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Original Article

Classification of 3097 patients from the Japanese melanoma study database using the American joint committee on cancer eighth edition cancer staging system

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ABSTRACT

Background: The American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging System was implemented in 2018; however, it has not been validated in an Asian melanoma population.

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Objective: The purpose of this study was to validate the new system using a cohort of Japanese melanoma patients.
Methods: The AJCC 7th and 8th Editions were used for TNM classification of patients in a database established by the Japanese Melanoma Study Group. Patient data with sufficient information to be applicable to the AJCC 8th staging were selected. The Kaplan–Meier method was used to estimate disease-specific survival and relapse-free survival.
Results: In total, data for 3097 patients were analyzed. The 5-year disease-specific survival according to the 7th and 8th Edition staging system were as follows: IA = 98.5%/97.9%; IB = 95.4%/96.2%; IIA = 94.2%/94.1%; IIB = 84.6%/84.4%; IIC = 72.2%/72.2%; IIIA = 76.2%/87.5%; IIIB = 60.7%/72.6%; IIIC = 42.0%/55.3% and IIID = none/26.0%. The 5-year relapse-free survival according to the 7th and 8th Edition staging was as follows: IA = 94.5%/92.7%; IB = 85.4%/85.3%; IIA = 80.1%/79.4%; IIB = 71.4%/70.6%; IIC = 56.8%/55.7%; IIIA = 56.8%/69.4%; IIIB = 42.6%/56.8%; IIIC = 20.0%/33.3% and IIID = none/6.5%.
Conclusion: The results show that new staging system could efficiently classify our Japanese melanoma cohort. Although there was no difference in Stage I and II disease between the 7th and 8th Edition systems, we should be careful in managing Stage III disease since the survival curves of the 8th Edition staging were completely different from the 7th Edition. Moreover, our results indicate that adjuvant therapies for Stage IIB and IIC should be developed, since the relapse-free survival for these stages were equivalent to Stage IIIA and IIIB, respectively.

1. Introduction

The American Joint Committee on Cancer (AJCC) released the 8th Edition of its Cancer Staging Manual in 2017 [1] and it was first implemented in January 2018. The new edition includes several major changes to TNM categories, prognostic stage groups, and criteria, especially among the Stage 3 subclasses. This latest new staging system was created based on data for 43,792 patients who had Stage I through III melanoma at initial diagnosis and had received treatment since 1998. The database included patient data from 10 institutes in the United States, Europe, and Australia; thus, less Asian populations were perhaps underrepresented in their analyses. As previous reports have suggested, the proportion of clinical types of melanoma differ between Caucasian and Asian populations; in Caucasian populations, superficial spreading melanoma (SSM) is the major clinical type and there are very few occurrences of acral lentiginous melanoma (ALM) while in Asian populations, ALM constitutes half of all melanoma [2–4] and there is less occurrence of SSM [5,6]. Thus, the aim of this study is to verify the AJCC 8th Edition Staging System using our Japanese Melanoma Study Group database and also compare the survival curves of 7th and 8th Editions in our cohort.

2. Materials and methods

In this study, we used a database established by the Committee of Statistical Survey of Skin Cancer Prognosis of the Japanese Skin Cancer Society, a survey named the "Japanese Melanoma Study (JMS)". The JMS, which began in 2005, not only involves collecting new patient information but also updating prognostic information of patients previously submitted. The JMS includes all types of melanoma such as mucosal melanoma, ocular, and unknown primary melanoma, but for our analyses we included only melanoma of cutaneous origin. Data selection strategy is shown in Fig. 1. After selection, patients were classified using both the AJCC 7th and 8th Edition systems and their classification efficacy was compared.

Chi-square test was used to calculate *P*-values of categorical difference, Kaplan-Meier method was used to estimate survival curves, and Generalized Wilcoxon test was used to calculate *P*-values. All statistical analysis was performed using the free statistical analysis software R and *P*-values of less than 0.05 were considered as significant.

