The extent of surgery for stage III melanoma: how much is appropriate?

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Since the first documented lymph node dissection in 1892, many trials have investigated the potential effect of this surgical procedure on survival in patients with melanoma. Two randomised controlled trials were unable to demonstrate improved survival with completion lymph node dissection versus nodal observation in patients with sentinel node-positive disease, although patients with larger sentinel node metastases (>1 mm) might benefit more from observation than from dissection, and could potentially be considered for adjuvant systemic therapy instead of complete dissection. Adjuvant immunotherapy with high-dose ipilimumab has led to improvements in overall survival, whereas therapy with nivolumab and pembrolizumab has improved relapse-free survival with greater safety. Furthermore, adjuvant-targeted therapy with dabrafenib and trametinib has improved survival outcomes in *BRAF*^{V600E} and *BRAF*^{V600K}-mutated melanomas. Three neoadjuvant trials have all shown high response rates, including complete responses, after short-term combination therapy with ipilimumab and nivolumab with no recurrences so far, although follow-up is still short. Despite the absence of a survival benefit with completion lymph node dissection in patients with sentinel node-positive or negative disease, the use of sentinel node staging will increase because of the introduction of effective adjuvant therapies. However, routine completion lymph node dissection for sentinel node-positive disease should be reconsidered. Accordingly, existing clinical guidelines are currently being revised. For palpable (macroscopic) nodal disease, the type and extent of surgery could be reduced if the index node can accurately predict the response and if studies show that lymph node dissection can be safely foregone in patients with a complete response. Overall, the appropriate type and extent of surgery for stage III melanoma is changing and becoming more personalised.

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Introduction

The first surgeon to operate on melanoma was John Hunter in 1787, and the first to use the term melanosis was Rene Laennec in 1804.[1,2] In 1968, D C Bodenham confirmed Hunter's original diagnosis through a review of the original specimen.[3,4] The first surgeon to describe a prophylactic lymph node dissection was Herbert Snow in *The Lancet* in 1892.[5] Snow is now recognised as one of the founding fathers of one of the world's leading melanoma clinics, the Royal Marsden Hospital in London.

The first studies on elective lymph node dissection (ELND) were done in the 1970s. In 1977, Veronesi and colleagues[6] compared 267 patients with melanoma of the extremities who received ELND with 286 patients who underwent observation alone. They found no differences in outcome between the treatments or in any patient subgroups. Sim and colleagues[7] did a study of 54 patients who had ELND, 56 patients with 3 months delayed ELND (their hypothesis was that any spread that was in-transit would have arrived at the nodal basin after 3 months), and 63 patients in an observation group. They showed that none of the regimens differed significantly from the others in survival or time to metastases, thus concluding that ELND was not beneficial in the management of melanoma.

Second-generation studies include the trial by Balch and colleagues,[8] in which a larger cohort of 383 patients who received ELND was compared with 356 patients who received observation. Some subgroups of patients were found to benefit from ELND, including those younger than 60 years of age (p=0·042), patients with non-ulcerated melanomas (p=0·018), and those with intermediate Breslow (1–2 mm) melanomas (p=0·031). Cascinelli and colleagues[9] compared immediate ELND (n=122 patients) versus delayed node dissection or observation (n=118) in patients with solely trunk melanomas and reported a 5-year survival of 61·7% in the ELND group versus 51·3% in the delayed or observation group (p=0·09) and also showed that patients with node-positive disease could benefit in terms of 5-year overall survival from ELND (p=0·04). These studies formed the basis of the target population of the Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) study,[10,11] which compared sentinel node biopsy versus nodal observation in patients with intermediate-thickness, node-positive melanoma. The investigators enrolled these patients with intermediate-thickness melanoma based on the concept that thin melanomas have little or no metastatic spread and that any therapeutic effects of prophylactic surgery would be difficult to show, while thick melanomas already have a high chance of haematogenous metastases and could therefore not benefit from prophylactic surgery.

Since the era of ELND, the concept of melanoma surgery has evolved. The principle of sentinel nodes was first observed in parotid surgery and first used in penile cancer surgery,[12,13] whereas lymphatic mapping for melanoma was first described by Morton and colleagues in 1992.[14] Further defining the sentinel node as the first draining lymph node from a primary location led to two concepts. The first of these was the idea of the sentinel node being an incubator, facilitating orderly progression of the primary tumour to regional lymph nodes and

