Fallen dogmas – recent advances in locoregionally advanced melanoma

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Short title: Fallen dogmas – recent advances in locoregional melanoma

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Abstract

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that surgical dogmatic approach that all sentinel node melanoma metastasis warrants completion lymphadenectomy is no longer valid; omission of completion lymphadenectomy in large proportion of sentinel node positive melanoma patients has no negative impact on survival rates.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

Key words: adjuvant therapy, lymphadenectomy, melanoma, stage III, sentinel lymph node biopsy
Introduction

Melanoma is a unique disease, as it combines clinical features of both epithelial (pattern of spread) and mesenchymal (rapid and aggressive behaviour) malignancies. Adding that characteristic to the steeply raising incidence of melanoma (particularly in Western countries) over last decades, creates a significant problem for health care. Moreover melanoma is characterized by one of the widest gaps in survival rates between particular stages of the disease among all malignancies, ranging from nearly 99% chances for being completely cured in early cases like superficial, thin melanoma (e.g. T1a) to virtually no chances for cure in advanced cases.[1,2]

Last decade brought new achievements in stage III (locoregionally advanced) melanoma research, which resulted in an important changes in the clinical decisions, as well as fall of traditional dogmas of therapy in this field. We will summarize these changes with particular focus on practical conclusions.

Fallen dogma 1: All sentinel node melanoma metastasis warrants completion lymphadenectomy

Since the advent of sentinel node concept in oncology it was universally accepted that presence of metastatic cells within sentinel node is a clear and straightforward indication for completion lymphadenectomy (CLND), i.e. removal of 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 crack in that dogmatic rule was seen in breast cancer, when the size of metastatic focus in the sentinel lymph node was corelated with actual risk of non-sentinel lymph node positivity. It was shown, that single breast cancer cells (isolated tumor cells) present in the sentinel lymph node
actually do not impact survival at all, and should not lead to completion of lymphadenectomy. The same correlation was seen for so-called micrometastatic sentinel node (i.e. metastatic focus measuring from 0.2 to 2.0 mm). Therefore clinically meaningful “positivity” of sentinel lymph node evolved from – at first – presence of absence of metastatic cells in the lymph node to – later – more complex tri-step classification with different therapeutic consequences to the patients. It was only a matter of time to observe the same evolution in the clinical consequences of sentinel node positivity in melanoma patients. Two studies presented below proved this expected change to become true.

Multicenter Selective Lymphadenectomy Trial II (MSLT-II), an international, phase 3 study, initiated in 63 centres, randomized melanoma patients with sentinel-node metastases detected by standard pathological assessment or a multimarker molecular assay to completion regional lymph node dissection (n = 972) or sonographic observation only (no further surgery; n = 968). It needs to be underlined, that until initiation of this study observation only was not in line with the general rule at that time, which warranted CLND in all melanoma sentinel lymph node positive patients. The results of MSLT-II after 3-years follow-up showed no clinical benefit in terms of melanoma-specific survival from immediate completion lymph node dissection (ITT 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). Of note, however, is that two third of patients in this trial had a low-volume nodal tumor burden, i.e. the diameter of metastatic focus within sentinel node not exceeded 1 mm.[3]

German Dermatologic Cooperative Oncology Group phase III trial (DeCOG-SLT) randomized 483 melanoma patients with positive sentinel node biopsy into two arms: classical surgical completion regional lymphadenectomy (n = 242) versus observation only (no further surgery; n = 241). Recently final results of DeCOG-SLT after median follow-up of
72 months was published, showing neither significant difference in the 5-year distant metastasis free survival (DMFS) 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 (OS; HRs, 1.01 and 0.99, respectively). It should be underlined, that as in the MSLT-II trial, almost 2/3 of patients in DeCOG-SLT trial had minimal tumour burden in sentinel 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 SLN metastasis. Meta-analysis of the two aforementioned randomized controlled trials3,4,5 and additional cohort studies was published in 2019. Altogether thirteen studies were included in the quantitative pooled analysis, which showed similar survival in CLND group and observation group (risk ratio [RR] for death 0,85, 95% CI 0,71 to 1,02) and similar recurrence rate (RR 0,91, 0,79 to 1,05).[6] Table 1. compares DeCOG-SLT and MSLT-II studies.