This study was approved by the institutional review board (59-1) and Japanese Dermatology Association.

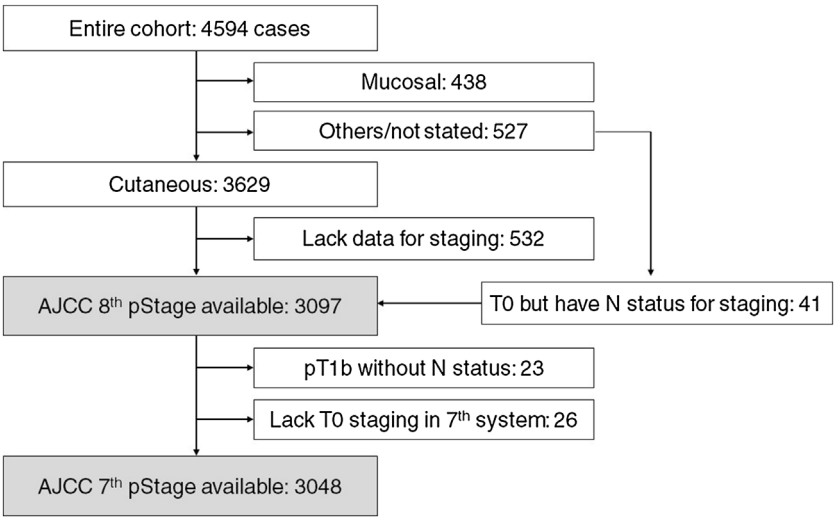

Fig. 1. Patient selection strategy. AJCC: American Joint Committee on Cancer, pStage: pathological stage 338 x 190 mm (96 × 96 DPI).

3. Results

The JMS database, from 2005 to 2017, included data of 4594 patients. After the data selection, data for 3097 patients were qualified for AJCC 8th staging system. Of those 3097 patients, 3048 patients were re-classified according to the AJCC 7th Edition. The correspondence data is shown in Table 1. In the AJCC 8th Edition, patients with T1a and T1b tumors are classified as Stage IA if lymph node metastasis was not detected clinically, meaning that no pathological assessment of the draining lymph node is required. As shown in Table 1, 23 patients in Stage IA by AJCC 8th Edition were classified as clinical Stage IB by AJCC 7th Edition because AJCC 7th Edition only allows for T1a classification of patients as who did not require pathological lymph node assessment. Other localized diseases (stage I and II) were classified in the AJCC 8th Edition with similar criteria to the 7th Edition (Tables 1 and 2). On the other hand, the classification criteria for patients with lymph node metastasis (stage III) have changed greatly, including a new subclass, Stage 3D, in addition to Stage IIIA-C. As a result, the number of patients classified as Stage IIIA and IIIB according to the AJCC 7th Edition was reduced by more than 50% when classified according to the 8th Edition, and the number of patients classified as Stage IIIC doubled. One fourth of those classified as Stage IIIC according to the AJCC 7th Edition were classified into a new subclass, Stage IIID with the AJCC 8th Edition. In the AJCC 8th Edition, patients with have pathological lymph node metastasis and unknown primary tumor, were classified as either IIIB or IIIC according to the level of lymph node involvement. As a result, 41 such patients with lymph node metastasis and unknown primary tumor were classified as IIIB or IIIC.

Next we compared disease-specific survival (DSS), determined using the Kapan-Meier method. As shown in Fig. 2, the DSS curves of Stage IIA to IIC disease classified according to both AJCC 7th and 8th Edition were clearly divided. Although the curves were not crossed, there was no statistical difference between Stage IA and IB by either system. There were no major differences between AJCC 7th and 8th Edition with regard to survival.