	Study design	Median follow-up	Outcome data					
			Relapse-free survival hazard ratio	Distant metastasis-free survival hazard ratio for surgery versus observation	Melanoma specific survival hazard ratio for surgery versus observation	3-year overall survival or melanoma-specific survival	5-year overall survival or melanoma-specific survival	10-year overall survival or melanoma-specific survival
MSLT-1[10,11]	Sentinel node biopsy *vs* observation in patients with intermediate-thickness melanoma	120 months	0·76 (95% CI 0·62–0·94, p=0·01)	0·62 (95% CI 0·42–0·91, p=0·015)	0·84 (95% CI 0·64–1·09, p=0·18)	..	87·1% (biopsy) *vs* 86·6% (observation)	81·4% (biopsy) *vs* 78·3% (observation)
MSLT-2[22]	Completion lymph node dissection *vs* observation in patients with sentinel node-positive melanoma	43 months	..	1·10 (95% CI 0·92–1·31, p=0·31)	1·08 (95% CI 0·88–1·34, p=0·31)	86% (dissection) *vs* 86% (observation)	..	..
DeCOG-SLT[23,24]	Completion lymph node dissection *vs* observation in patients with sentinel node-positive melanoma	72 months	1·01 (90% CI 0·80–1·28, p=0·94)	1·08 (90% CI 0·83–1·39, p=0·65)	0·99 (90% CI 0·74–1·31, p=0·93)[25]	81·2% (dissection) *vs* 81·7% (observation)	..	..

Table 1: **Trials of lymph node biopsy or dissection versus observation**

subsequently potentially to distant organs. Early removal of the sentinel node (with or without lymph node dissection) would potentially prevent further spread and improve survival. The second concept is that of the sentinel node being an indicator, wherein the sentinel node status merely illustrates the metastatic potential, and removal cannot prevent further spread, because metastasis is thought to be simultaneously occurring through the blood.

The prognostic value of the sentinel node is no longer debated, and many prospective and retrospective studies have proven it to be a very useful tool in staging patients with melanoma.[10,11] More specifically, sentinel node tumour burden seems to further improve the accuracy of staging and prognosis. Many factors (eg, size [for which there are several ways of measuring and different cutoffs], surface area, percentage of involved nodes, and microanatomic location) have been proposed, but the sentinel node tumour burden, measured as the longest diameter of the longest lesion according to the Rotterdam criteria, seems to have the best reproducibility.[15–18] The 1mm cutoff according to these Rotterdam criteria has been adopted by the European Organisation for Research and Treatment of Cancer (EORTC) and has been used as a threshold to define high-risk versus low-risk stage III disease for the new generation of adjuvant therapy trials.[19–21]

Sentinel node biopsy

Only one randomised controlled trial has been done to investigate the effect of sentinel node biopsy on survival. The MSLT-1 study (table 1),[10] by Morton and colleagues, randomly assigned 1347 patients in a 6:4 ratio to receive either a sentinel node biopsy or nodal observation. The prognostic value of the sentinel node was investigated in this trial, and sentinel node status was concluded to be the strongest predictor of disease recurrence or death from melanoma, in a multivariate analysis.[11] Several other studies have evaluated and confirmed that increasing sentinel node tumour burden, irrespective of how it is measured, confers a worse prognosis compared with less extensive sentinel node disease.[15–18]

As for the MSLT-1 study, even after the publication of the final 10-year results, the conclusions are still a matter of debate. At 10 years, the primary endpoint of melanoma-specific survival in a population of patients with intermediate-thickness melanoma (Breslow 1·2–3·5 mm) was 81·4% in the biopsy group versus 78·3% in the observation group (hazard ratio 0·84 [95% CI 0·64–1·09], p=0·18; table 1).[11] However, the heavily debated subgroup analyses from the MSLT-1 trial seem to indicate a potential benefit of biopsy versus observation (10-year melanoma-specific survival in sentinel node-positive patients 62·1% with biopsy *vs* 41·5% with observation; hazard ratio 0·56; 95% CI 0·37–0·84; p=0·006). A new statistical method to correct for lead-time bias effect, accelerated failure time latent subgroup analysis, further supported this claim.[11] Latent subgroup statistical methods were used to estimate the treatment effect of sentinel node biopsy with immediate lymphadenectomy in the subgroup of patients with nodal metastases.[17] Among patients with intermediate-thickness melanomas, both disease-free and distant disease-free survival were improved in the biopsy group; the estimated treatment effect on disease-free survival was 1·17 (p<0·001), and the estimated effect on distant disease–free survival was 0·73 (p=0·04). For melanoma-specific survival, the estimated treatment effect was 0·68 (p=0.05). These treatment effects on disease-free survival, distant disease–free survival, and melanoma-specific survival indicate an increase in survival times by factors of 3·2, 2·1, and 2·0, respectively.[11]

