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Inter-observer variation in the histopathology reports of head and neck melanoma; a comparison between the seventh and eighth edition of the AJCC staging system

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ABSTRACT

Background: TNM staging of melanoma has recently been altered by the introduction of the 8th edition of the AJCC Cancer Staging manual. The purpose of this study is to analyze the inter-observer variation of histopathology reports and its effect on recommended treatment policy.
Methods: We retrospectively analyzed 296 cases, diagnosed as primary cutaneous head and neck melanoma (2005–2016), referred to the Netherlands Cancer Institute (NCI) for treatment after prior diagnosis in another hospital (non-NCI). All reports were analyzed for patients demographics, tumor characteristics and histopathologic features.
Results: In 53% and 40% of the cases, the histopathologic parameters were discordant, according to AJCC 7th and 8th edition, respectively. This indicated a perfect inter-observer agreement for the measurement of Breslow thickness (Intraclass correlation coefficient (ICC) = 0.981) and a substantial agreement for subtype (kappa statistic (κ) = 0.648) and ulceration (κ = 0.802), while only moderate for dermal mitotic activity (κ = 0.472). After NCI review, recommended treatment policies were changed in 13% and 11% of the patients when applying TNM 7 and TNM 8, respectively. Scheduling sentinel lymph node biopsy (SLNB) changed in 14 (5%) and 10 (3%) cases when using TNM 7 and TNM 8, respectively.
Conclusion: Review by a NCI pathologist of histopathologic parameters of primary cutaneous head and neck melanoma led to significant changes in treatment decision. Introduction of the AJCC 8th edition led to slightly less discordances between NCI and non-NCI reports and consequently smaller impact on treatment planning. Expert review remains indicated when a SLNB is considered for additional staging in selected cases.

Introduction

For the last decades, worldwide and in the Netherlands, the incidence of cutaneous melanoma is increasing faster than any other potentially preventable cancer due to an increasing sun exposure [1,2]. Histopathologic parameters have enormous prognostic impact and are leading in clinical decision making [3]. Pathology reports are decisive for estimating the width of excision margins, and the need for sentinel lymph node biopsy (SLNB) [4].

The key pathologic parameters for determining stage, prognosis, treatment and follow-up of melanoma patients are Breslow thickness (BT), mitotic activity in the dermal part of the tumor (DMA), ulceration and the proximity of the tumor to the diagnostic excision margins [5]. In the 7th edition of the AJCC staging system, the mitotic activity criterion replaced Clark's level to increase correct classification of high-risk thin melanoma patients (pT1b). Recently, the 8th edition of the AJCC staging system has been introduced and

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implemented in the Netherlands since 2018. However, with the implementation of the 8th edition, DMA is no longer used as a T-classification criterion and pT1b is classified as melanomas with BT of ≥0.8–1.0 mm (mm) or BT of <0.8 mm with ulceration [6]. The study of Oude Ophuis et al. suggests that DMA criterion for pT1b classification and the recommendation to perform SLNB for pT1b melanomas should be reconsidered regarding the increasing indication of SLNB without difference in surival [7]. The indications for SLNB are strongly dependent on staging, it is recommended in pathologic stage IB and IIA according to the Dutch melanoma guidelines, which indicates the importance of histological down- and upstaging [4,5,8].

Our study focused on head and neck melanoma, because treatment at this site knows more variations and complications than other sites of the body. Moreover, SLNB in the head and neck area is known as a difficult technique due to the complex anatomy, interlacing lymph vessels and unexpected drainage patterns. Although the risk of complications is low, SLNB remains an invasive and expensive surgical procedure. This is also one of the reasons of the considerable regional variations in SLNB practice in the Netherlands, which means that SLNB of head and neck melanoma is mostly performed in tertiary centers, according to the Dutch melanoma guidelines [8,9]. This creates a unique opportunity to study an unbiased group of melanoma patients referred to our institute.

Histopathologic diagnosis and staging of melanoma depends strongly on the expertise of the individual pathologist. Therefore, inter-observer variation between pathologists is inevitable and many studies have reported on diagnostic disagreements by second opinions in diagnostic surgical pathology. The reported major diagnostic disagreement rates vary from 2 to 28%, depending mainly on the organ system that is studied [10].

Also for primary cutaneous melanoma, many reports have discussed the reproducibility of the histopathology [11–18]. Assessment of BT appeared to be the most reproducible parameter with an excellent level of inter-observer concordance (ICC = 0.96). The other parameters, as presence of ulceration ($\kappa = 0.83$) and DMA ($\kappa = 0.76$), also have high levels of concordance [18].