As for the Stage III disease, although both the 7th and 8th Editions did not reach statistical significance between Stage IIIA and IIIB, 8th Edition, other subclasses were clearly divided by both systems (Fig. 2). Notably, all DSS curves of Stage IIIA to IIIC disease by AJCC 8th Edition were better than that of AJCC 7th Edition. On the other hand, survival of Stage IIID was very poor, even comparable to Stage IV disease although there was statistical significance dividing Stage IIID and Stage IV.

As for relapse-free survival (RFS), there was no statistical difference between Stage IIA and IIB disease when classified according by either edition, but the RFS of Stage IIC disease was statistically lower compared with IIB (Fig. 3). On the other hand, the RFS of Stage III disease was clearly classified by both editions (Fig. 3). Collectively, the 8th Edition could classify patients with lymph node metastasis more specifically than the 7th Edition; there being 4 subclasses from low risk to high risk in the 8th Edition.

The 3-year and 5-year DSS and RFS for each stages according to the 8th Edition are shown in Table 3. Regarding DSS, Stage IIC had only 72.2% at 5 years, equivalent to that of Stage IIIB (72.6%). Interestingly, although Stage IIID disease does not harbor distant organ metastasis, 5-year survival of Stage IIID had only 26.0%, half that of Stage IIIC (55.3%) and rather close to Stage IV (21.4%). RFS showed a similar trend as that of DSS, Stage IIC had similar survival to that of Stage IIIB. Of note, Stage IIA or higher stages of disease had <80% RFS at 5 years.

We have previously reported that the patients with ALM of stage IIIA were shown to associate with worse survival compared with SSM in our analysis of the JMS dataset classified using AJCC 7th Edition [7]. Therefore, we analyzed the current data to see whether ALM is associated with survival in stage IIIA using the AJCC 8th Edition. As a result, although not significant, ALM showed a tendency toward worse survival compared with SSM ($P = 0.086$, data not shown).

Table 1
Distribution of each staging.

	8th staging											
7th staging	Stage	0	1A	1B	2A	2B	2C	3A	3B	3C	3D	4
	0	743										
	1A		434									
	1B		75	225								
	2A			5	222							
	2B				2	246						
	2C					2	168					
	3A							61	58	53		
	3B							3	51	239		
	3C								6	181	76	
	4											198
	Clin-1B		23									
	NC								8	18		

Clin-: clinical staging; NC: not classifiable.

4. Discussion

In the AJCC 8th Edition, the classification of patients with regional disease has been greatly changed from the 7th Edition [1]. In this study, we showed that classification of patients with Stage III disease in a database Japanese melanoma with the AJCC 8th Edition was more efficient than 7th Edition, as was the case with the original cohort upon which the 8th Edition was based. [1]. With the updates made to the system, more than half of patients with lymph node metastasis (Stage III) were classified as Stage IIIC (Table 1) and only one third of classifications of Stage IIIA and IIIV disease made according to the AJCC 7th remained in the same stage when reclassified using AJCC 8th Edition. As a result, both the DSS and RFS of Stage IIIA disease improved when compared with AJCC 7th Edition, which was equivalent to that of Stage IIB (Table 3). Similarly, the DSS and RFS of Stage IIIB and IIIC improved compared to the 7th Edition. On the other hand, the new Stage IIID disease subclass was comprised of patients with poor prognosis, with a similar DSS to that of Stage IV disease. Therefore, we should be careful when interpreting the results of previous clinical studies being aware that the DSS and RFS of Stage IIIA to IIIC completely differ from the 7th and 8th Editions: For example the CheckMate 238 study [8] which evaluated adjuvant nivolumab against ipilimumab, included patients classified as Stage IIIB, IIIC, and IV, according to the 7th Edition and thus, most of the patients would have been classified as Stage IIIA and IIIB with the 8th Edition were not included in this study (Table 1). This fact raises the possibility that nivolumab could provide survival benefit for patients with 8th Stage IIIA and IIIB disease according to 8th Edition classification.

