REVIEW ARTICLE

Fallen dogmas: recent advances in locoregionally advanced melanoma

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ABSTRACT

The last decade has brought new achievements in the research on melanoma, which resulted in important changes in the clinical management of patients with stage III disease. Our review summarizes recent updates with particular focus on practical aspects. Results from surgical studies, the MSLT-II (Multicenter Selective Lymphadenectomy Trial II) and the DeCOG-SLT (German Dermatologic Cooperative Oncology Group), showed that the dogmatic surgical approach that all sentinel lymph node melanoma metastases warrant completion lymph node dissection is no longer valid; omission of completion lymph node dissection in a large proportion of patients with sentinel lymph node–positive melanoma has no negative impact on survival rates. Moreover, oncological trials (COMBI-AD, EORTC 1325-MG/KEYNOTE-054, and CheckMate 238) showed that in patients with stage III melanoma, chances of recurrence-free survival can be improved by 10% to 20% by modern immunotherapy and/or molecular targeted therapy. These findings led to the fall of another dogma in oncology: there is no effective adjuvant therapy for stage III melanoma at acceptable toxicity. At the end of the day, in 2021, a modern multidisciplinary approach incorporating newest findings offers patients with stage III melanoma less surgical complications of better tailored surgery and longer survival as a result of efficient adjuvant therapy.

Introduction Melanoma is a unique disease, as it combines clinical features of both epithelial (pattern of spread) and mesenchymal (rapid and aggressive behavior) malignancies. This, together with a steep rise in incidence of melanoma (particularly in Western countries) over the last decades, creates a significant issue for the healthcare system. Moreover, compared with other malignancies, melanoma is characterized by one of the widest gaps in survival rates between particular stages of the disease, ranging from a nearly 99% chance for complete cure in early stages, such as superficial, thin melanoma (eg, T1a), to virtually no chance for cure in advanced stages.[1,2]

The last decade has brought new achievements in the research on stage III (locoregionally advanced) melanoma, which resulted in important changes in clinical decision making and led to the fall of traditional dogmas of therapy in this field. We summarize these changes with a particular focus on practical implications.

Fallen dogma 1: all sentinel lymph node melanoma metastases warrant completion lymph node dissection

Since the advent of the sentinel lymph node concept in oncology, it has been universally accepted that metastatic cells within a sentinel lymph node are a clear and straightforward indication for completion lymph node dissection (CLND), that is, removal of the regional lymph node basin in order to improve locoregional control of the disease and subsequently lower the risk of locoregional recurrence. It was true both for breast cancer and melanoma. However, the first rupture in that dogmatic rule was seen in breast cancer, when the size of a metastatic focus in the sentinel lymph node was

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TABLE 1 The DeCOG-SLT (German Dermatologic Cooperative Oncology Group) and the MSLT-II (Multicenter Selective Lymphadenectomy Trial II)

Characteristics		DeCOG-SLT	MSLT-II
Patients, n		473	1934
Follow-up, mo, median		72	36
Tumor thickness, mm, median		2.4	2.1
Sentinel node metastasis measuring <1 mm in diameter, %	Observation only	68	65.5
	CLND	63	66.8
Risk ratio (95% CI) for recurrence		0.89 (0.67–1.18)	0.88 (0.78–1)

Abbreviations: CLND, completion lymph node dissection

correlated with the actual risk of non–sentinel lymph node positivity. It was shown that single breast cancer cells (isolated tumor cells) in the sentinel lymph node actually do not impact survival at all, and should not lead to CLND. The same correlation was seen for the so-called micrometastatic sentinel node (ie, metastatic focus measuring from 0.2 to 2.0 mm). Therefore, the definition of a clinically meaningful "positivity" of a sentinel lymph node evolved over time: from presence or absence of metastatic cells in the lymph node, to a more complex 3-step classification with different therapeutic consequences for patients. It was only a matter of time before a similar evolution took place in the understanding of the clinical consequences of sentinel node positivity in melanoma patients. Two studies presented below proved this expected change to become true.