To determine the need of expert review of head and neck melanoma and its impact on management of head and neck melanoma patients we studied inter-observer variation between histopathology reports of primary cutaneous melanoma in the NCI and referring hospitals. Also we were interested to know whether the introduction of the 8th edition of TNM staging by AJCC has changed the incidence of significant discrepancies.

Methods

Patients and reports

This is a retrospective observational patient file study. At the Netherlands Cancer Institute (NCI), from all patients referred for melanoma treatment, the slides of the primary melanoma are routinely reviewed by NCI melanoma pathologists (pathologists specialized in melanoma) to confirm the diagnosis and to document the histopathologic prognostic parameters. Pathology reports were collected from both referring general pathologists and NCI pathologists between 2005 and 2016.

All patients were diagnosed with a primary invasive melanoma of the head and neck by general pathologists at the referring hospitals. The histological features are extracted from pathology records received from the nationwide pathology network PALGA, as well as from the hospital discharge registry. Only reviews of histopathology reports of primary cutaneous head and neck melanoma were considered for this study. Cases sent to our institution by an external pathologist requesting pathology consultation were not included. Also, cases in which a diagnosis of melanoma was made by a specific melanoma pathologist elsewhere (working in the NCI as well) were not included. Pathology reports, in which more than 2 histopathologic parameters were missing, were excluded. Referred reports of institutes outside the Netherlands were not included. Furthermore, patients referred with confirmed primary histological diagnosis of dermal metastasis of melanoma were excluded as well.

Pathological parameters and clinical relevance

Reports were analyzed for variations in the following pathological parameters: BT as continuous variable (measured in millimeters) and categorized in T-category groups according to the version of the AJCC 7th edition (2009) and the most recent version of the AJCC 8th edition (2017), the presence or absence of ulceration and of DMA, and the melanoma histologic subtype according to the WHO classification, categorized as superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), desmoplastic melanoma and melanoma not otherwise specified (NOS) [19]. Furthermore, excision margins and recommendation for SLNB following the guidelines of both AJCC 7th and 8th edition were also analyzed.

Changes of over- and under-diagnosis were defined within the perspective of clinical relevance. A shift from an invasive melanoma to non-invasive or benign melanoma was classified as over-diagnosis (under-diagnosis is not possible because non-invasive melanomas were not included in this study). A change from a narrower to a wider surgical excision margin or vice versa was considered as under- and over-diagnosis, respectively. A change from a SLNB to no SLNB or vice versa was considered as over- and under-diagnosis, respectively, leading to inevitable consequences for therapy, follow-up and prognosis.

The margin of the therapeutic excision is determined by BT. In our institute we perform for Mis an excision margin of 0.5 cm according to the Dutch melanoma guidelines [8], which were equally employed across the head and neck surgeons involved. For melanoma with BT ≤ 2.0 mm, a therapeutic excision margin of 1 cm is used. For melanoma with BT > 2.0 mm, an excision margin of 2 cm is used. The indication for SLNB in melanoma patients is a melanoma staged as ≥ PT1b without clinical lymph node involvement. All SLNBs have been performed in the same session with the re-excision of the primary melanoma.

Statistics

Baseline patient and tumor characteristics were summarized with medians and interquartile ranges (IQR) or numbers of patients with percentages. Agreement between paired reports describing continuous pathologic parameters, like BT, was analyzed using the Intraclass Correlation Coefficient (ICC) [20]. Values for ICC below 0.40 indicate poor agreement, 0.40–0.59 fair agreement, 0.60–0.74 good agreement and above 0.75 perfect agreement. Agreement on categorical pathologic parameters (melanoma histologic subtype, BT stratified into groups used for pathologic T-classification in the AJCC staging system (<0.8 mm, 0.8–1.0 mm, >1.0–2.0 mm, >2.0–4.0 mm, >4.0 mm), DMA and ulceration) was evaluated with the Cohen's kappa statistic (κ) [21]. A κ value of 0.00–0.20 indicates poor agreement, 0.21–0.40 as fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and 0.81–1 (almost) perfect agreement [22].