The AJCC 8th Edition system included classification of patients with unknown primary tumor, but who have lymph node metastasis. This modification enabled 41 patients in our cohort, who were categorized as “unable to classify” with the 7th Edition to be classified as Stage IIIB or IIIC. However, this classification is considered as a temporary staging and may be modified after the accumulation of data. One further change in the 8th Edition is that patients with T1b tumor do not require sentinel lymph node biopsy to be classified as Stage IA disease in the 8th Edition system. This means that tumors with a thickness of less than 1 mm were considered as having a very low risk of metastasis; indeed, we

Table 2
Number of patients in each stages. The number in () indicates the number of change from 7th to 8th staging system.

Stage	0	1A	1B	2A	2B	2C	3A	3B	3C	3D	4
7th staging	743	434	300	227	248	170	172	293	263	–	198
8th staging	743(±0)	532(+98)	230(-70)	224(-3)	248(±0)	168(-2)	64(-108)	123(-170)	491(+228)	76(new)	198(±0)

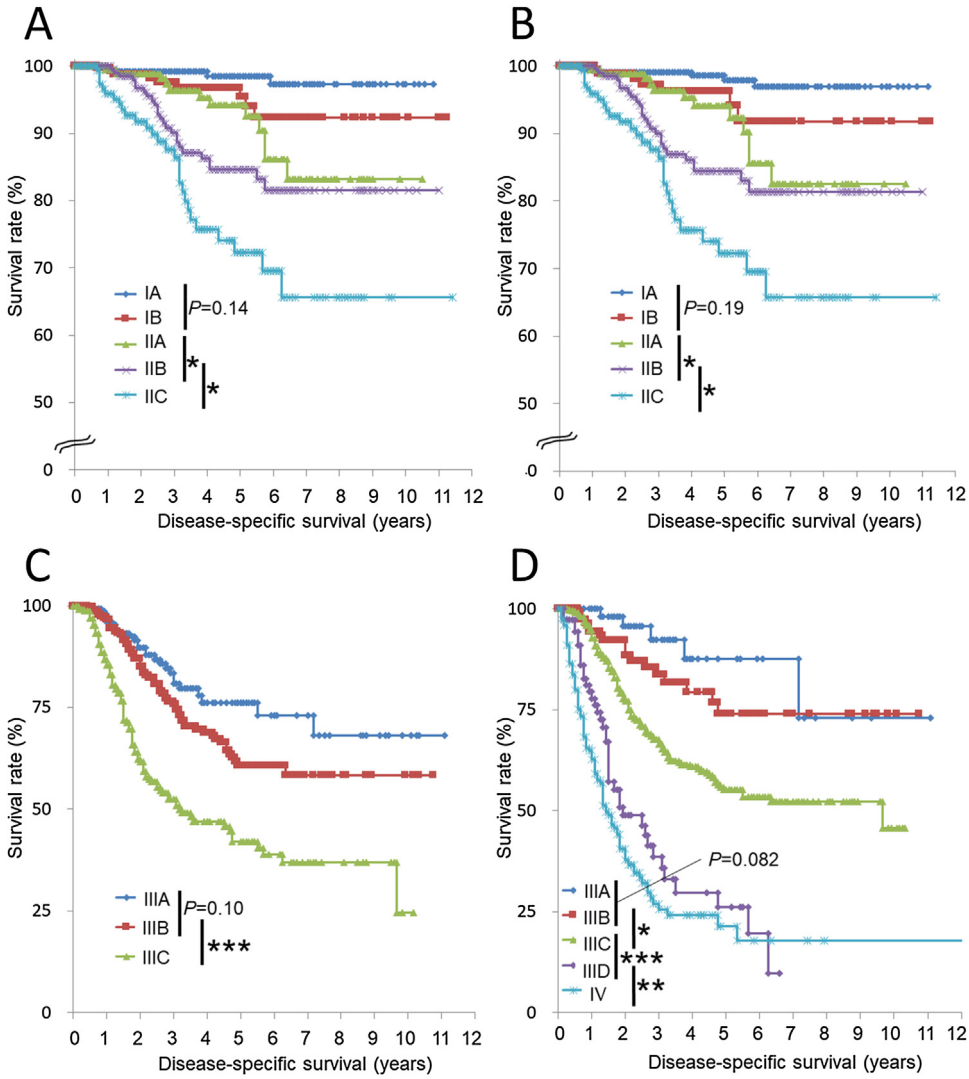

Fig. 2. Disease-specific survival curves for Stage I-III disease.
A) Stage I and II by AJCC 7th Edition staging.
B) Stage I and II by AJCC 8th Edition staging.
C) Stage III by AJCC 7th Edition staging.
D) Stage III by AJCC 8th Edition staging.
*: P < 0.05, **: P < 0.01, ***: P < 0.001.