The MSLT-II (Multicenter Selective Lymphadenectomy Trial II),[3] an international phase 3 study initiated in 63 centers, randomized patients with melanoma and sentinel node metastases detected by standard pathological assessment or a multimarker molecular assay to CLND (n = 972) or sonographic observation only (no further surgery; n = 968). It needs to be emphasized that until the initiation of this study, observation only was not in line with the general dogma, and CLND was recommended in all melanoma sentinel lymph node–positive patients. The results of the MSLT-II after 3-year follow-up showed no clinical benefit in terms of melanoma-specific survival from immediate CLND (intention-to-treat analysis; 3-year rate of melanoma-specific survival was virtually the same in the dissection group and the observation group [86% vs 86%] at a median follow-up of 43 months). However, two-thirds of patients in this trial had a low-volume nodal tumor burden, that is, the diameter of metastatic focus within the sentinel node did not exceed 1 mm.[3]

The DeCOG-SLT (German Dermatologic Cooperative Oncology Group)[4,5] phase III trial randomized 483 melanoma patients with positive sentinel node biopsy results into 2 arms: CLND (n = 242) and observation only (no further surgery; n = 241). Recently, the final results of the DeCOG-SLT after a median follow-up of 72 months have been published, showing neither significant difference in the 5-year distant metastasis–free survival between the groups (64.9% vs 67.6%; hazard ratio [HR], 1.08), nor in the 5-year recurrence-free survival (RFS) and overall survival (HR, 1.01 and 0.99, respectively). It should be underlined that as in the MSLT-II trial, almost two-thirds of patients in the DeCOG-SLT trial had minimal tumor burden in the sentinel lymph node (the mean and median size of metastasis in the sentinel node did not exceed 1 mm).[4,5]

Both DeCOG-SLT and MSLT-II studies support not recommending CLND in patients with sentinel lymph node metastasis. A meta-analysis of the 2 aforementioned randomized controlled trials[3-5] and additional cohort studies was published in 2019. Altogether 13 studies were included in the quantitative pooled analysis, which showed similar survival in the CLND group and the observation group (risk ratio for death 0.85; 95% CI, 0.71–1.02) and similar recurrence rate (0.91; 95% CI, 0.79–1.05).[6] The DeCOG-SLT and MSLT-II studies are compared in **TABLE 1**.

The noninferiority of omitting CLND has been proved as presented above. There is, however, additional, extremely meaningful clinically positive effect of abandoning CLND, which refers to the quality of life. In the MSLT-II trial, extremity lymphedema, serious and long-lasting postsurgical complication of CLND, which significantly impacts quality of life, was observed in 24.1% of patients in the CLND group and only in 6.3% of those in the observation group.[3] Four-fold lower risk of extremity lymphoedema further supports observation over CLND in the selected group of melanoma patients.

It is not surprising that, based on data from the above studies, major clinical practice recommendations have been rapidly updated.[1,2,7,8] Currently, the preferred approach to sentinel lymph node–positive metastatic melanoma with limited sentinel lymph node tumor burden and no other risk factors listed in **TABLE 2** is not to dissect regional lymph nodes, but provide strict follow-up including regular sonography of the regional lymphatic basin.[7-9] However, clinically detected regional metastatic lymph nodes still remain a clear indication for surgical removal of the regional group of lymph nodes.[1,9]

TABLE 2 High- and low-risk factors for sentinel lymph nodes positive for melanoma[a]

High-risk features	Low-risk features
• Extracapsular spread/extension • Concomitant microsatellitosis of the primary tumor • >3 involved nodes • >2 involved nodal basins • Immunosuppression therapy	• No high-risk features • Other specific clinicopathological features (eg, difficult access to high-quality sonography of left in situ regional lymph nodes)

a High- and low-risk features of the sentinel node are defined on the basis of exclusion criteria of the MSLT-II trial[3]