Results

During the study period, 483 patients with head and neck (non-

invasive) melanoma were reviewed at NCI. In total 187 cases were excluded; 101 reports cases referred with histopathologic confirmed metastases of melanoma, 64 cases were diagnosed as non-invasive melanoma at the peripheral centers, 2 cases were reclassified as non–melanocytic tumor after review in the NCI (atypical fibroxanthoma and malignant peripheral nerve sheath tumor), 2 cases were referred from institutes outside the Netherlands, 15 reports contained more than two missing histopathologic parameters and 3 cases were considered as second opinion (Fig. S1).

This resulted in a study population of 296 patients (58% male). Baseline patient and tumor characteristics are shown in Table 1. The median age at time of revision was 63 years (IQR 49–74). The cutaneous melanomas were most frequently located on the scalp, in 81 patients (Fig. S2). The overall levels of agreement between NCI and non-NCI pathologists on each pathologic parameter are presented in Table 2 and separate levels of agreement over the period of 2 years (2007–2016) are illustrated in Fig. 1.

Melanoma subtype

Seventy-four reports (25%) had discordant diagnosis in subtype of melanoma. The majority of the discordances were seen in the melanoma NOS group classified by non-NCI pathologists (Table S1). Among the 296 cases diagnosed as invasive melanoma by non-NCI pathologists, 4 cases had clinical impact. Four reports represented an over-diagnosis; 3 melanomas were downgraded to melanoma in situ and 1 report was downgraded to superficial atypical melanocytic proliferation of uncertain significance (SAMPUS). The concordance of subtype melanoma between non-NCI and NCI pathologists was moderate ($\kappa = 0.648$) as shown in Table 2.

Breslow thickness

Of all cases, 49 (17%) showed discordance in BT after review (Table S2A). The T-categories were upgraded in 20 reports after review and were downgraded in 21 reports. In 23 reports (8%), this change of T-category had clinical consequence for planned excision margins when adopting the AJCC 7th edition. The concordance of BT measured in millimeter was perfect (ICC: 0.981, 95% confidence interval: 0,976-0.985). The concordance of BT, when stratified into groups according to the T-categories of the AJCC 7th edition, was substantial ($\kappa = 0.775$) when all cases were included (Table 2). The level of agreement of BT according to the T-categories did not change significantly when using the AJCC 8th edition instead of the 7th edition ($\kappa = 0.776$). The concordance of BT, when unreported cases were deleted, was perfect when using AJCC 7th and 8th edition, respectively ($\kappa = 0.808/\kappa = 0.806$). Again, in 23 patients (8%) there were clinical consequences due to adjusted surgical excision margins when adopting the AJCC 8th edition (Table S2B).

Table 1
Baseline characteristics.

Characteristics	N	%
Gender		
Female	123	41.6
Male	173	58.4
Age (years) at time of revision		
Median/IQR	63	49–74
Location melanoma		
Frontal	18	6.1
Cheek	77	25.9
Nose	18	6.1
Scalp	81	27.6
Ear	67	22.6
Eyebrow	2	0.7
Neck	33	11.1

IQR; interquartile range. Percentages may not sum up to 100 because of rounding.

Ulceration

In 23 cases (8%) a discordance was noticed regarding presence or absence of ulceration (Table S3). Ulceration was reported in 9 cases after review by the NCI pathologist, while not mentioned in the referral report. In 6 cases ulceration was reported at the referring hospitals, while these were considered as non-ulcerative melanomas after review by NCI. There was a substantial concordance between referred and NCI reports in the evaluation of ulceration. The kappa statistic was 0.802 when the cases in which ulceration was not reported were assumed as non-ulcerative (Table 2), and the kappa statistic was 0.843 when those cases were eliminated from the analysis and considered as perfect.

Dermal mitotic activity

Of all cases, 77 (26%) had discordance in the evaluation of DMA (Table S4). Forty-four cases with reported dermal mitotic figures were reclassified as having no DMA after NCI review. Twenty-seven cases of melanomas without reported dermal mitosis were reclassified as having DMA after NCI review. In some cases, DMA was not reported by the referral pathologist. The concordance between NCI and non-NCI reports in the evaluation of DMA was moderate when the cases in which DMA was not reported were classified as absence of dermal mitoses ($\kappa = 0.472$) (Table 2), and substantial ($\kappa = 0.710$) when those cases were eliminated.