Non-inferiority of omission of CLND has been proved, as presented above. There is however additional, clinically extremely meaningful positive effect of abandoning CLND, which refers to the quality of life. In 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 the patients in the CLND group and only in 6.3% of those in the observation group.[3] Four times lower risk of extremity lymphoedema further supports observation over CLND in the selected group of melanoma patients.

It is not surprising that based on the data from both above presented studies major clinical practice recommendations has been rapidly updated.1,2,7,8 Currently the preferred approach to sentinel node positive metastatic melanoma with limited SN tumour burden and no other risk factors listed in table 2. is not to dissect regional lymph nodes, but provide strict observation including regular sonography of 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]

**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 melanoma patients with regional lymph nodes involvement (stage III disease). There has been attempts made with various compounds to increase survival and decrease recurrence rates in these patients, 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 alpha (IFN-alpha) was registered in the adjuvant therapy of melanoma.[10] A meta-analysis of 14 studies with IFN-alpha showed a 3% improvement in OS (HR 0.89, 95% CI, 0.83 to 0.96) and a 7% improvement in DFS (HR 0.82, 95% CI, 0.77 to 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, during last decade three landmark studies have been published, which changed the landscape and management in the field of adjuvant therapy in locoregional advanced melanoma: COMBI-AD trial, Keynote-054 trial and CheckMate-238 trial. All these trials have been updated in 2020 with long-term follow-up data.[12-14] All proved that there is efficient post-surgical therapy for stage III melanoma patients with acceptable toxicity, causing another oncological dogma to fall (table 3.)

COMBI-AD trial investigated 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 III), with BRAF (V600E or V600K) mutation. After 5 years of follow-up recently updated data showed, that recurrence-free survival in trametinib plus dabrafenib group was 52% compared to 36% in 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, 0.44-0.70). Of note is that 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 placebo group. This undoubtedly provides important clinical benefit for stage III BRAF-mutated melanoma patients.[12]

Updated 3-year follow-up results of the European Organisation for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 randomized phase III double-blind study were reported, as well. The study included 1019 stage IIIA (lymph node metastasis >1 mm), IIIB, or IIIC (without in-transit metastasis) melanoma patients, who underwent lymphadenectomy. Patients were given pembrolizumab (n = 514) or placebo (n = 505) every 3 weeks for 1 year or until disease recurrence or unacceptable toxicity. After 1, 2 and 3 years of follow-up RFS was shown to be stably prolonged in the study population (RFS for 3 years of follow-up: 63.7% v 44.1%; HR, 0.56; 95% CI, 0.47 to 0.68), regardless of BRAF mutation status or regardless of stratification according to newer (2010) or older (2018) AJCC/TNM staging system. Clinical benefit in term of RFS was markedly >15% between study arms.[13]

CheckMate 238, international phase III trial, included 906 melanoma patients with 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. In CheckMate 238 study after median follow-up of 51 months, 4-year RFS in the nivolumab arm was 51.7% (95% CI, 46.8 to 56.3) versus 41.2% (36.4 to 45.9) in the ipilimumab arm (HR
0.71 [95% CI, 0.60 to 0.86]), yielding 10 point benefit for patients. However, of note, there was no difference in 4-year overall survival between study arms (77.9% vs 76.6%). [14]

**Falling dogma: there is no effective preoperative therapy for stage III melanoma**

As seen any many malignancies, just to mention breast and colorectal cancer, preoperative systemic therapy offers at least downsizing/downstaging of the disease, leading to less extensive surgery and lower recurrent risk, not to mention survival benefit in specific groups of patients. Several trials on neoadjuvant systemic treatment in advanced melanoma are in progress. Recent meta-analysis of 6 neoadjuvant trials (192 stage III melanoma patients) showed pathological complete response (pCR) in 40% patients. Two-years recurrence free survival in patients with pCR was markedly better as opposed to the remaining patients (89% versus 50%, p < 0.001). Moreover, 2-years overall survival was improved by neoadjuvant therapy, regardless of the type of systemic therapy (immunotherapy or kinase inhibitors) (95% versus 83%, p = 0.027). [15] Therefore update of clinical guidelines for patients at high risk for relapse after surgery can be expected in the coming years – and another dogma to fall soon.

