THE CANADIAN MELANOMA CONFERENCE

February 22 to 25, 2018, Banff, Alberta

THE CANADIAN ASSOCIATION OF PSYCHOSOCIAL ONCOLOGY (CAPO) ANNUAL CONFERENCE

May 30 to June 1, 2018, Toronto, Ontario

Report from the Canadian Melanoma Conference

The 12th annual Canadian Melanoma Conference was held in Banff Alberta February 22 to 25, 2018, chaired by Dr. Scott Ernst, Professor at the University of Western Ontario. Videos from many of the conference presentations are now available on the Oncology Education website at: www.oncologyeducation.com.

Below, we present summaries of some of the outstanding presentations that describe the evolving understanding of cutaneous melanoma and its treatment. This continues coverage provided in the May 2018 issue of *Oncology Exchange*, featuring summaries of talks by Dr. Jason Luke on "Adjuvant therapy in high-risk melanoma," and Dr. Ian Watson on "The landscape of driver mutations in melanoma: creating a framework for targeted and immune therapy." See the May 2018 issue at www.oncologyex.com.

American Joint Committee on Cancer (AJCC) staging criteria for cutaneous melanoma

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In his presentation at the conference, Dr. Charles Balch discussed the changes to the American Joint Committee on Cancer (AJCC) staging criteria for cutaneous melanoma. Detailed information on this 8th edition is available in the November 2017 edition of CA Cancer: A Journal for Clinicians, the Journal of the American Cancer Society.[1]

There were two reasons for the changes between the 7th and 8th editions of the AJCC TNM (tumour, node, metastasis) staging criteria. First, it is based on a new melanoma staging database from a variety of high-profile institutions in the US, Australia and Europe, involving over 49,000 patients treated since 1998. It includes patients with stages I to III melanoma where tumour and sentinel node biopsy information is available, providing a dataset with full pathologic data. Second, with new agents now available or under development, it is very important to stratify a natural history of melanoma in stages that enable more accurate determination of the treatment outcome being studied.

THE CHANGES

Tumour thickness

It is impractical to reproducibly measure the vertical height and depth, the so-called "thickness," of cutaneous melanoma down to a level of 0.01 mm. The recommendation now for registrars is to record information rounded to the nearest tenth of a millimetre (0.1 mm). Patients with T1 melanomas (i.e. under one millimetre) should be measured to the nearest hundredth of a millimetre (0.01 mm) but be recorded rounded off to a tenth of a millimetre (0.1 mm). The T1 category, then, will be subcategorized by tumour thickness using a 0.8 mm threshold. Therefore, a T1a melanoma will now include those up to 0.75 mm; beyond that, up to 1.04 mm would be a T1b melanoma. In staging, mitotic rate is no longer included, though the information remains important as an independent and significant prognostic factor for stage I and II disease.

The 8th edition of the AJCC cancer staging system

defines primary tumour categories as T1a for melanomas less than 0.8 mm without ulceration; T1b includes any T1 melanoma with ulceration, as well as T1 melanoma measuring between 0.8 and 1.0 mm, with or without ulceration. Ulceration is defined as any disruption of the epithelium overlying an invasive melanoma that has a shoulder, not a vertical edge due to trauma or scratching. For T2 melanoma, there is a 4% difference in 10-year survival with ulceration; for T3, a 7% difference; and for melanomas ≥4 mm, an 8% difference. The endpoint in staging should be survival rates. The stage groupings integrate ulceration and thickness, reflecting that outcomes in ulcerative melanoma are the same as with thicker melanoma that is not ulcerated.

In clinical use, the risk of a patient dying of a distant metastatic disease in 10 years is the converse of the 10-year survival rate. For example, a stage IIa patient has an 88% 10-year survival rate, which means they have a 12% probability of harbouring metastasis at the initial visit. This low risk should be taken into account when contemplating adjuvant systemic therapies, some of which have considerable toxicity and cost.

Lymph nodes

The 8th edition changes the nomenclature in node staging, so that "microscopic" is now referred to as "clinically occult" and "macroscopic" is now termed "clinically detected." "Clinically occult patients would be clinical N0 patients found to have metastasis after a sentinel lymph node biopsy," explained Dr. Balch, "versus those who present with clinical or radiologic detection of melanoma metastasis. The definitions of N1, N2 and N3 a/b/c are unchanged, but the 8th edition clarifies the role of satellites and in-transit disease in defining N1b and c, with or without regional lymph nodes."

The number of regional metastatic nodes has been known for decades to increase the probability of patients having distant disease at the time of diagnosis and staging. Ten-year survival probability drops from 96% in patients with 1 metastatic lymph node to 86% for those with between 4 and 10 nodes, and 77% for those with 11 or more. With intralymphatic regional metastases, there is no difference in 10-year survival between patients with only in-transit metastases (61%), only satellite metastases (61%), or both (62%). They are therefore categorized as one group of intralymphatic metastases, regardless of the setting they present clinically.

Stage III is somewhat complicated: subcategories are based on the number of metastases and include the integration of the number of intralymphatic metastases, regardless of their presentation. Integrating intralymphatic metastases based on their number is tricky: 10-year survival rates differ significantly between the N1 and N3 categories based on the number of regional metastases, from 75% in the N1 group to 47% in the N3 group. Subcategories are based on significant differences in 10-year survival within each N stage: while it is 71% for N2a and b, it drops to 59% in patients with N2c staging. Differences are also seen between N3 subcategories.