Clinical consequences

After internal review, non-NCI pathologist and NCI pathologist showed overall discordance in 158 reports (53%) according to AJCC 7th edition. Thirty-eight reports (13%) had discrepancies in diagnosis that had impact on further treatment. Scheduling SLNB changed in 14 reports (5%) after review. In 10 patients the recommendation of SLNB has been rejected after NCI review (over-diagnosed) and vice versa in 4 patients (under-diagnosed) (Table 3A). The driving factors of changing SLNB recommendation are explained in Table 5.

Pathology review at NCI led to changes in the recommended surgical excision margins of the primary lesion in 29 patients (10%) (Table 4). Ten reports finally represented under-diagnosis and led to a wider excision margin from 1 cm to 2 cm. Thirteen reports represented over-diagnosis and led to a narrower excision margin. In 10 cases of these the excision margin changed from 2 cm to 1 cm and in three from 1 cm to 0.5 cm (melanoma in situ). In 6 patients one of the referral or NCI reports did not contain the essential parameter for defining recommendation for surgical margins.

Clinical consequences staged according to AJCC 8th edition

There was overall discordance of 40% according to AJCC 8th edition. Thirty-two reviews (11%) led to clinical consequences for treatment. Scheduling SLNB changed in 10 cases (3%) after review. For 6 patients the recommendation of SLNB has been rejected after NCI review (over-diagnosis) and vice versa in 4 (under-diagnosis) (Table 3B). The driving factors of changing SLNB recommendation are explained in Table 5. The discordances of surgical excision margins (10%) were identical between AJCC 7th and 8th edition.

Table 2
Agreement between non-NCI and NCI pathologist on pathologic features.

Pathologic feature	Statistical test	Valid cases	Agreement	Strength of agreement
Melanoma subtype	Kappa	296	0.648	Substantial
Breslow thickness	ICC	285	0.981	Perfect
	Kappa	296	0.775[b]/0.776[c]	Substantial
	Kappa	285[a]	0.808[b]/0.806[c]	Perfect
Ulceration	Kappa	296	0.802	Substantial
		258[a]	0.843	Perfect
Dermal mitotic activity	Kappa	296	0.472[b]	Moderate
		189[a]	0.710	Substantial

ICC, Intraclass Correlation Coefficient; NCI, Netherlands Cancer Institute.
[a] Cases deleted when not reported.
[b] TNM 7.
[c] TNM 8.

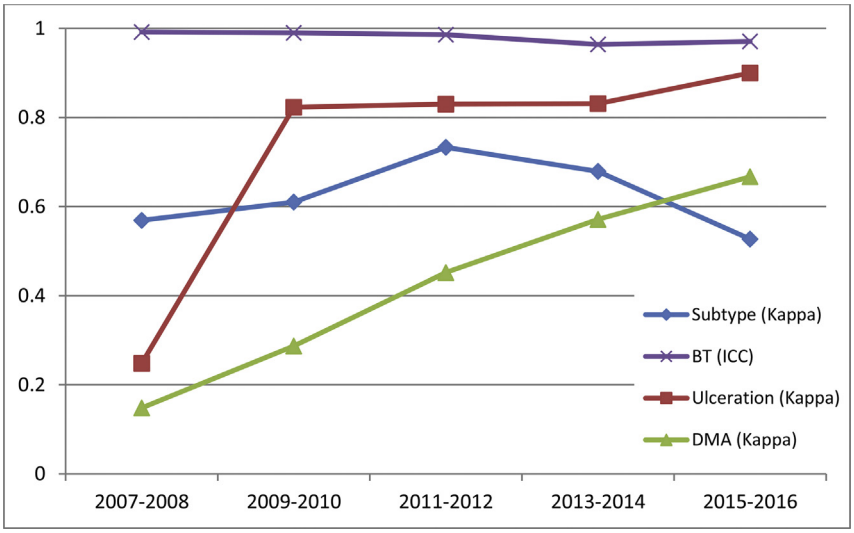

Fig. 1. Inter-observer agreement (ICC or kappa) for the period 2007–2016.

Discussion

The aim of this study was to analyze the inter-observer variation in histopathology reports of primary cutaneous head and neck melanoma between the melanoma pathologists at the NCI versus reports of non-NCI pathologists in the perspective of the renewed AJCC staging (8th edition). Treatment policies regarding width of excision and indication for SLNB are strongly determined by histopathologic parameters. Moreover, the histopathologic features also have impact on patients' inclusion in clinical trials.

In this study we excluded Clark's level of invasion. The Clark's level of invasion, previously used in defining stages pT1a and pT1b, was excluded in the AJCC 7th edition of TNM staging, since DMA and ulceration are stronger independent determinants of prognosis [5,23]. Moreover, Clark's level is less reproducible amongst pathologists and less accurate than BT [16].