**Conclusion and clinical recommendations for non-oncologists**

During past decades oncologists were managing melanoma patients according to dogmatic principles: 1) all metastatic regional lymph nodes warrant subsequently completion lymphadenectomy and 2) there is no evidently efficient adjuvant therapy for stage III (i.e. regional lymph nodes metastatic melanoma) at an acceptable toxicity, leaving in real life surgery as the solely method for most stage III patients. Both dogmas has recently fallen, as briefly present above. Moreover we are witnessing how another dogma is falling, as trials on neoadjuvant therapy are showing promising results.
Results of surgical studies (MSLT-II and DeCOG-SLT) proved that in selected patients limitation of extent of surgery in stage III melanoma does not decrease patients’ chances for long-term survival.[3-5] Data from oncological trials (COMBI-AD, EORTC 1325/KEYNOTE-054 and CheckMate 238) showed that in stage III melanoma patients’ chances of recurrence-free survival after surgery can be further improved by modern immunotherapy and/or molecular targeted therapy.[12-14]

Both fallen dogmas, as well as 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 stage III melanoma patients suffer less from surgical complications of tailored surgery and live longer in result of efficient adjuvant therapy.
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**Table 1.** German Dermatologic Cooperative Oncology Group (DeCOG-SLT) and Multicenter Selective Lymphadenectomy Trial II (MSLT-II) studies

|                                | DeCOG-SLT[5] | MSLT-II[3]   |
|--------------------------------|--------------|--------------|
| Number of patients             | 473          | 1934         |
| Median follow-up               | 72 months    | 36 months    |
| Median tumor thickness         | 2.4 mm       | 2.1 mm       |
| Sentinel node metastasis       | 68 vs 63%    | 65.5 vs 66.8%|
| measuring <1 mm in diameter (observation vs CLND) |             |              |
| Risk ratio for recurrence      | 0.89 (0.67-1.18) | 0.88 (0.78-1.00) |

CLND – completion lymph node dissection, German Dermatologic Cooperative Oncology Group – DeCOG-SLT, Multicenter Selective Lymphadenectomy Trial II – MSLT-II
**Table 2. High and low-risk factors for melanoma positive sentinel lymph node**

| High-risk                                | Low-risk                                                                 |
|------------------------------------------|--------------------------------------------------------------------------|
| Extracapsular spread/extension           | Patients without high-risk features                                       |
| Concomitant *microsatellitosis* of the primary tumour | Other specific clinicopathological features (e.g. difficult access to high quality sonography of left *in situ* regional lymph nodes), after thorough discussion with the patient |
| Greater than three involved nodes        |                                                                           |
| Greater than two involved nodal basins   |                                                                           |
| Immunosuppression of the patient         |                                                                           |
| 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

| Study                  | CheckMate 238 [14] | EORTC 1325 (KEYNOTE-054) [13] | COMBI-AD [12] |
|------------------------|--------------------|--------------------------------|---------------|
| **Inclusion criteria** | AJCC7 stage IIIB, IICC or IV | AJCC7 stage IIIA (micrometastasis >1 mm if N1a), IIIB or IICC | AJCC7 IIIA (lymph node metastasis >1 mm), IIIB or IICC |
| **Compound and dosing** | 1 year of nivolumab 3 mg/kg iv every 2 weeks *versus* ipilimumab 10 mg/kg iv every 3 weeks for four doses, and then every 12 week | 1 year of pembrolizumab 200 mg every 3 weeks *versus* placebo | 1 year of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily *versus* placebo |
| **Mechanism of action** | Immunotherapy: nivolumab is an antibody against PD-1 receptor, which is present of lymphocytes T; inhibition of PD-1 activates | Immunotherapy: pembrolizumab is humanized antibody against PD-1 receptor; inhibition of PD-1 activates lymphocytes against melanoma cells. | Molecular targeted therapy: trametinib is reversible inhibitor of MEK1/2 activation and kinase activity. dabrafenib is an BRAF inhibitor (inhibits BRAF-
lymphocytes against melanoma cells. associated enzyme B-Raf).

| BRAF status  | Regardless of BRAF mutation status | Regardless of BRAF mutation status | Only BRAF V600E/K-mutated |
|--------------|------------------------------------|------------------------------------|---------------------------|

AJCC7 – American Joint Committee on Cancer, revision 7; PD-1 - programmed death 1;