338 × 381 mm (96 × 96 DPI).

could not find a difference between Stage IA in the 7th and 8th Edition staging regarding both DSS and RFS, despite of the addition of T1b tumor with or without sentinel lymph node biopsy in the 8th Edition (Figs. 2 and 3).

The patients with high-risk Stage II (Stage IIB and IIC) had a higher risk of recurrence than Stage IIIA and IIIB (Table 3), indicating the need for adjuvant therapy for high-risk Stage II disease. However, all therapies ipilimumab, nivolumab, pembrolizumab, and BRAF inhibitors were tested on Stage III and/or IV (Stage IIIB to IV for nivolumab [8] and Stage IIIA to IIIC for ipilimumab [9], pembrolizumab [10], and BRAF inhibitor [11], according to AJCC 7th Edition staging) and Stage II disease was not included in the clinical studies. Currently, a randomized controlled phase 3 study to test pembrolizumab for patients with Stage IIB and IIC has just begun enrolling patients (Keynote-716, NCT03553836) [12], which means that there is a chance of pembrolizumab gaining approval for high-risk Stage II disease in the near future. On the other hand, to the best of our knowledge, no randomized controlled study to test nivolumab for patients with high-risk Stage II disease has been planned; however, a single-arm phase 2 study is ongoing (NCT03405155) [13]. As for the BRAF inhibitors, we could not find any trial planned for

