



The advent of minimally invasive lymphadenectomy in melanoma

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Lymphadenectomies have been a cornerstone in the management of melanoma for centuries (1). This is not only because of the well-recognized propensity of this tumour to generate lymphatic metastasis in up to 20% of the patients during its course, but also due to the luck until recently of systemic therapies which can alter its natural history (2). However, the only noteworthy advancement of this operation since its introduction in melanoma therapy was a gradual reduction in its indications. From the era of elective lymphadenectomies for every patient with primary melanoma in the first half of 20th century we have progressed to the lymphatic mapping and sentinel node biopsy in 80s and 90s where only patients at reasonable risk for nodal metastasis would undergo lymph node dissection (3-5). These are the patients with positive sentinel node biopsy after lymphatic mapping who constitute 20% of the patients with primary tumours thicker than 1mm. Whether, sentinel node biopsy and subsequent selective lymphadenectomy improves overall survival is still a matter of controversy. The only randomized controlled trial on this topic failed to demonstrate a benefit in terms of disease specific survival for the overall population, however it showed a likely benefit for patients with intermediate thickness melanomas (1-4 mm) (5). Moreover, patients who underwent sentinel node biopsy and selective node dissection were less likely to develop regional lymph node metastasis and less likely to require deep groin dissection than patients who underwent lymphadenectomy for clinical nodal metastasis (5,6). In the prospective trial of DeCOG-SLT patients with a primary melanoma of the trunk or extremities and a positive sentineal node

biopsy were randomized to undergo either completion lymphadenectomy or nodal observation. This study did not show any survival benefit for the patients undergoing completion lymphadenectomy; however, its results were hampered by low accrual rates (7). The results of the ongoing MSLT-2 trial will provide a final answer as to whether completion lymphadenectomy benefits patients with positive sentinel node biopsy but they are not expected to become available before 2022. Finally, the EORTC 1208 (MINITUB) study investigates whether completion lymphadenectomy can be safely spared in a subgroup of patients with minimal burden in the sentinel node. Its results are expected in 2020. In the meantime, most melanoma surgeons around the world would recommend completion lymphadenectomy following sentinel node biopsy (8).

Despite this, only half of the patients actually undergo completion lymphadenectomy in the USA (8,9). This is mainly attributed to the significant morbidity of the procedure in combination with an unproven survival benefit. Indeed, morbidity rates for completion lymphadenectomy vary from 20-50% for axillary dissection, 17-90% for inguinal dissection and lower rates for neck dissection (10). In the most recent and methodologically most sound reports, the overall complication rates following lymphadenectomy for cutaneous melanoma average 30-40%. Approximately 20% of them comprise lymphoedema of various stages, 20% develop wound infection/dehiscence and delayed wound healing and 20% will develop seromas and lymphatic fistulas. Understandably a significant number of patients will develop a combination of the

aforementioned complications (7,11-13).

Minimally invasive lymph node dissection (MILND) is a three trocar endoscopic approach of inguinal lymphadenectomy developed to minimize the morbidity associated with the traditional open technique. The safety and feasibility of this MILND has been recently reported in the SAFE-MILND study (NCT01500304) which is a multicenter, phase II clinical trial in patients with melanoma (14). In this multicenter study, twelve surgeons from ten participating centers without any previous MILND experience completed a course which included a 20-minute video and two operations in cadavers. Eighty-eight patients were included in the study with a conversion to open rate of 11.5% and the postoperative complications were assessed meticulously. The overall complication rate was 71% but 45% were minor (grades 1 and 2) and only 26% were significant ones (grade 3). There were no grade 4/5 adverse effects. Wound dehiscence occurred in only 2% of the patients and wound infection necessitating an intervention (antibiotics or procedure) occurred in 11%. Lymphoedema developed in 54% and in its vast majority was mild causing minor or no impairment of the quality of life. Symptomatic seromas necessitating aspiration or drainage occurred in only 10%. Importantly, the median number of removed lymph nodes was eleven which is similar to that reported for conventional groin lymphadenectomies from high volume centres (15-17). Thus, there was no evidence that MILND is an oncologically inferior operation.

It is apparent to everyone who performs this operation that the outcomes reported in the SAFE-MILND are excellent. Particularly wound dehiscence is completely eliminated with this technique; the rate of this complication has been reported to range around 50% in open lymphadenectomy (7,10,13,18-20). Interestingly this does not come at the cost of wound collections/infections and seromas and it is tempting to suggest that it results from the preservation of the blood flow to the poorly perfused skin of the groin. The comparison of the results of this study with published prospective data is not plausible due to different methods of recording and likely underreporting of mild to moderate complications in studies with other endpoints. Similarly, the rate of significant lymphoedema grade 3 is extremely low which can be explained by less disruption of collateral lymphatic drainage channels and perhaps less infections and wound dehiscences. Nevertheless, as the authors fairly point out in their discussion this complication was not captured reliably in SAFE-MILND because only half of the patient returned for the three months' follow-up.

Oncological safety was the main outcome of the SAFE-MILND study. The mean and median numbers of removed lymph nodes was identical with those of prospective randomized trials on open lymphadenectomy i.e. the Sunbelt and the MSLT-1 trials. However, one has to recognize that in the SAFE-MILND the technique must have been applied to a selected group of patients. This is probably the reason why only 88 patients were included from ten high volume institutions over a period of 2 years. This equals with less than five cases per centre per year. So, these results might not be generalizable to the general population of melanoma patients and a randomized trial might be necessary to confirm the superiority of MILND versus conventional inguinal lymphadenectomy in melanoma. The costs of the procedure should also be addressed with appropriate cost effectiveness analyses. The mean duration of MILND is 2-3 times longer than conventional lymphadenectomy and the costs of the laparoscopic equipment have to be considered as well. Nevertheless, it is not unlikely that MILND will be proven to more cost-effective than open lymphadenectomy given the low risk of complications and short hospital stay.

An area for debate on the SAFE-MILND is the training of the surgeons and the learning curve of this procedure. Apparently the surgeons of the study were allowed to perform a cancer operation that they had never done before following an intensive course which however, could have lasted a single day. Undoubtedly, experienced surgeons might be able to perform operations safely after simulation training in cadavers but one has to appreciate that this should not be the training pathway for a challenging endoscopic cancer operation. Training with direct supervision by experienced surgeons until the trainee reaches the learning curve should be the rule in the modern surgical training. It is likely that with the accumulation of experience on this pioneering method, the results will be improved and MILND might gain wide acceptance. Finally, it has to be mentioned that MILND refers for the moment only to superficial groin dissection. Many authors advocate deep ilioobturator dissection for melanoma even in the absence of clinical disease in the pelvis in order to improve local control. It has been shown that up to 20% of the patients who undergo completion lymphadenectomy will have involved ilioobturator nodes (21). It is not clear if this practice improves survival or local control in melanoma but it would be appealing for the patients if a complete minimally invasive technique combining videoendoscopic superficial lymphadenectomy and laparoscopic ilioobturator

technique was available for them. This represents an area for further development (22).

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