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QUALITY ASSESSMENT BY EXPERT OPINION IN MELANOMA PATHOLOGY: EXPERIENCE OF THE PATHOLOGY PANEL OF THE DUTCH MELANOMA WORKING PARTY

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SUMMARY

Some cutaneous melanocytic lesions are notoriously difficult to diagnose by histopathology. For that reason, the Pathology Panel of the Dutch Melanoma Working Party was instituted and is regularly approached to provide an expert opinion on problem cases. In order to identify the most common diagnostic problems, 1069 consecutive referral cases of submitted lesions (1992 to 1994 inclusive) were analysed. About 60 per cent of the requests came from small laboratories, with up to three consultant pathologists. Two-thirds of the lesions reviewed concerned women and nearly 50 per cent of the patients were 30 years of age or younger. In 8 per cent of the cases, the referring pathologists felt unable to make a confident diagnosis; in 14 per cent, melanoma was suspected; and in 12 per cent, a differential diagnosis only had been formulated. The panel felt able to provide an unequivocal diagnosis in 93 per cent of the requests. Of the 158 lesions classified as 'invasive melanoma' by the referring pathologists, 22 were considered to be benign by the panel. Conversely, 108 invasive melanomas (panel diagnosis) had originally been considered as benign lesions, dysplastic naevi or melanoma *in situ*. These high numbers of discordancies reflect the intrinsic difficulty of the differential diagnoses in this selected material submitted to the panel. Diagnostic difficulties were most often encountered with Spitz naevi and dysplastic naevi. Although the rate of overdiagnosis and underdiagnosis is quite high, in the majority of cases the diagnosis of the referring pathologist matched the diagnosis of the panel. This may reflect a proper awareness of difficult melanocytic lesions in pathology practice. The activities of the Pathology Panel of the Dutch Melanoma Working Party contribute to the improvement of the quality of diagnosis in cutaneous melanocytic lesions, as they increase the number of unequivocal diagnoses and reduce the number of incorrect diagnoses. On the basis of the systematic comparison of the diagnosis by the referring pathologist and the panel, postgraduate teaching and quality control can be more focused on specific diagnostic problems. © 1997 by John Wiley & Sons, Ltd.

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KEY WORDS—melanoma; histopathology; diagnosis; quality; naevus; naevus, epithelioid and spindle cell; dysplastic naevus; Spitz naevus

INTRODUCTION

Quality assurance is of great importance in the diagnosis and treatment of cancer patients. This is underscored by the current policy of various international organizations which stimulate quality control projects in different aspects of the management of cancer patients. As an example, in the field of cutaneous melanoma, quality control within the framework of the EORTC (European Organization for Research and Treatment of Cancer) melanoma cooperative group is executed in the context of clinical trials, i.e., by means of site visits by an expert surgeon to centres which have patients entered treated with isolated perfusion therapy.¹ With regard to

the histological diagnosis and micro-staging of lesions from patients entered in such studies and others, quality assurance is pursued by the reviewing of the slides by expert pathologists.

High quality standards within the framework of international collaboration are not possible without a continuous effort to maintain and improve the care of melanoma patients at the national and regional level. Thus, melanoma working parties are now active in several countries, including The Netherlands. The Dutch Melanoma Working Party was founded in 1986. It consists of a multi-disciplinary forum of the various specialties involved in melanoma management, aiming at improving the prevention, early diagnosis, and treatment of melanoma. Three consensus texts on melanoma were prepared by the group under the guidance of the National Organization for Quality Assurance in Hospitals.² Members of the working party also act as consultants for colleagues with less experience in

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Table I—Categorization of separate diagnoses into diagnostic categories