TABLE 3 Landmark studies on adjuvant therapy in locoregionally advanced melanoma

Characteristics	CheckMate 238	EORTC 1325-MG/KEYNOTE-054	COMBI-AD
Inclusion criteria	*AJCC 7* stage IIIB, IIIC, or IV	*AJCC 7* stage IIIA (micrometastasis >1 mm if N1a), IIIB, or IIIC	*AJCC 7* IIIA (lymph node metastasis >1 mm), IIIB, or IIIC
Compound and dosing	1 year of nivolumab 3 mg/kg intravenously every 2 weeks vs ipilimumab 10 mg/kg intravenously every 3 weeks for 4 doses, and then every 12 weeks	1 year of pembrolizumab 200 mg every 3 weeks vs placebo	1 year of dabrafenib 150 mg twice daily + trametinib 2 mg once daily vs placebo
Mechanism of action	Immunotherapy: nivolumab is an antibody against PD-1 receptor, which is present of lymphocytes T; inhibition of PD-1 activates lymphocytes against melanoma cells.	Immunotherapy: pembrolizumab is a humanized antibody against PD-1 receptor; inhibition of PD-1 activates lymphocytes against melanoma cells.	Molecular targeted therapy: trametinib is a reversible inhibitor of MEK1/2 activation and kinase activity. Dabrafenib is a *BRAF* inhibitor (inhibits BRAF-associated enzyme B-Raf).
BRAF status	Regardless of *BRAF* mutation status	Regardless of *BRAF* mutation status	Only *BRAF* V600E/K-mutated

Abbreviations: *AJCC 7*, *American Joint Committee on Cancer Staging Manual, 7th edition*; PD-1, programmed cell death 1

Fallen dogma 2: there is no clinically meaningful benefit from adjuvant therapy in stage III melanoma

For many decades, there was no efficient adjuvant therapy in patients with melanoma and involvement of regional lymph nodes (stage III disease). There were attempts with various compounds to increase survival and decrease recurrence rates in that population, with minimal success. The efficacy of cytotoxic chemotherapy and vaccines in the adjuvant treatment of melanoma has been disappointing. In 1996, based on the Eastern Cooperative Oncology Group Trial EST 1684, interferon α was approved for the adjuvant therapy of melanoma.[10] A meta-analysis of 14 studies with interferon α showed a 3% improvement in overall survival (HR, 0.89; 95% CI, 0.83–0.96) and a 7% improvement in disease-free survival (HR, 0.82; 95% CI, 0.77–0.87) at a price of high toxicity. Until 2018, interferon was the only approved option for adjuvant treatment of stage III melanoma after surgery, with low efficacy and high toxicity.[11]

Fortunately, over the last decade, 3 landmark studies have been published, which changed the landscape and management in the field of adjuvant therapy in locoregional advanced melanoma: COMBI-AD, the European Organisation for Research and Treatment of Cancer (EORTC) 1325-MG / KEYNOTE-054, and CheckMate 238. All these trials have been updated in 2020 with long-term follow-up data.[12-14] All showed that there is efficient postsurgical therapy for patients with stage III melanoma with an acceptable level of toxicity, causing another dogma in the field of oncology to fall (TABLE 3).

The COMBI-AD trial investigated the effect of combination of MEK and BRAF inhibitors (trametinib and dabrafenib). The study included 870 patients who had regional lymph nodes resected (stage IIIA [lymph node metastasis >1 mm], IIIB or IIIC), with a *BRAF* (V600E or V600K) mutation. After 5 years of follow-up, recently updated data showed that RFS in the trametinib plus dabrafenib group was 52% compared with 36% in the placebo group (HR for relapse or death, 0.51; 95% CI, 0.42–0.61), with no difference in serious adverse events. Distant metastasis–free survival was also better in the treated group as opposed to the placebo group (65% vs 54%; HR for distant metastasis or death, 0.55; 95% CI, 0.44–0.7). Of note, the beneficial effect of adjuvant therapy was stable during the follow-up at 36 months (59% vs 39%), 48 months (55% vs 38%), and 60 months, adding at least 15% to survival rates as opposed to the placebo group. This undoubtedly provides an important clinical benefit for patients with stage III melanoma and a *BRAF* mutation.[12]

