Survival of patients with early invasive melanoma down-staged under the new eighth edition of the American Joint Committee on Cancer staging system

To the Editor: The eighth edition of the American Joint Committee on Cancer (AJCC) melanoma staging took effect in January 2018.[1] In this new edition, classification of T1 melanomas was modified whereby mitotic rate is no longer a staging criterion and 0.8 mm, not 1.0 mm, has become the thickness boundary between T1a and T1b.[1] To better appreciate specific consequences of the new system for patients with early melanoma, we assessed disease-free survival (DFS) as a surrogate of overall survival in patients with early invasive melanoma whose tumors were down-staged from T1b to T1a under the eighth edition.

Study participants were enrolled in an ongoing follow-up study of high-risk primary melanoma at the time of their diagnosis with T1b to T4b cutaneous melanoma according to the seventh edition AJCC staging from 2010 to 2014 in Queensland, Australia.[2] Two institutional human ethics committees approved the study. Patients age 16 years or older were recruited via public hospitals, private clinics, and pathology services. Clinical and patient information was collected at diagnosis via questionnaires, and histopathology reports provided information on tumor characteristics. Melanoma recurrences were self-reported through follow-up questionnaires administered every 6 months and confirmed by histopathology and imaging.

T1b tumors were reclassified by using the eighth AJCC edition, and distributions of patient and tumor characteristics were analyzed according to AJCC edition. Three-year DFS was obtained by Kaplan–Meier analysis for patients whose tumors remained at stage T1b and those whose tumors were down-staged to T1a, after which the analysis was repeated with stratification by mitotic rate.

Of 208 patients with T1b melanomas according to the seventh edition, 111 (53%) had their tumors remain at stage T1b and 97 (47%) had their tumors

Table I. Patient characteristics by AJCC edition and tumor stage

	Seventh edition	Eighth edition		
Characteristic	T1b, n (%)	Down-staged to T1a, n (%)	Remained at T1b, n (%)	*P* value*
Total	208 (100)	97 (47)	111 (53)	
Age, y				
<65	117 (56)	55 (57)	62 (56)	.90
≥65	91 (44)	42 (43)	49 (44)	
Sex				
Male	96 (46)	44 (45)	52 (47)	.83
Female	112 (54)	53 (55)	59 (53)	
Subtype				
SSM†	126 (60)	66 (62)	66 (60)	.70
Nodular	14 (7)	5 (5)	9 (8)	
Other	68 (33)	32 (33)	36 (32)	
Body site				
Head/neck	32 (15)	12 (12)	20 (18)	.26
Other	176 (85)	85 (88)	91 (82)	
Personal history				
No	176 (85)	85 (88)	91 (82)	.26
Yes	32 (15)	12 (12)	20 (18)	
SLNB‡				
No	165 (82)	90 (93)	82 (74)	.0002
Yes	36 (18)	7 (7)	29 (26)	
SLNB positivity				
No	35 (97)	7 (100)	28 (96)	.81§
Yes	1 (3)	0 (0)	1 (4)	

AJCC, American Joint Committee on Cancer; *SLNB*, sentinel lymph node biopsy; *SSM*, superficial spreading melanoma.
*Chi-square test.
†Superficial spreading melanoma.
‡Sentinel lymph node biopsy.
§Fisher's exact test.

down-staged to T1a under the eighth edition (Table I). The patients whose tumors were down-staged to T1a were those with a diagnosis of melanoma less than 0.8 mm thick without ulceration and with mitotic rates of 1 to 3/mm^2 (n = 87) or more than 3/mm^2 (n = 10). Five recurrences occurred within 3 years of diagnosis in this down-staged subgroup, equating to an overall DFS rate of 95%. When stratified by mitotic rate, patients with 1 to 3 mitoses/mm^2 and more than 3 mitoses/mm^2 had DFS rates of 96% and 80%, respectively. The DFS of patients with tumors down-staged to T1a under the eighth AJCC edition remains comparable to the 93% DFS of patients with T1b melanomas.