Separate diagnosis	Category
No diagnosis	No diagnosis
Common acquired naevus (CAN)	Common acquired naevus (CAN)
Spitz naevus	Spitz naevus
Congenital naevus	Other special type of naevus
Pigmented spindle cell naevus	Other special type of naevus
Blue naevus	Other special type of naevus
Combined naevus	Other special type of naevus
Dysplastic naevus	Dysplastic naevus
Lentigo maligna	Melanoma <i>in situ</i>
Melanoma <i>in situ</i>	Melanoma <i>in situ</i>
Melanoma <i>in situ</i> with dysplastic naevus	Melanoma <i>in situ</i>
Suspicion of malignant melanoma	Suspected melanoma
Superficial spreading melanoma	Invasive melanoma
Nodular melanoma	Invasive melanoma
Lentigo maligna melanoma	Invasive melanoma
Acral lentiginous melanoma	Invasive melanoma
Melanoma unclassified	Invasive melanoma
Melanoma in congenital naevus	Invasive melanoma
Melanoma in pre-existing naevus	Invasive melanoma
Melanoma metastasis	Invasive melanoma
Differential diagnosis	Differential diagnosis
Other diagnosis	Other

melanoma diagnosis. In addition, the working party provides continuous education in melanoma pathology. In order to make such efforts as effective as possible, insight is required into the problems encountered by pathologists. This is of importance since it provides subjects for targeted training.

About 300 cases are sent annually to the Pathology Panel of the Dutch Melanoma Working Party for expert opinion. The purpose of this article is to report on a consecutive series of 1069 such cases, with emphasis on the specific diagnostic problems and major discrepancies between the diagnoses of referring pathologists and panel pathologists. Recommendations are made with respect to targeted quality control and continuous education.

PATIENTS, MATERIALS, AND METHODS

Working methods of the Pathology Panel and materials

The Pathology Panel of the Dutch Melanoma Working Party consists of three pathologists (WJM, DJR, and ES). It operates on a consultative basis: pathologists who have difficulties in making an unequivocal diagnosis of a lesion may send representative slides and/or paraffin blocks of the lesion along with a tentative diagnosis to a member of the panel. The referring pathologist receives a written report from the panel member within 1 week. Where doubt remains, the panel member may send the slides to other panel members. The cases are discussed among the panel members at regular bi-monthly meetings. Very occasionally, this panel discussion leads to a

clinically relevant change in the original panel diagnosis, which is then promptly communicated in an additional report.

Requests are received from pathologists throughout The Netherlands and occasionally from abroad. Each consultation is recorded in the national computerized system for pathological diagnoses (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief, PALGA) which facilitates retrieval of follow-up data. From each consultation, data are collected by registering items through a standard list: gender, date of birth, site of the lesion, name of the hospital/department of the referring colleague, name of the pathologist consulted, diagnosis of the referring pathologist, available material, and panel diagnosis. The panel members use information mentioned in the report and the accompanying letter from the referring pathologist to complete this list.

The diagnoses of the referring pathologists and the panel pathologist(s) are registered as standard entities listed in Table I. For this study, these entities were grouped into the following categories: no diagnosis, common acquired naevus (CAN), Spitz naevus, other special type of naevus, dysplastic naevus, melanoma *in situ*, suspected melanoma, invasive melanoma, and others. The category 'differential diagnosis' was also included.

Methods used for evaluation of the data

Comparison of the referring pathologists' and the panel's diagnoses was made in terms of overdiagnosis and underdiagnosis.

Table II—Age and gender of the patients

	All lesions		Panel diagnosis 'invasive melanoma'	
	♂	♀	♂	♀
	389 (37%)	658 (63%)	120 (34%)	237 (66%)
Age (years)				
0–15	74 (19%)	56 (9%)	7 (6%)	5 (2%)
16–30	101 (26%)	215 (33%)	20 (17%)	49 (21%)
31–45	95 (25%)	201 (31%)	38 (32%)	78 (33%)
46–60	62 (16%)	107 (16%)	28 (24%)	58 (24%)
61–75	36 (9%)	59 (9%)	14 (12%)	37 (16%)
75+	18 (5%)	14 (2%)	12 (10%)	10 (4%)
Unknown	3	6	1	—
Gender unknown	22		7	

Overdiagnosis was defined from the perspective of clinical relevance, including therapeutic consequences. The following situations were regarded as overdiagnosis: the diagnostic category of the referring pathologist was 'suspected melanoma' or 'invasive melanoma', while the diagnostic category of the panel was 'common acquired naevus', 'Spitz naevus', 'special type of naevus', 'dysplastic naevus' or 'melanoma *in situ*'.

