ABOUT THE AUTHOR

Jennifer Beecker, MD

Dr. Beecker is a staff dermatologist at The Ottawa Hospital, Assistant Professor at The University of Ottawa. She is a Royal College and American Board of Dermatology certified dermatologist, trained and certified in 3 medical specialties: dermatology, emergency medicine and family medicine. Her interests include medical dermatology, pigmented lesions, in-patient hospital dermatology, and research. She is the Research Director for the Division of Dermatology at The Ottawa Hospital. Dr. Beecker founded the Pigmented Lesion and Melanoma Clinic at the Ottawa Hospital, where she follows patients at high-risk for melanoma with digital dermoscopy and total body photography. Dr. Beecker is the Vice President of the Canadian Dermatology Association's Board of Directors. She trains medical residents and students and serves on the Executive Committee for the Royal College of Physicians and Surgeons Dermatology Examination.

MELANOMA UPDATE AND REVIEW: AJCC STAGING AND ADJUVANT TREATMENT

In an era of rapidly changing medical guidelines it is important for dermatologists to be aware of the current recommendations for disease management. This summary article will highlight the 'need-to-know' information for the clinical dermatologist on staging, sentinel lymph node biopsy recommendations, and new therapeutic options including adjuvant therapy for the management of patients with melanoma.

AJCC Update

In 2016, the American Joint Committee on Cancer (AJCC) expanded its staging guidelines to incorporate additional evidence-based prognostic factors. In January 2018, the AJCC 8th Edition was implemented, and shortly thereafter, the National Comprehensive Cancer Network (NCCN) revised its management guidelines which were updated again in March 2019 (and more recently in May 2020).[2] New stage classifications were produced as the previous versions included patients from before sentinel lymph node biopsies were routine. The AJCC 7th Edition stage I and II patients likely included patients with occult microscopic regional disease, and therefore a worse survival. In the 8th edition, a new definition for T1a and T1b Tumor staging was introduced and there were significant changes to the Stage III data set.[1] Some of the 8th Edition AJCC changes are listed in **Table 1** below.

CATEGORY	CHANGE
T category	• T staging changes: o T1a <0.8 mm without ulceration o T1b<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration o Mitoses removed from staging • Pathology measurements of Breslow thickness measured to the nearest 0.1 mm instead of 0.01 mm
N Category	• Microsatellites, satellites, an in-transit metastases definitions dropped, and categorization based on number of lymph nodes involved • The terms "clinically occult" and "clinically detected" replace the descriptors "microscopic" and "macroscopic"
M category	• M1 category defined by anatomic site and LDH level o 0-LDH normal o 1-LDH elevated o non-visceral site M1a, lung M1b, visceral non-CNS M1c, CNS M1d • New M1d stage for distant CNS metastases
STAGE GROUPINGS	• Four Stage III groupings, increased from three • New Stage: IIID: for thick and ulcerated tumours (T4b+N3c-c)