Other experts have argued that such subgroup analyses unfairly exclude patients with false-negative sentinel nodes, who also represent a part of the intention-to-treat

population with a very poor prognosis that is actually even worse than that of node-positive patients in the observation group. Moreover, both biologically and mathematically, there seems to be an issue with patients with false-positive sentinel nodes. Thomas calculated the effect of false-positive nodes on the trial results on the basis of the interim results after 5 years.[26] If one uses his calculation on the final results, one would estimate that 15·6% of patients had false-positive sentinel nodes (figure).[27] Moreover, review studies have indicated that approximately 10–15% of sentinel node-positive disease are incorrectly diagnosed as such or as S100-positive benign capsular nevi, or melanophages are mistaken for metastases (Franke V, unpublished).[28] The newly presented accelerated failure time latent subgroup analysis has been developed together with the MSLT-1 trial's statistician on the interim results of the MSLT-1 study[10] and has not been validated on other data. This fact suggests a potential conflict of interest and a bias; therefore, the analysis cannot be used as validation of the perceived subgroup benefit of sentinel node biopsy.[27]

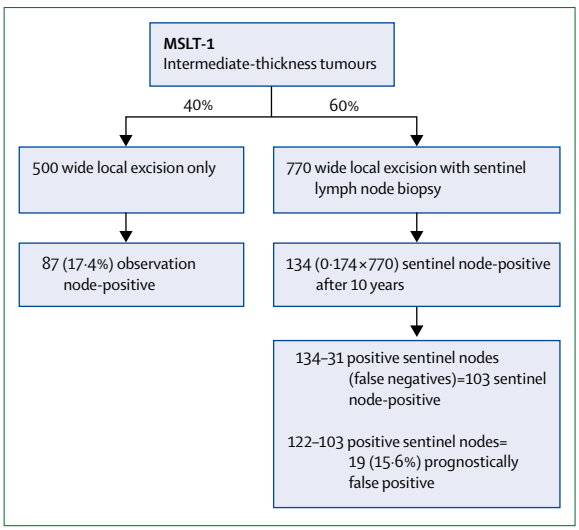

Figure: **False-positive sentinel node biopsy**[11]
MSLT-1=Multicenter Selective Lymphadenectomy Trial 1.

Completion lymph node dissection

Two randomised controlled trials have assessed the effect of an immediate completion lymph node dissection compared with sequential ultrasound observation (and delayed node dissection in case of recurrence) of the lymph node basin (observation) on survival after detection of a positive sentinel node. The first to report results was the German DECOG-SLT study (table 1).[23] In this study, the investigators screened 5549 patients to find 1269 patients with a positive sentinel node. Of those, only 483 agreed to enrol in the study. Both the patients' and the physicians' preferences are likely to have had a role in this difficulty in recruitment, because patients might not want to be randomised to a major surgical procedure, whereas physicians might have personal preferences as to how to manage their patients. After a median follow-up of 35 months, distant metastasis-free survival did not differ between the immediate completion lymph node dissection and observation groups (74·9% *vs* 77·0%; hazard ratio 1·03; 95% CI 0·71–1·50; p=0·87).[23] An update of these results presented during the American Society of Clinical Oncology 2018 Annual Meeting (Chicago, IL, USA) confirmed this with a median follow-up of 72 months (table 1).[23,24]

The larger MSLT-2 study presented its results around the same time (table 1).[22] This study also randomly assigned 1934 patients to either an immediate completion lymph node dissection or sequential ultrasound observation (and delayed node dissection in case of recurrence) of the lymph node basin (observation). After a median follow-up of 43 months, the melanoma-specific survival was equal in the two groups (86% [SE 1·3%] in the completion lymph node dissection group *vs* 86% [1·2%] in the observation group; p=0·42; table 1).[22] Both the intention-to-treat and the per-protocol analyses yielded similar results. Both the DECOG-SLT[23,24] and MSLT-2[22] studies seem to have enrolled more patients with smaller sentinel node tumour burden (<1 mm) than MSLT-1. However, with about a third of patients with larger sentinel node metastases (>1 mm), the MSLT-2 study did not seem to indicate any benefit of immediate completion lymph node dissection in this subgroup, and actually suggests the contrary—ie, that this subgroup favours observation—which might indicate that these patients are at high risk for systemic micrometastatic spread and should be considered for adjuvant systemic therapy rather than adjuvant completion lymph node dissection.