Underdiagnosis was defined as the situation in which lesions were classified as 'common acquired naevus', 'Spitz naevus', 'special type of naevus', 'dysplastic naevus' or 'melanoma *in situ*' by the referring pathologist and as 'suspected melanoma' or 'invasive melanoma' by the panel.

RESULTS

The Pathology Panel examined a total number of 1069 cases over a 3 year period: 333 in 1992, 359 in 1993, and 377 in 1994.

Referring pathologist

The requests came from pathologists working in hospitals or institutes throughout The Netherlands and from some pathologists abroad (8 cases in 1992, 24 cases in 1993, and 24 cases in 1994). The number of requests per institute varied from 1 to 35 per year. Four institutes sent 15 or more cases per year. The institutes were grouped according to the number of pathologists into the following categories: small institutes (1–3 pathologists); intermediate (4–6 pathologists); large (>6 pathologists); and unknown. Thirty-five small institutes over the 3 year period submitted 614 cases (median: 30; range: 1–88), 14 'intermediate' institutes sent in 194 cases (median: 13; range: 2–33) and ten large institutes

sent in 179 cases (median: 12.5; range: 2–61). Thus, small institutes with fewer pathologists sent in more cases.

Age and gender of the patients

In Table II the distribution of gender and age of all submitted cases and of the cases with a panel diagnosis of 'invasive melanoma' are presented. About two-thirds of all submitted cases concerned women and nearly half of the patients were 30 years of age or younger. The younger the age, especially in children, the more lesions that were submitted, but few invasive melanomas were identified by the panel in childhood cases (Table II). Nevertheless, the percentage of invasive melanomas in young individuals among the invasive melanomas diagnosed by the panel was high, when compared with the age distribution in the general population. In the panel's series, about 25 per cent of invasive melanomas were from patients 30 years or younger, while in the Dutch cancer registry only about 10 per cent of invasive melanoma patients are under the age of 30.³ This reflects the particular difficulties encountered by pathologists in diagnosing lesions in younger patients, as well, perhaps, as a reluctance to diagnose invasive melanoma in a young patient without seeking a second opinion. Of the submitted cases in male patients younger than 16 years of age, 9 per cent (7 of 74) were diagnosed as invasive melanoma, whereas the corresponding figure was 67 per cent (12 of 18) in patients over 75 years of age (Table II).

With regard to gender, the panel diagnosed more cases of invasive melanoma in females than in males, compared with the general population: 34 per cent males and 66 per cent females diagnosed by the panel against 41 per cent and 59 per cent respectively, in the general population.³ This may be due to the overall surplus of lesions from females submitted for consultation.

Table III—Diagnosis of the referring pathologist versus diagnosis of the Pathology Panel

Diagnosis of referring pathologist	Pathology Panel										
	No diagn. ¹	CAN ²	Spitz naevus	Special naevus ³	Dyspl. naevus ⁴	Mel. i.s. ⁵	Suspected	Invasive mel. ⁶	Diff. ⁷	Other	Total
No diagnosis	1	8	21	12	12	3	6	21	2	4	90
Comm. acq. naevus ⁸	0	48	5	12	3	2	1	11	1	1	84
Spitz naevus	0	2	109	11	2	0	8	17	5	3	157
Special naevus ³	1	1	3	39	0	1	3	4	2	0	54
Dysplastic naevus	1	24	16	20	56	13	9	35	2	0	176
Melanoma <i>in situ</i>	1	1	1	1	5	16	2	18	1	0	46
Suspected melanoma	2	11	25	8	8	3	16	71	4	3	151
Invasive melanoma	0	3	10	4	2	3	2	133	1	0	158
Diff. diagnosis ⁹	1	5	34	15	11	4	3	51	5	2	131
Other	0	0	1	4	0	0	0	3	0	14	22
Total	7	103	225	126	99	45	50	364	23	27	1069