Table 1. Notable 8th edition AJCC changes; adapted from Gershenwald et al., 2018

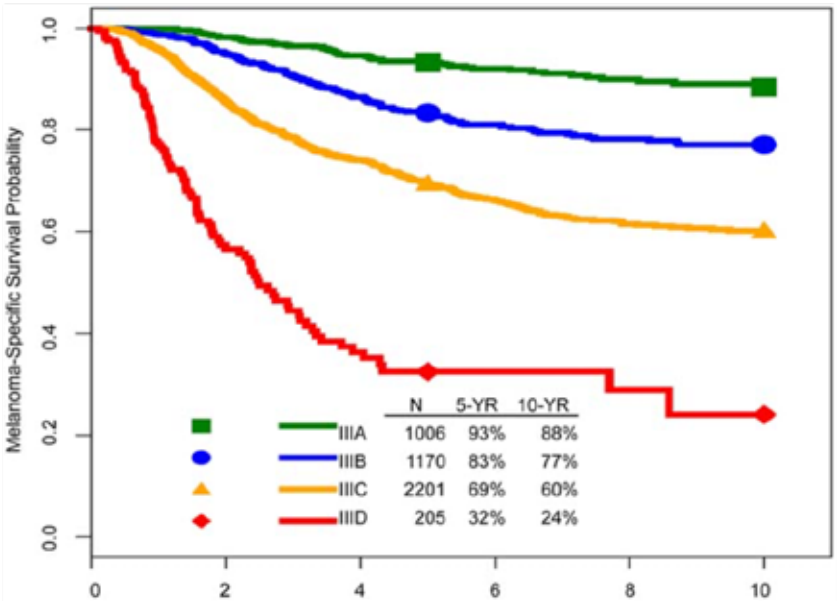

Figure 1. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups; American Joint Committee on Cancer 8th Edition Cancer Staging Manual 1

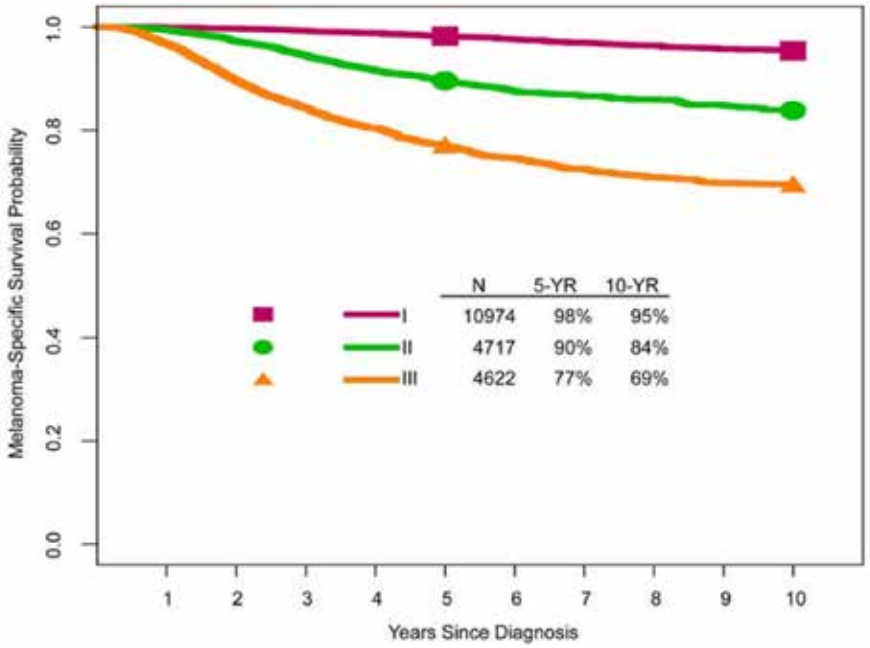

Figure 2. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage in Patients With Stage I to III Melanoma From the Eighth Edition International Melanoma Database.

Importantly for dermatologists, it is now recommended to discuss a sentinel lymph node biopsy in every patient except those with T1a (<0.8mm and no ulceration) or in situ disease. Of note, histological regression is not noted in the AJCC 8th Edition Guidelines and is not felt to be an indication for a sentinel lymph node biopsy in a thin melanoma.[1]

With regard to the clinical workup for melanoma, there is no imaging indicated for Stage 0, Stage I, or Stage IIA disease, due to both the high rate of false positives and the lack of positive impact on treatment, progression, or survival.[1,2]

Additionally, the MSLT-2 trial (NCT00297895) demonstrated a lack of prognostic benefit for performing a complete lymph node dissection in patients with a positive sentinel lymph node biopsy.[3] Instead, these patients are largely observed with serial ultrasounds of the lymph node basins every 3 months for 2 years and then every 6 months for 3 years.