Since the publication of the DECOG-SLT and MSLT-2 data, a few other arguments have been proposed to support the continuation of routine completion lymph node dissection in sentinel node-positive disease. The first argument is that it helps in accurate staging of patients with melanoma. However, although about 15% (11·5% in MSLT-2 and 18% in DECOG-SLT) of patients has been identified as having more nodes positive on completion lymph node dissection, this finding does not equate to immediate upstaging.[22–24,29] Two studies by Verver and colleagues[30] and Madu and colleagues[31] showed similar results, with only 5·8% and 5·9% of patients, respectively, upstaged after completion lymph node dissection. Therefore, in around 94% of cases, the procedure does not upstage patients, and considering the potential morbidity associated with the surgery (eg, chronic lymphoedema in 24·1% of patients undergoing immediate dissection *vs* 6·3% in the observation group), this completion dissection does not seem warranted. In situations in which the staging instrument was sentinel node-positive completion lymph node dissection, we are moving towards staging with sentinel node biopsy alone, redistributing a few patients

	Study design	Median follow-up	Efficacy by melanoma stage*				Efficacy outcomes					
			Stage IIIA	Stage IIIB	Stage IIIC	Stage IV	Relapse-free survival HR for experimental group *vs* control group	Distant metastasis-free survival HR for experimental group *vs* control group	Overall survival HR for experimental group *vs* control group	2-year relapse-free survival	3-year relapse-free survival	5-year relapse-free survival
EORTC 18071[19,45,46]	Ipilimumab 10 mg/kg *vs* placebo	5·3 years	Sentinel node >1 mm, HR 0·91 (99% CI 0·49–1·68)	HR 0·77 (99% CI 0·54–1·08)	HR 1·00 (99% CI 0·56–1·80), 1–3n; HR 0·48 (0·28–0·81), ≥4n	..	0·76 (95% CI 0·64–0·89, p<0·001)	0·76 (95·8% CI 0·64–0·92, p=0·002)	0·72 (95·1% CI 0·58–0·88, p=0·001)	51% (ipilimumab) *vs* 42% (placebo)	NR	41% (ipilimumab) *vs* 30% (placebo)
EORTC 1325[20]	Pembrolizumab 200mg *vs* placebo	15·1 months	Sentinel node >1 mm, HR 0·38 (99% CI 0·11–1·31)	HR 0·58 (99% CI 0·38–0·88)	HR 0·58 (99% CI 0·38–0·86)	..	0·57 (98·4% CI 0·43–0.74, p<0·001)	0·53 (99% CI 0·37–0·76)†	NR	NR	NR	..
Checkmate 238[47,48]	Ipilimumab 10 mg/kg *vs* nivolumab 3 mg/kg	NR, minimum 24 months	..	HR 0·68 (95% CI 0·47–1·00)	HR 0·68 (95% CI 0·52–0·91)	HR 0·68 M1a/b; HR 1·0 M1c†	0·66 (95% CI 0·54–0·81, p<0·0001)	0·76 (95% CI 0·59–0·98, p=0.0349)	NR	63% (ipilimumab) *vs* 50% (nivolumab)	..	..
ECOG 1609[49]	Ipilimumab 10 mg/kg *vs* ipilimumab 3 mg/kg *vs* high-dose interferon-α2b intravenous 20 MU/m² per day (5 days a week for 4 weeks) followed by subcutaneous 10 MU/m² (3 days a week for 48 weeks)	3·1 years	..	HR NR	HR NR	HR NR, M1a–b	1·0 (95% CI 0·81–1·24)	NR	NR	NR	54% (ipilimumab 3 mg/kg) *vs* 56% (ipilimumab 10 mg/kg)	..
BRIM-8[38]	Vemurafenib 960 mg twice daily *vs* placebo; cohort 1: stage IIC–IIIB disease; cohort 2: stage IIIC disease	Cohort 1: 30·8 months; cohort 2: 33·5 months	Sentinel node >1 mm, HR 0·52 (95% CI 0·22–1·23)	HR 0·63 (95% CI 0·41–0·96)	HR 0·80 (95% CI 0·54–1·18)	..	0·54 (95% CI 0·37–0·78, p=0·0010; stage IIC–IIIB); 0·8 (95% CI 0·54–1·18, p=0·2598; stage IIIC)	NR	NR	Cohort 1: 72·3% (vemurafenib) *vs* 56·5% (placebo); cohort 2: 46·3% (vemurafenib) *vs* 47·5% placebo	NR	..
COMBI-AD[21,50]	Dabrafenib 150mg twice daily plus trametinib 2 mg once daily *vs* two matched placebos	44 months (dabrafenib plus trametinib); 42 months (placebo)	Sentinel node >1 mm, HR 0·58 (95% CI 0·32–1·06)	HR 0·49 (95% CI 0·37–0·66)	HR 0·46 (95% CI 0·34–0·61)	..	0·49 (95% CI 0·34–0·70)	0·53 (95% CI 0·41–0·69)	0·57 (95% CI 0·42–0·79, p=0·0006)‡	67%(dabrafenib and trametinib) *vs* 44% (placebo)	59% (dabrafenib and trametinib) *vs* 40% (placebo)	NR
SWOG S1404 (NCT02506153)§	Ipilimumab 10 mg/kg *vs* pembrolizumab 200 mg *vs* high-dose interferon-α MU/m² per day (days 1–5 of weeks 1–4) followed by 10 MU/m² per day	..	..	..	..	..	..	..	..	..	..	..
Checkmate 915 (NCT03068455)§	Nivolumab 240mg plus ipilimumab 1 mg *vs* nivolumab 480 mg	..	..	..	..	..	..	..	..	..	..	..

