing clinical trials, further studies are needed in order to draw any definitive conclusions.
References


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