Diagnosis

The discordances in melanoma subtype (25%) leads to clinical consequences in 4 over-diagnosed patients. This observed rate likely represents an underestimate of the actual rate, as benign

Table 3A
Number of cases with a change in SLNB recommendation after NCI review (TNM 7). Overall concordance 279/296 (94.3%).

	NCI			
	No SLNB	SLNB	Unknown	Total
Peripheral				
No SLNB	**34**	2	1	**37**
SLNB	10	**243**	2	**255**
Unknown	0	2	**2**	**4**
Total	**44**	**247**	**5**	**296**

NCI, Netherlands Cancer Institute.
Unknown: invasive melanoma cases where non-NCI or NCI pathology report did not contain the essential parameters for defining recommendations for SLNB.

Table 3B
Number of cases with a change in SLNB recommendation after NCI review (TNM 8). Overall concordance 284/296 (95.9%).

	NCI			
	No SLNB	SLNB	Unknown	Total
Peripheral				
No SLNB	**39**	2	0	**41**
SLNB	4	**243**	2	**249**
Unknown	0	4	**2**	**6**
Total	**43**	**249**	**4**	**296**

NCI, Netherlands Cancer Institute.
Unknown: invasive melanoma cases where non-NCI or NCI pathology report did not contain the essential parameters for defining recommendations for SLNB.

Table 4
Number of cases with a change in surgical margin recommendation after NCI review (TNM 7/TNM 8). Overall concordance 267/296 (90.2%).

	NCI				
	0.5 cm	1 cm	2 cm	Unknown	Total
Peripheral					
1 cm	3	**139**	10	1	**153**
2 cm	0	10	**125**	2	**137**
Unknown	0	1	2	**3**	**6**
Total	**3**	**150**	**137**	**6**	**296**

NCI, Netherlands Cancer Institute.
Unknown: invasive melanoma cases where non-NCI or NCI pathology report did not contain the essential parameters for defining recommendations for surgical margins.

Table 5
Driving factors of under- and over-diagnosis in changing SLNB recommendation. Under- and over-diagnosis are based on the referred reports and changed after NCI review.

	Subtype	BT	DMA	Ulceration	Total
TNM 7					
Under-diagnosis	NA[a]	–	3	1	**4**
Over-diagnosis	–	5	5	–	**10**
TNM 8					
Under-diagnosis	NA[a]	3	NA[b]	1	**4**
Over-diagnosis	1	5	-	-	**6**

NCI, Netherlands Cancer Institute; BT, Breslow thickness, DMA, Dermal mitotic activity; NA, not applicable.
[a] Not applicable: non-invasive melanoma were not included.
[b] Not applicable: DMA removed in TNM 8.

lesions and non-invasive melanoma are not routinely referred to the NCI and second opinions were excluded [13,14,24–29]. Throughout the years, the inter-observer agreement for melanoma subtypes increases from a moderate to substantial agreement in our series with a decline to moderate for the last two years (Fig. 1). External pathologists diagnose melanoma more frequently as melanoma NOS than NCI pathologists, who sub-stratify melanoma in different types of melanoma.

Breslow thickness

BT is the most important determinant for the prognosis of cutaneous melanoma, which has become the main allocator for the different T-categories (pT) [3,18,23]. The level of agreement of BT is perfect between non-NCI and NCI pathologists for both AJCC 7th and 8th edition in this study. According to many international studies, BT is the most reproducible parameter with perfect agreement for many years [11–13,15,16,18]. Fig. 1 shows a consistent perfect reproducibility of BT over the years 2005–2016.

Ulceration

The level of agreement of reporting ulceration is substantial. Ulceration is defined as full thickness absence of an intact epidermis with associated host reaction above the primary melanoma, i.e. fibrin deposition and neutrophils [30].

The assessment of ulceration is described as highly reproducible in the international literature, because it is perfectly recognizable by pathologists [15,16,18,31]. Both BT and ulceration are strong independent prognostic factors, which made these the sole criteria for determining T-classification in melanoma patients [23,32–34]. Interestingly, we could find an increased concordance in assessing ulceration since the implementation of ulceration in the AJCC 6th edition (2003) (Fig. 1). Difficulties in assessment of ulceration can occur when there is an apparent focal loss of the epidermis as a result of a prior biopsy procedure or a sectioning artifact [18].