HR=hazard ratio. NR=not reported. *Staging is according to the American Joint Committee on Cancer 7th Edition. †Preliminary results. ‡No updated results from these trials have been reported yet. §No results reported yet.

Table 2: **Adjuvant trials**

from stage IIIB or IIIC to IIIA or IIIB (as defined by the American Joint Committee on Cancer Cancer Staging Manual, seventh edition[32]).

Another potential reason to continue the routine practice of completion lymph node dissection was the possible loss of local control. In the MSLT-2 trial, adjuvant radiotherapy was given to 8·1% of patients in the completion lymph node dissection group and 6·5% of those in the observation group. Although we cannot be completely confident purely on the basis of these percentages from one study, this finding seems to indicate that a local relapse detected by ultrasound does not equate to the loss of local control.[29]

Some experts have suggested that few patients with larger volume disease (>1 mm in sentinel node tumour burden)[16–18] were included in the DECOG-SLT and MSLT-2 trials and that we should, therefore, reserve the practice of completion lymph node dissection for patients with this larger volume disease. However, as mentioned earlier, the forest plot subgroup analysis of the MSLT-2 study (in which around 30% patients had >1 mm sentinel node tumour burden) did not support this idea.[22] Conversely, outcomes in patients with large volume disease seemed to favour observation over dissection, which is probably due to the high chance of micrometastatic disease in these patients, which prevents them from benefiting from a completion lymph node dissection. For this reason, disease with a high sentinel node tumour burden should be considered for adjuvant systemic therapy rather than adjuvant surgery.

Adjuvant therapies

Historically, in the absence of effective drugs for stage IV melanoma, many studies have examined the use of interferon-α in the adjuvant setting. Although the results were not unequivocal, they showed some benefit in terms of relapse-free survival, yet little to none in terms of overall survival.[33–44]

Now, with the availability of several effective drugs for stage IV melanoma, some notable advances in adjuvant therapies for melanoma have been achieved. The first trial in the new era of adjuvant therapies to show any benefit of adjuvant therapy was the EORTC 18071 study (table 2).[45] In this study, the investigators randomly assigned patients to receive four courses of high-dose ipilimumab (10 mg/kg) followed by maintenance courses of the same dose every 12 weeks for a maximum of 3 years or to a placebo. The study showed improved relapse-free survival in the patients who received ipilimumab, which led to US Food and Drug Administration approval of the drug for this indication on Oct 28, 2015.[45] Longer follow-up verified these results and showed a similar benefit in terms of overall survival.[19] However, toxicity was a major problem in this adjuvant study, with 45% of patients in the ipilimumab group developing grade 3–5 adverse events.

These adjuvant immunotherapy results have since been surpassed by two randomised trials examining an anti-PD-1 adjuvant therapy. The first of these trials[47] was a study of nivolumab (3 mg/kg) every 2 weeks compared with high-dose ipilimumab (10mg/kg). This study reported both an improved relapse-free survival (hazard ratio 0·66, 95% CI 0·54–0·81, p<0·0001) and less toxicity (14% *vs* 46%) in the nivolumab group.[47] The second trial[20] to report its findings was the EORTC 1325 study (table 2), which randomly assigned patients to receive a flat dose of 200 mg pembrolizumab or a placebo. After 18 months follow-up, relapse-free survival was 75·4% in the pembrolizumab group versus 61·0% in the placebo group.[20]

Finally, for *BRAF*^{V600E}-mutated or *BRAF*^{V600K}-mutated melanomas, the COMBI-AD study[21] also showed a benefit for adjuvant targeted therapy with dabrafenib plus trametinib versus a double placebo in terms of relapse-free survival (hazard ratio 0·49, 95% CI 0·34–0·70; table 2). This trial has also reported an interim overall survival analysis, which also showed improved overall survival in the adjuvant-targeted therapy group after 3 years.[21]

Despite the absence of any benefit in terms of overall survival with completion lymph node dissection in sentinel node-positive or node-negative melanoma, all these recent developments in terms of effective adjuvant therapies make the necessity of adequate staging in stage I–II melanoma even more important. Therefore, the use of sentinel node biopsy will not decrease after failing to show a survival benefit in sentinel node positive or negative disease, but rather will increase to adequately identify patients who might benefit from adjuvant therapy, until other biomarkers (eg, gene expression profiles) can replace it. In our opinion, completion lymph node dissection, however, can be safely abandoned after failing to show any survival benefit.