Our early results suggest that mitoses remain an important prognostic feature of thin melanomas, which constitute the majority of melanomas diagnosed today.[3] Our results also estimate that nearly half of T1b tumors according to the seventh edition will be down-staged to T1a tumor with the eighth edition, compared with a suggested 8% up-staging of T1a to T1b tumors.[4] The main limitations of this study are its short follow-up and relatively small study population. Although we do not know the DFS rate for all patients with T1a tumors, we do know that the 5-year cause-specific survival rate for those with T1a melanoma is around 99%.[5]

The subset of patients with T1a melanomas with mitoses according to the eighth edition AJCC classification may not share the same prognosis as those with T1a melanomas without mitoses. Although the eighth edition AJCC classification brings new clarity to melanoma staging overall, if our findings are corroborated in a larger patient cohort, clinicians will need to be alerted to the higher risk for disease recurrence in this patient subgroup. Without specific flagging of these higher-risk patients, their poorer outcomes will be indistinguishable from and diluted by the better outcomes among the low-risk majority of patients with T1a melanomas without mitoses.

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Pharmacy costs of specialty medications for plaque psoriasis in the United States

To the Editor: The 2013 American Academy of Dermatology report on the national burden of skin disease estimated that $15.6 billion was spent on prescription drugs and vaccines for skin disease, with specialty drugs (including biologic and newer oral agents for plaque psoriasis) accounting for 15% of that cost.[1] Drugs used in dermatology represent 3 of the 5 most expensive drugs in the United States by spending, with adalimumab, etanercept, and infliximab accounting for $13.6 billion, $7.4 billion, and $5.3 billion in total expenditures across all indications, respectively.[2]

Despite this growing problem of rising costs of specialty medications, it is difficult to find accurate estimates of the costs of individual drugs. Currently, most estimates of the costs of specialty medications use average wholesale price and wholesale acquisition cost, which are benchmarks reported by manufacturers without significant standardized oversight. These measures do not account for discounts, rebates, and price reductions, all of which are commonplace in the pricing of prescription medications.

To remedy this problem, the US Centers for Medicare & Medicaid Services have developed nationwide surveys of invoice prices for prescription medications from retail community pharmacies to create a new metric, the National Average Drug Acquisition Cost. This new pricing benchmark is representative of the costs of medications to pharmacies and accounts for manufacturer-to-pharmacy price reductions, which are not disclosed in manufacturer-reported measures. Therefore, this measure provides a more accurate representation of the actual costs of prescription medications.

NADAC data from the Medicaid Pharmacy Pricing database from November 28, 2013, to October 4, 2017, were analyzed for this study. Annual costs of specialty medications (biologic or small molecule therapies) were calculated on the basis of standard on-label approved dosing regimens for plaque psoriasis.

The first-year cost of specialty medications in 2017 for plaque psoriasis per Medicaid patient ranged from $34,213.37 to $91,404.58, whereas the annual cost of maintenance treatment ranged from $34,401.88 to $79,217.30 per patient (Table I). From 2013 to 2017, the cost of biologic and small molecule medications rose at an annual rate of 9% for ustekinumab, 16% for apremilast, 17% for etanercept, and 18% for adalimumab (Fig 1). Rates of increase in the cost of psoriasis medications were the same for treatment in the first year and maintenance treatment.

One limitation of NADAC is that it does not account for manufacturer-to—pharmacy benefits manager rebates and manufacturer-to—health plan discounts, yet these also contribute significantly to rising drug costs. Additionally, specialty pharmacies dispense a large portion of biologic medications and may negotiate medication pricing rates different from those of retail pharmacies but were not surveyed for NADAC. Health care spending in the United States is expected to rise 6% annually over the next 7 years, with increasing drug prices implicated as 1 of the primary reasons for this.[3] Specialty drugs in particular contribute disproportionally to overall drug spending in the United States, and this cost is expected to continue increasing on account of increased adoption and rising costs of these drugs.[4] Greater transparency in the pricing of prescription

Table I. Changes in the cost of the first year of treatment per patient for specialty medications for plaque psoriasis from November 28, 2013, to October 4, 2017

Drug	January 22, 2014	January 20, 2016	October 4, 2017	Average annual change	Annual rate of change
Adalimumab	$30,056.40	$41,116.07	$52,552.91	$6343.77	18%
Apremilast	—	$27,806.13	$34,213.37	$4220.33	16%
Etanercept	$40,186.62	$59,668.81	$70,339.64	$8294.33	17%
Ustekinumab (45 mg)	$33,459.82	$40,879.91	$45,507.84	$3255.02	9%
Ustekinumab (90 mg)	$64,755.99	$81,137.70	$91,404.58	$6918.02	9%