FIGURE 1. AJCC eighth edition stage III subgroups

N Category	T Category								
	T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
N1a	N/A	A	A	A	B	B	C	C	C
N1b	B	B	B	B	B	B	C	C	C
N1c	B	B	B	B	B	B	C	C	C
N2a	N/A	A	A	A	B	B	C	C	C
N2b	C	B	B	B	B	B	C	C	C
N2c	C	C	C	C	C	C	C	C	C
N3a	N/A	C	C	C	C	C	C	C	D
N3b	C	C	C	C	C	C	C	C	D
N3c	C	C	C	C	C	C	C	C	D

Instructions
(1) Select patient's N category at left of chart.
(2) Select patient's T category at top of chart.
(3) Note letter at the intersection of T&N on grid.
(4) Determine patient's AJCC stage using legend.

N/A=Not assigned, please see manual for details.[4]

Legend

A	Stage IIIA
B	Stage IIIB
C	Stage IIIC
D	Stage IIID

"AJCC Eighth Edition Stage III Subgroups Based on T and N Categories", in Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, Lazar AJ, Faries MB, Kirkwood JM, McArthur GA, Haydu LE. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA: a cancer journal for clinicians.* 2017 Nov;67(6):472-92.
Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

In stage III disease, tumour thickness and ulceration of the primary tumour need to be integrated because they are also independent predictors of outcome. To provide better stratification for clinical trials, the 8th edition of the AJCC cancer staging system includes 4 stages of N3 melanoma: N3a, N3b, N3c and a category termed stage N3d, which refers to ulcerated thick melanomas with multiple metastases, regardless of whether they are in the regional nodes or are lymphatic metastases. The AJCC Melanoma Committee provides a figure (see **Figure 1**) that facilitates consideration of tumour and node classifications.

Melanoma-specific survival for each of the new stage III groupings reflects significant heterogeneity, Dr. Balch pointed out: "The substages are based upon the T factors, tumour thickness in the presence of ulceration, and the N category, which is the number of regional node metastases and whether those are clinically detectable or not, along with the presence or absence of intralymphatic disease, regardless of where they occur anatomically." Differences in 10-year survival are considerable, ranging from 88% in patients with stage II Ia disease, to 60% with stage IIIc, and just 24% in stage IIId melanoma. This is important for

deciding which patients should be included in adjuvant therapy trials, where they could potentially be exposed to cost and toxicity without clinical benefit. Stage IIId patients have almost a 75% risk of dying of distant disease. In this group, the vast majority are harbouring distant metastasis subclinically at the time of staging, and are good candidates for these systemic trials.

According to the criteria used in the 8th edition, there is a good delineation in 10-year survival between stage I (96%), stage II (84%) and stage III disease (69%).

Metastatic disease

The 8th edition is not based on new data for metastatic disease, partly due to difficulties in obtaining initial data about the presentation and location of distant metastases, given that in the melanoma referral centres, most patients who come in with stage IV have already been treated at some other medical centre. "There is still not a good database in this category," said Dr. Balch.

Two important changes were made in the 8th edition for distant metastasis. First, it provides a different definition of how to use elevated serum lactate dehydrogenase (LDH) at the time of staging. M1 is defined through anatomic sites of distant metastasis and serum LDH value. The second change is a separate category for patients with brain metastasis. The new M1d designation is for patients who have central nervous system (CNS) metastasis, regardless of their LDH status and whether they have metastasis at other sites. This should help to separate this group of patients for the purposes of design and interpretation of clinical trials. As a result, the designation M1c no longer includes CNS metastasis. Elevated levels of serum LDH no longer defines M1c. LDH has been shown to be an independent predictor of survival in patients with stage IV disease. "At a mechanism level," Dr. Balch considered, "it probably reflects rapidly growing tumours that are in an anaerobic stage of glycolysis and are using up a lot of LDH, which is spilling out into the serum."

Stage IV disease has no substages, as there is not enough difference in outcomes, so differences are described in the M category. The M1a designation involves skin, soft tissue or distant lymph nodes; M1b is lung with or without skin, soft tissue or distant lymph node metastasis; M1c is all other metastatic sites except for the CNS; and M1d is CNS metastasis. Within each of those categories there would be a designation in parentheses of (0) if the serum LDH is not elevated, or (1) if it is elevated.

ADDITIONAL FACTORS

Features providing additional value in stratification for clinical trials and prognosis include the primary tumour mitotic rate, level of invasion, the presence of tumour-infiltrating lymphocytes, lymphovascular invasion, neurotropism, melanoma tumour burden and location of sentinel nodes, extranodal extension, and the number of distant metastases. Patient age may also be important, as there are differences in outcome between younger and older patients, though the reasons are not clear.

Summary of changes in the 8th edition of the AJCC cancer staging system for cutaneous melanoma

- Tumour thickness is to be recorded to the nearest 0.1 mm, not to the nearest 0.01 mm.
- T1a and T1b criteria have been revised so that T1a is up to 0.8 mm without ulceration; T1b is between 0.8 mm and 1 mm with or without ulceration or less than 0.08 mm with ulceration.
- Mitotic rate is no longer used as a T category criterion but should be included in reporting for prognosis.
- The stage III grouping has increased from 3 to 4 subgroups, to include a stage IIId category that describes thick, ulcerated melanomas and regional metastases that have poor prognosis.
- The presence of microsatellites, satellites and in-transit metastases should now be referred to as intralymphatic disease because there is no difference in outcome, regardless of the anatomic location where they occur, which was the original definition. They are now included in the definitions of N1c, N2c, and N3c based on the number of tumour-involved regional lymph nodes, the integration of both regional intralymphatic metastasis, and the number of regional lymph node metastases.
- Descriptors have been added to each of the M1 categories, including a separate designation with presence or absence of serum LDH elevation.
- Serum LDH elevation no longer upstages to M1c, and there is a new M1d designation for CNS metastasis, regardless of metastasis at other sites and of serum LDH level.

References

1. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017;67(6):472–92.