Neoadjuvant therapy

The latest development in the treatment of stage III melanoma is the use of neoadjuvant therapy. Three studies, albeit with far fewer patients than the previously discussed adjuvant trials, have reported very high proportions of patients achieving responses, including complete responses after short-term treatment with the combination of ipilimumab plus nivolumab.[51–53] None of the patients who achieved a pathological complete or pathological near complete response (<10% viable tumour cells, estimated for the total tumour specimen) have recurred so far, although follow-up is still relatively short and the number of patients is small.[54] However, all patients have still undergone a lymph node dissection after their neoadjuvant therapy. Thus, the question now arises of whether this lymph node dissection is still warranted considering these high—and seemingly durable—responses. Perhaps lymph node dissection can be foregone if the index node already shows a pathological complete or pathological near complete response. The recently opened PRADO study (NCT02437279) will address this research question.

Search strategy and selection criteria

We systematically searched PubMed for published randomised controlled trials using the search terms "melanoma" and "stage III melanoma", combined with "surgery", "adjuvant therapy", or "survival", with date restriction from Jan 1, 2014, up until Oct 1, 2018. We did not exclude commonly referenced and highly regarded older publications. The search was restricted to the English language. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. We also added research from the 2018 American Society of Clinical Oncology Annual Meeting and European Society for Medical Oncology 2018 Congress, which we attended.

In-transit metastases

In-transit metastases represent a specific niche of stage III melanoma, which has historically been treated with surgery and other locoregional treatments. Talimogene laherparepvec (T-VEC) is given to patients with stage IIIb–IVM1a melanoma with injectable cutaneous, subcutaneous, or lymph node metastases as monotherapy or as combination therapy with systemic immunotherapy.[55] A large multicentre trial (NCT02263508) is assessing the potential abscopal and synergetic effects of pembrolizumab plus T-VEC versus pembrolizumab plus placebo for unresectable stage IIIB–IVM1c melanoma.[56] The combination of T-VEC with systemic immunotherapy has also been investigated in the neoadjuvant setting.[57]

The first real-world data of T-VEC monotherapy look very promising (response rates 56·5–82·6%) in retrospective analyses of prospectively collected data.[58,59] Retreatment with T-VEC is also feasible in patients who have recurrence of disease after a previous complete response on T-VEC. Although the drug was designed for irresectable stage IIIB–IV melanoma,[60] whether T-VEC or systemic therapies are preferable to repeated (morbid) surgical resection can now be questioned.

Conclusion

The sentinel node biopsy is needed for accurate staging of patients with melanoma. No significant additional staging information is provided by completion lymph node dissection. Furthermore, completion lymph node dissection does not improve survival in patients with melanoma and can be potentially morbid. Thus, routine completion lymph node dissection should be reconsidered for sentinel node-positive disease. Patients with larger (>1 mm) sentinel node metastases might benefit more from effective adjuvant systemic therapy than adjuvant completion lymph node dissection. With promising responses in neoadjuvant studies, the question arises whether lymph node dissections are still warranted if these responses prove to be durable. Possibly, although not yet proven in larger studies, lymph node dissections could be foregone if the index node indicates a pathological complete or near complete response to the neoadjuvant therapy, which then becomes medical management rather than neoadjuvant treatment. Thus, the appropriate type and extent of surgery for stage III melanoma is changing and will become less extensive and more personalised in the coming years.

Contributors

Both authors wrote the Review and contributed to the final version. Both authors reviewed the final version.