While sentinel lymph node biopsy itself has not been shown to improve disease-specific survival, a positive result upstages a patient to stage III. It is still recommended to conduct a sentinel lymph node biopsy (T1b or higher) to gain important staging and prognostication information and facilitate adjuvant therapy decision making. Adjuvant therapy has been shown to improve recurrence-free survival (RFS) and overall survival (OS) in selected high-risk stage III patients.[8-14]

As mentioned above, in the AJCC 8th Edition, Stage III was divided and a new category was added to include a group that had a worse prognosis: Stage IIID for thick and ulcerated tumours (T4b+N3c-c) with a 32% 5-year survival **(Figure 1)**.[1]

What does a dermatologist need to know about systemic treatment?

Systemic therapies can be broadly divided into 2 categories: targeted treatments (TT) or immuno-oncology (IO) agents. Despite several relatively recent Health Canada approvals for melanoma therapies, a large percentage of patients with advanced metastatic melanoma remain at significant risk of mortality. Thus, an unmet need remains for effective therapies in patients with melanoma **(Figure 2)**[1,4,5,6.]

Systemic therapies

In 2011, ipilimumab was approved for the treatment of unresectable metastatic melanoma as monotherapy. This was the first of 7 new agents that have

demonstrated improvement in overall survival in metastatic melanoma **(Table 2)**

TARGETED THERAPY (TT)	IMMUNO-ONCOLOGY AGENT (IO)
VEMURAFENIB (BRAF INHIBITOR)	IPILIMUMAB (ANTI-CTLA-4)
COBIMETINIB (MEK INHIBITOR)	PEMBROLIZUMAB (ANTI-PD-1)
DABRAFENIB (BRAF INHIBITOR)	NIVOLUMAB (ANTI-PD-1)
TRAMETINIB (MEK INHIBITOR)	

Table 2. Canadian approved therapies for the treatment of metastatic melanoma.

Adjuvant therapy

Adjuvant therapy is a strategy to prevent, and reduce recurrence of, metastatic disease.[5] The goal of adjuvant melanoma treatment is to provide a potential cure before disease recurrence and progression to an advanced stage. Most traditional chemotherapies have proven ineffective as adjuvant treatment, and systemic therapies (e.g. checkpoint inhibitors, targeted therapies) are now preferred options for adjuvant therapy in advanced melanoma.[7]

Surgery is the preferred treatment for localized melanoma, however, patients with lymph node involvement are at high risk of relapse after surgery. Patients with AJCC stages IIB or higher melanoma (TNM N > 0) have a high risk of recurrence and death when treated with surgical management alone. Adjuvant therapy is appropriate for patients with no evidence of macroscopic metastases, but who have a high risk for microscopic metastases. Adjuvant therapy is typically started within weeks of surgery.[2,6,7]

Systemic therapies such as targeted treatments and immuno-oncology agents were first studied and approved in patients with Stage IV disease. Currently, most adjuvant trials are aimed at improving RFS and OS in patients with Stage III disease.[1,2,8] There are now 3 treatments approved by Health Canada for melanoma in adult patients with regional lymph node involvement as adjuvant therapy after complete resection: nivolumab, pembrolizumab and combination dabrafenib and trametinib **(Table 3)**.

High dose Interferon- alpha 2b is also currently approved for adjuvant treatment for high risk melanoma, but it is no longer used due to low efficacy and high toxicity (15 RCTs and 3 meta-analyses, 7% absolute disease-free survival and 3% overall survival benefit). Radiation is used to decrease risk of recurrence locally if present: multiple lymph nodes, large lymph nodes, or extra-nodal extension. Recently at