Dermal mitotic activity

With the introduction of the 7th edition of AJCC, DMA replaced Clark's level to improve classification of high-risk thin melanoma patients (pT1b) [5]. In our study, the level of agreement of DMA is moderate, which is little lower than described in the international literature [18]. This could be explained by the fact that we maintained AJCC 7th edition for all included patients (even if diagnosed in 2005 when DMA was not included in AJCC 6th edition, which is a limitation of the study.). The level of agreement is substantial, when cases in which DMA was not reported were eliminated, which corresponds to international literature [18]. Throughout the years, DMA agreement among pathologists is increasing as shown in Fig. 1. Nevertheless, with the implementation of AJCC 8th edition, DMA is excluded as a T-classification criterion. It remains a major determinant of prognosis in thin melanomas, but was removed from the 8th edition of the AJCC staging system because sub-stratifying T1 using tumors using a 0.8 mm cut off point gives more prognostic information than when using DMA [6]. Moreover, with implementation of DMA more melanomas were classified as pT1b and therefore SLNB indication increased. It has been recently shown that this increase did not have any impact on survival in melanoma patients [7,30].

Clinical consequences

Our secondary aim was to determine the consequences of these inter-observer variations for the management and prognosis of melanoma patients. There was a 53% versus 40% discordance between pathologists according to AJCC 7th and 8th edition, respectively; the difference was mostly related to exclusion of DMA in AJCC 8th edition.

Using AJCC 7th edition, 13% of the discordances led to clinical consequences for treatment of melanoma patients versus 11% using AJCC 8th edition. Recommendations for surgical excision margins changed in 10% of the cases after NCI review. An earlier study by Niebling et al. showed that discordances in T-category caused 6% changes in recommended excision margin [35]. On the basis of their results, they recommend that pathology review should be considered for all patients being treated not in melanoma expert centers.

Along with the implementation of AJCC 7th edition, the indication for SLNB increased due to the increasing classification of tumors as pT1b [7]. In this study, based on the T1b criterion, the recommendation of SLNB has been rejected in 10 patients after NCI review and recommended in 4 cases. After the introduction of AJCC 8th edition rejections of SLNB recommendations decrease to 6 patients after NCI review. The number of SLNB recommendations remained 4. Although this is a slight difference between both AJCC editions, it is of great importance for the individual patient whether the patient is undergoing SLNB or not.

The results of MSLT-II showed that complementary lymph node dissection versus wait-and-see policy does not provide evidence of better survival in sentinel node positive patients, which means that SLNB has no treatment consequences [36]. SLNB is an invasive surgical staging procedure, and possible complications warrant for a restrictive policy to prevent overtreatment [37,38].

However, SLNB contains prognostic values for high-risk thin and thick melanoma which may be of great relevance for future adjuvant immunotherapies [36]. In our opinion, expert review remains

indicated when a SLNB is considered for additional staging in selected cases.

Our study includes only referred invasive melanoma, whereas non-invasive melanoma, which could possibly being upstaged to invasive melanoma by NCI pathologists, are not included. Including reports of non-invasive melanoma would lead to a selection bias, since non-invasive melanomas are also treated outside the NCI in non-specialized centers.

The study of Kuijpers et al. reported an overall inter-observer discordance rate vary from 2 to 28% [10]. This raises the question, is clinically relevant disagreement rate of 11% according the AJCC 8th edition acceptable? Our study indicates that 89% of cases were revised without subsequent clinical implications, which may raise questions on time-management and cost-effectiveness.

In our opinion, selecting only borderline-risk thin melanomas for review will improve the efficiency and cost-effectiveness of review. The study of Verver et al. showed that the introduction of AJCC 8th edition has improved stratification of thin melanomas into high- and low-risk groups [39]. The results of our study are in line with their findings, emphasizing the importance of maintenance of expert review of pathology reports, particularly in view of the new developments in the prognostic value of SLNB. Future study analysis of time-management and cost-effectiveness in review of referred pathology reports would be recommended.

Conclusion

Review of primary cutaneous head and neck melanoma by an NCI pathologist leads to significant changes in some patients. In 13% or 11% patients when adopting the AJCC 7th and 8th edition of TNM staging, respectively, these discordances result in a slight change of the recommended clinical management. Especially when a SLNB is considered, expert review of the primary melanoma can contribute to clinical decision making in the NCI.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.10.529.

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