Declaration of interests

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References

1 Home E. Case XIII. Of cancer in the breast, in which the swelling of the arm, in consequence of the operation, occasioned the patient's death. In: Home E. Observations on cancer. London: W Bulmer and Co, 1805: 62–63.
2 Laennec RTH. Sur les melanoses, extrat du memoire de Laennec. *BEMS* 1806; **1:** 24–26 (in French).
3 Bodenham DC. Malignant melanoma. *Br J Dermatol* 1968; **80:** 190–92.
4 Bodenham DC. A study of 650 observed malignant melanomas in the South-West region. *Ann R Coll Surg Engl* 1968; **43:** 218–39.
5 Snow H. Abstract of a lecture on melanotic cancerous disease. *Lancet* 1892; **140:** 872–74.
6 Veronesi U, Adamus J, Bandiera DC, et al. Inefficacy of immediate node dissection in stage 1 melanoma of the limbs. *N Engl J Med* 1977; **297:** 627–30.
7 Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomized study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma. Preliminary results. *Cancer* 1978; **41:** 948–56.
8 Balch CM, Soong SJ, Bartolucci AA, et al. Efficacy of an elective regional lymph node dissection of 1 to 4 mm thick melanomas for patients 60 years of age and younger. *Ann Surg* 1996; **224:** 255–66.
9 Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial. *Lancet* 1998; **351:** 793–96.
10 Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006; **355:** 1307–17.
11 Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med* 2014; **370:** 599–609.
12 Gould EA, Winship T, Philbin PH, Kerr HH. Observations on a "sentinel node" in cancer of the parotid. *Cancer* 1960; **13:** 77–78.
13 Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer* 1977; **39:** 456–66.
14 Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127:** 392–99.
15 Murali R, Cochran AJ, Cook MG, et al. Interobserver reproducibility of histologic parameters of melanoma deposits in sentinel lymph nodes: implications for management of patients with melanoma. *Cancer* 2009; **115:** 5026–37.
16 van Akkooi AC, de Wilt JH, Verhoef C, et al. Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? *Ann Oncol* 2006; **17:** 1578–85.
17 van der Ploeg AP, van Akkooi AC, Haydu LE, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: an international, multicenter study of 1539 sentinel node-positive melanoma patients. *Eur J Cancer* 2014; **50:** 111–20.

18 van der Ploeg AP, van Akkooi AC, Rutkowski P, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. *J Clin Oncol* 2011; **29:** 2206–14.

19 Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016; **375:** 1845–55.

20 Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018; **378:** 1789–801.

21 Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. *N Engl J Med* 2017; **377:** 1813–23.

22 Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. *N Engl J Med* 2017; **376:** 2211–22.

23 Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2016; **17:** 757–67.

24 Leiter UM, Stadler R, Mauch C, et al. Final analysis of DECOG-SLT trial: survival outcomes of complete lymph node dissection in melanoma patients with positive sentinel node. *J Clin Oncol* 2018; **36** (suppl)**:** 9501 (abstr).

25 Leiter UM, Stadler R, Mauch C, et al. Final analysis of DECOG-SLT trial: survival outcomes of complete lymph node dissection in melanoma patients with positive sentinel node. *J Clin Oncol* 2018; **36** (suppl)**:** 9501 (abstr).

26 Thomas JM. Prognostic false-positivity of the sentinel node in melanoma. *Nat Clin Pract Oncol* 2008; **5:** 18–23.

27 van Akkooi AC. Sentinel node followed by completion lymph node dissection versus nodal observation: staging or therapeutic? Controversy continues despite final results of MSLT-1. *Melanoma Res* 2014; **24:** 291–94.

28 Scolyer RA, Murali R, McCarthy SW, Thompson JF. Pathologic examination of sentinel lymph nodes from melanoma patients. *Semin Diagn Pathol* 2008; **25:** 100–11.

29 Coit D. The enigma of regional lymph nodes in melanoma. *N Engl J Med* 2017; **376:** 2280–81.

30 Verver D, van Klaveren D, van Akkooi ACJ, et al. Risk stratification of sentinel node-positive melanoma patients defines surgical management and adjuvant therapy treatment considerations. *Eur J Cancer* 2018; **96:** 25–33.

31 Madu MF, Franke V, van de Wiel B, et al. External validation of the 8th Edition Melanoma Staging System of the American Joint Committee on Cancer (AJCC): effect of adding EORTC sentinel node (SN) tumor burden criteria on prognostic accuracy in stage III. *J Clin Oncol* 2018; **36** (suppl)**:** 9500 (abstr).

32 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. ACJJ cancer staging manual, 7th edn. New York, NY: Springer, 2010.

33 Agarwala SS, Lee SJ, Yip W, et al. Phase III randomized study of 4 weeks of high-dose interferon-alpha-2b in stage T2bNO, T3a-bNO, T4a-bNO, and T1–4N1a-2a (microscopic) melanoma: a trial of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (E1697). *J Clin Oncol* 2017; **35:** 885–92.

34 Eggermont AMM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet* 2008; **372:** 117–26.

35 Eggermont AMM, Suciu S, Testori A, et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma *J Clin Oncol* 2012; **30:** 3810–18.

36 Grob JJ, Dreno B, de la Salmoniere P, et al. Randomised trial of interferon α-2a as adjuvant therapy in resected primary melanoma thicker than 1·5 mm without clinically detectable node metastases. *Lancet* 1998; **351:** 1905–10.

37 Hauschild A, Weichenthal M, Rass K, et al. Efficacy of low-dose interferon α2a 18 versus 60 months of treatment in patients with primary melanoma of ≥ 1·5 mm tumor thickness: results of a randomized phase III DeCOG trial. *J Clin Oncol* 2010; **28:** 841–46.

38 Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000; **18:** 2444–58.