The updated 3-year follow-up results of the EORTC 1325-MG / KEYNOTE-054 randomized phase III double-blind study were reported as well. The study included 1019 patients with melanoma stage IIIA (lymph node metastasis >1 mm), IIIB, or IIIC (without in-transit metastasis) who underwent lymphadenectomy. Patients were given pembrolizumab (n = 514) or placebo (n = 505) every 3 weeks for 1 year, or until disease recurrence, or until unacceptable toxicity. After 1, 2, and 3 years of follow-up, RFS was shown to be

prolonged in the study population (RFS for 3 years of follow-up: 63.7% vs 44.1%; HR, 0.56; 95% CI, 0.47–0.68), regardless of the *BRAF* mutation status or regardless of stratification according to the newer (2010) or older (2018) American Joint Committee on Cancer TNM (tumor, node, metastasis) staging system. Clinical benefit in term of RFS was larger than 15% between the study arms.[13]

The CheckMate 238 international phase III trial included 906 patients with melanoma and resected stage IIIB–C or IV disease, who received nivolumab (n = 453) or ipilimumab (n = 453) until 1 year of treatment, disease recurrence, or unacceptable toxicity, whichever occurred first. After a median follow-up of 51 months, 4-year RFS in the nivolumab arm was 51.7% (95% CI, 46.8–56.3) as compared with 41.2% (95% CI, 36.4–45.9) in the ipilimumab arm (HR 0.71 [95% CI, 0.6–0.86]), yielding 10-point benefit for patients receiving nivolumab. However, of note, there was no difference in 4-year overall survival between study arms (77.9% vs 76.6%).[14]

Falling of a dogma: there is no effective preoperative therapy for stage III melanoma As demonstrated, in many malignancies, for example, breast and colorectal cancer, preoperative systemic therapy offers at least downsizing / downstaging of the disease, leading to less extensive surgery and lower recurrence risk, not to mention survival benefit in specific groups of patients. Several trials on neoadjuvant systemic treatment in advanced melanoma are in progress. A recent meta-analysis of 6 neoadjuvant trials (192 patients with stage III melanoma) showed complete response in 40% patients. Two-year RFS in patients with pathological complete response was markedly better as opposed to the remaining patients (89% vs 50%; $P < 0.001$). Moreover, 2-year overall survival was improved by neoadjuvant therapy, regardless of the type of systemic therapy (immunotherapy or kinase inhibitors) (95% vs 83%; $P = 0.027$).[15] Therefore, an update of clinical guidelines for patients at high risk for relapse after surgery can be expected in the coming years—and subsequently, another dogma can be expected to fall soon.

Conclusions and clinical recommendations for non-oncologists Over the past decades, oncologists were managing patients with melanoma according to the following dogmatic principles: 1) all metastatic regional lymph nodes warrant subsequent CLND and 2) there is no evidently efficient adjuvant therapy for stage III melanoma (ie, regional lymph nodes metastatic melanoma) at an acceptable level of toxicity, leaving surgery in real-life settings as the sole treatment modality for most patients in this population. Both dogmas have recently fallen, as briefly presented above. Moreover, we are witnessing the fall of another dogma, as trials on neoadjuvant therapy are showing promising results.

The results of surgical studies (MSLT-II and DeCOG-SLT) proved that in selected patients with stage III melanoma, limiting the extent of surgery does not decrease chances for long-term survival.[3-5] Data from oncological trials (COMBI-AD, EORTC 1325-MG / KEYNOTE-054, and CheckMate 238) showed that in patients with stage III melanoma, chances of RFS after surgery can be further improved by modern immunotherapy and / or molecular targeted therapy.[12-14]

Both fallen dogmas, as well as the currently falling dogma referring to neoadjuvant therapy, clearly illustrate additive effect of modern, multidisciplinary oncology: we can offer less extensive and less mutilating surgery with the same therapeutic efficacy and combine that with much more effective and less toxic adjuvant therapy. At the end of the day, in 2021, patients with stage III melanoma have less surgical complications of tailored surgery and live longer as a result of efficient adjuvant therapy.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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