STUDY NAME	COMBI-AD[9]	CHECKMATE238[10]	KEYNOTE-054[11]
NUMBER OF PATIENTS	870	906	1019
STUDY ARM	DABRAFENIB +TRAMETINIB (N = 438) VS PLACEBO (N = 432)	NIVOLUMAB (N = 453) VS IPILIMUMAB (N = 453)	PEMBROLIZUMAB (N = 514) VS PLACEBO (N = 505)
DISEASE STAGES INCLUDED (AJCC v7)	RESECTED STAGE IIIA (>1 MM METASTASIS), IIIB, IIIC	RESECTED STAGE IIIB/C OR STAGE IV	RESECTED STAGE IIIA (>1 MM METASTASIS), IIIB, IIIC
BRAF MUTATION-POSITIVE PATIENTS, %	100	41	48
PRIMARY ENDPOINT	➤ RFS	➤ RFS	➤ RFS
SECONDARY ENDPOINT	➤ OS ➤ DMFS ➤ Freedom from relapse ➤ Safety	➤ OS ➤ Safety & AE profile ➤ RFS by PD-L1 expression ➤ HR QoL	➤ DMFS ➤ OS ➤ Safety ➤ HR QoL
FOLLOW UP	5 YEARS AT ASCO 2020	3 YEARS AT ESMO 2019	3 YEARS AT ASCO 2020

Table 4. Pivotal adjuvant melanoma trials
DMFS= Distant Metastasis-Free Survival; OS= overall survival; RFS= relapse-free survival; AE= adverse event; HR QoL= Health- related Quality of Life

STUDY NAME	COMBI-AD[8,11,12] N=438	CHECKMATE238[9,10,13] N=453	KEYNOTE-054[11]
EFFICACY	Dabrafenib/ Trametinib	NIVOLUMAB (N = 453) VS IPILIMUMAB (N = 453)	PEMBROLIZUMAB
1-YEAR RFS, %	88%	70%	75%
2-YEAR RFS, %	67%	62%	68%
3-YEAR RFS, %	59%	58%	64%
4-YEAR RFS, %	55%	-	-
5-YEAR RFS, %	52%	-	-
RFS, HR VALUE (95% CI)	0.51 (0.42-0.61)	0.68 (0.56-0.82)	0.56 (0.47-0.68)
DISCONTINUATION DUE TO DISEASE RECURRENCE	5%	26%	21%
3-YEAR OS %	86%	-	-
SAFETY			
AEs (GRADE 3/4)	97 (41%)	96 (25%)	93 (31%)
AEs LEADING TO DISCONTINUATION	26%	9.7%	14%

Table 5. Pivotal melanoma trials: 5-year and 3-year data

THERAPIES APPROVED IN CANADA FOR ADJUVANT THERAPY FOR MELANOMA:
NIVOLUMAB (ANTI-PD1 ANTIBODY)
PEMBROLIZUMAB (ANTI-PD1 ANTIBODY)
DABRAFENIB AND TRAMETINIB (BRAF INHIBITOR AND MEK INHIBITOR COMBINATION)

Table 3. Therapies approved in Canada for Adjuvant therapy for melanoma.

the American Society of Clinical Oncology (ASCO) Annual Meeting in 2020, there were 3- and 5-year updates on pivotal adjuvant therapy trials **(see Table 4 and Table 5)**. The 5-year and 3-year adjuvant data shown at ASCO 2020 is reassuring, showing improvements in RFS and early evidence of improved OS.

Why should dermatologists know about adjuvant therapies?

The Breslow Paradox

It has been shown that more people die of thin melanomas than thick melanomas, due to sheer numbers, even though the absolute risk of dying is higher in thicker melanomas.

In addition, not all thin melanomas behave the same way as some are easily cured by surgery and some are biologically aggressive, metastasizing early.[15] In the future, clinicians may greatly benefit from companion diagnostics that can help determine which thin melanomas are biologically aggressive, so that these patients may benefit from adjuvant therapy early on, possibly in stage II or as early as stage I.

This may mean dermatologists could be prescribing these treatments more commonly in the future.

In summary, there is a rapid expansion of evidence-based information surrounding the diagnosis and management of melanoma including staging, the use of sentinel lymph node biopsy and the use of adjuvant systemic therapies. This review highlights the most important updates for daily clinical practice.

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