39 Kirkwood JM, Ibrahim JG, Sosman JA, et al. High-dose interferon alfa-2b significantly prolongs relapse-free and overall survival compared with the GM2-KLH/QS-21 vaccine in patients with resected stage IIB-III melanoma: results of intergroup trial E1694/S9512/C509801. *J Clin Oncol* 2001; **19:** 2370–80.

40 Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of Eastern Cooperative Oncology Group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004; **10:** 1670–77.

41 Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group trial EST 1684. *J Clin Oncol* 1996; **14:** 7–17.

42 McMasters KM, Egger ME, Edwards MJ, et al. Final results of the sunbelt melanoma trial: a multi-institutional prospective randomized phase III study evaluating the role of adjuvant high-dose interferon alfa-2b and completion lymph node dissection for patients staged by sentinel lymph node biopsy. *J Clin Oncol* 2016; **34:** 1079–86.

43 Payne MJ, Argyropoulou K, Lorigan P, et al. Phase II pilot study of intravenous high-dose interferon with or without maintenance treatment in melanoma at high risk of recurrence. *J Clin Oncol* 2014; **32:** 185–90.

44 Pectasides D, Dafni U, Bafaloukos D, et al. Randomized phase III study of 1 month versus 1 year of adjuvant high-dose interferon alfa-2b in patients with resected high-risk melanoma. *J Clin Oncol* 2009; **27:** 939–44.

45 Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015; **16:** 522–30.

46 Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab (IPI) vs placebo (PBO) after complete resection of stage III melanoma: final overall survival results from the EORTC 18071 randomized, double-blind, phase 3 trial. *Ann Oncol* 2016; **27** (suppl 6)**:** LBA2_PR (abstr).

47 Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017; **377:** 1824–35.

48 Weber JS, Mandalà M, Vecchio MD, et al. Adjuvant therapy with nivolumab (NIVO) versus ipilimumab (IPI) after complete resection of stage III/IV melanoma: updated results from a phase III trial (CheckMate 238). *J Clin Oncol.* 2018; **36** (suppl)**:** 9502 (abstr).

49 Tarhini AA, Lee SJ, Hodi FS, et al. A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): preliminary safety and efficacy of the ipilimumab arms. *J Clin Oncol* 2017; **35** (suppl)**:** 9500 (abstr).

50 Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected *BRAF*V600–mutant stage III melanoma. *J Clin Oncol* 2018; **35:** 3441–49.

51 Amaria RN, Reddy SM, Tawbi HA, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med* 2018; **24:** 1649–54.

52 Blank CU, Rozeman EA, Fanchi LF, et al. Neoadjuvant versus adjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma. *Nat Med* 2018; **24:** 1655–61.

53 Blank CU, Rozeman EA, Menzies AM, et al. LBA42OpACIN-neo: a multicenter phase II study to identify the optimal neo-adjuvant combination scheme of ipilimumab (IPI) and nivolumab (NIVO). *Ann Oncol* 2018; **29** (suppl 8)**:** LBA42 (abstr).

54 Tetzlaff MT, Messina JL, Stein JE, et al. Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. *Ann Oncol* 2018; **29:** 1861–68.

55 Chesney J, Puzanov I, Collichio F, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. *J Clin Oncol* 2018; **36:** 1658–67.

56 Long GV, Dummer R, Ribas A, et al. A phase I/III, multicenter, open-label trial of talimogene laherparepvec (T-VEC) in combination with pembrolizumab for the treatment of unresected, stage IIIb-IV melanoma (MASTERKEY-265). *J Immunother Cancer* 2015; **3** (suppl 2)**:** P181.

57 Andtbacka RHI, Dummer R, Gyorki DE, et al. Interim analysis of a randomized, open-label phase 2 study of talimogene laherparepvec (T-VEC) neoadjuvant treatment (neotx) plus surgery (surgx) vs surgx for resectable stage IIIB-IVM1a melanoma (MEL). *J Clin Oncol* 2018; **36** (suppl)**:** 9508 (abstr).

58 Franke V, Berger DM, Klop WM, et al. High response rates for T-VEC in early metastatic melanoma (stage IIIB/C-IVM1a). *Int J Cancer* 2019; published online Jan 29. DOI:10.1002/ijc.32172.

59 Perez MC, Miura JT, Naqvi SMH, et al. Talimogene laherparepvec (TVEC) for the treatment of advanced melanoma: a single-institution experience. *Ann Surg Oncol* 2018; **25:** 3960–65.

60 Andtbacka RH, Ross M, Puzanov I, et al. Patterns of clinical response with talimogene laherparepvec (T-VEC) in patients with melanoma treated in the OPTiM phase III clinical trial. *Ann Surg Oncol* 2016; **23:** 4169–77.