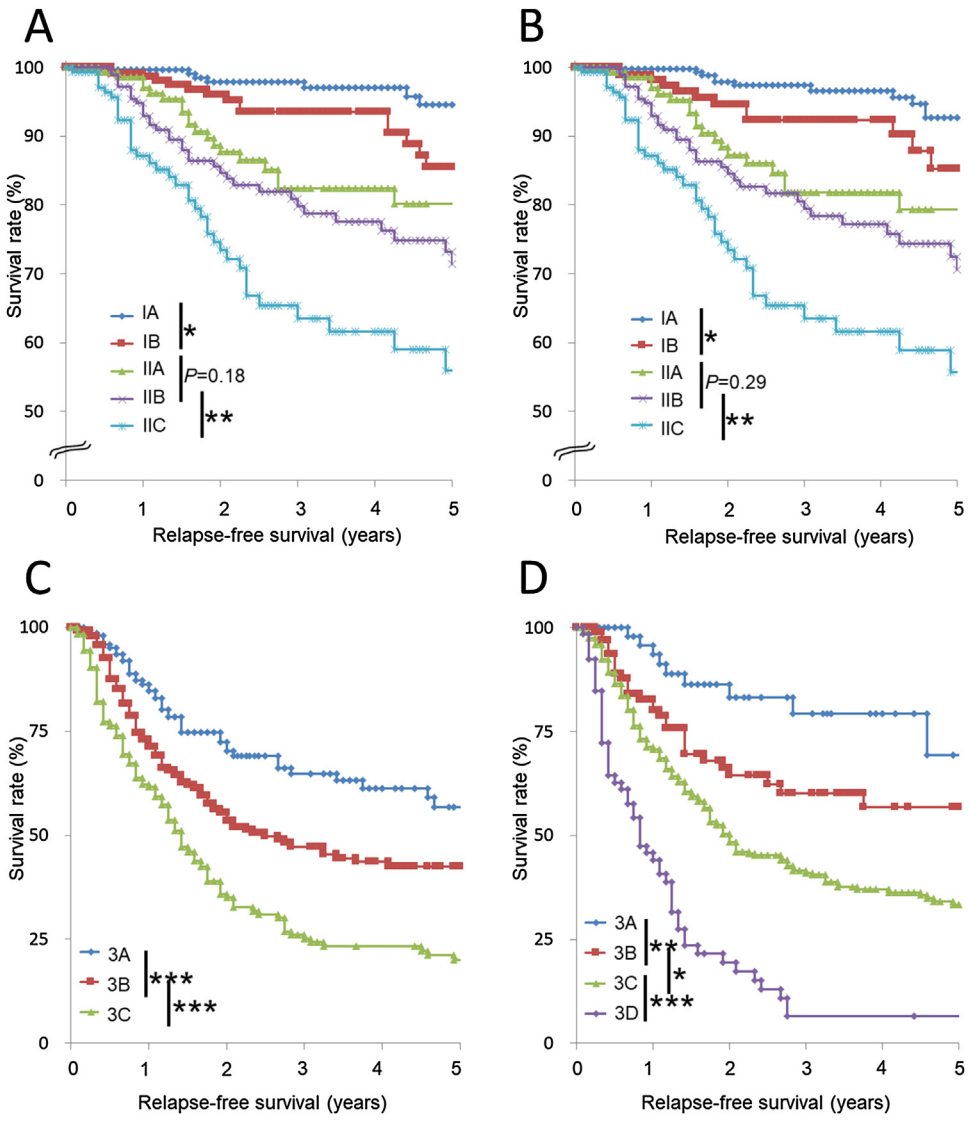

Fig. 3. Relapse-free survival curves for Stage I-III disease.
A) Stage I and II by AJCC 7th Edition staging.
B) Stage I and II by AJCC 8th Edition staging.
C) Stage III by AJCC 7th Edition staging.
D) Stage III by AJCC 8th Edition staging.
*: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$.
338 × 381 mm (96 × 96 DPI).

Table 3
The Disease-specific and relapse-free survival rate in each stages classified by 8th staging system.

	Stage	1A	1B	2A	2B	2C	3A	3B	3C	3D
DSS	3-year	99.1%	97.2%	96.3%	90.0%	87.6%	92.3%	82.5%	67.1%	38.5%
	5-year	97.9%	96.2%	94.1%	84.4%	72.2%	87.5%	72.6%	55.3%	26.0%
RFS	3-year	97.4%	92.4%	81.8%	80.6%	65.4%	79.3%	60.1%	41.6%	6.5%
	5-year	92.7%	85.3%	79.4%	72.5%	55.7%	69.4%	56.8%	34.1%	6.5%

RFS: relapse-free survival; DSS: disease-specific survival.

patients with high-risk Stage II disease. As the proportion of patients with high-risk Stage II disease in our cohort was 13.4%, we believe that adjuvant therapies for such patients needs to be developed.

5. Conclusion

In our study, the updated AJCC staging system of the 8th Edition could efficiently classify melanoma patients in Japanese Melanoma Study database. The DSS and RFS of patients with nodal involvement were clearly classified into 4 substages, and therefore, we could predict outcome more precisely. Furthermore, we should be careful when interpreting the result of previous clinical trials (published before the 8th Edition) because the survival of subclasses in Stage III disease differs greatly in between AJCC 7th and 8th Editions. Patients with Stage II, especially Stage IIB and IIC disease, had a considerably high rate of recurrence therefore, we believe adjuvant therapies for such patients needs to be developed.

Conflict of interest

None declared.

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