The bold numbers represent those cases for which the diagnostic category of the referring pathologist matched that of the panel.

¹ No diagn.: no diagnosis.

² CAN: common acquired naevus.

³ Special naevus: other special type of naevus.

⁴ Dyspl. naevus: dysplastic naevus.

⁵ Mel. i.s.: melanoma *in situ*.

⁶ Invasive mel.: invasive melanoma.

⁷ Diff.: differential diagnosis.

⁸ Comm. acq. naevus: common acquired naevus.

⁹ Diff. diagnosis: differential diagnosis.

Site of the lesion

The site of the lesion was recorded in 692 cases. The most common sites, in decreasing order of frequency, were legs 34 per cent (234); trunk 33 per cent (226); head/neck region 17 per cent (115); arms 12 per cent (85); and other sites 5 per cent (32). Other sites included conjunctiva (11), external genitals (10), juxtacutaneous mucosa (5), hip (1), abdominal cavity (3), lumbar spinal column (1), and lymph node (1).

Of the 364 lesions diagnosed by the panel as invasive melanoma, the sites were trunk 35 per cent (83); legs 32 per cent (76); head/neck region 19 per cent (44); arms 10 per cent (24); and other localizations 3 per cent (8). The site was unknown in 129 cases.

The body distribution of the invasive melanomas diagnosed by the panel was compared with the lesions coded in 1993 as invasive melanoma in the national computerized system PALGA. The distribution of the sites of the lesions in PALGA was legs 43 per cent (98); trunk 30 per cent (67); head/neck region 13 per cent (30); and arms 14 per cent (32). Compared with the distribution seen in the general invasive melanoma population, the panel invasive melanoma cases were somewhat less often localized on the legs and more often in the head/neck region. This may reflect a tendency to seek confirmation of the diagnosis of invasive melanoma preferentially in the head/neck region, since its impact in terms of surgical treatment and cosmetic consequences is greater than at other sites.

Diagnosis

Table III presents the diagnoses of the referring pathologist versus the diagnoses of the panel, after categorization. Relatively many of the lesions referred were diagnosed by the panel as Spitz naevus or other special types of naevus. The referring pathologists submitted many lesions with suspicion of malignancy, but few lesions with a diagnosis of 'melanoma *in situ*'.

From the total number of lesions categorized as 'other' by the referring pathologist or the panel (22+27), a substantial number were classified as non-melanocytic soft tissue tumour (20), melanocytic lesion of the conjunctiva (8), or melanocytic tumour not specified in the other mentioned categories (8). A final group of 13 lesions consisted of various other diagnoses, such as 'scar' and 'dermatitis'.

The total number of lesions in which the panel felt unable to arrive at a diagnosis was 7; five lesions were represented by a punch biopsy and two others had been mechanically damaged.

In 23 cases in which the panel had not reached an unequivocal diagnosis, the following differential diagnoses were given: Spitz naevus versus invasive melanoma (7); (dysplastic) naevus versus invasive melanoma (6); other special type of naevus versus invasive melanoma (5); melanoma *in situ* versus invasive melanoma (1). In four instances, other differential diagnoses were reported.

Table IV—Summary of the diagnostic category of the referring pathologist versus the diagnostic category of the panel

Referring pathologist	Panel					Total
	No diagnosis	Benign ¹ /DN ² /MIS ³	Differential diagnosis	Suspected	Invasive melanoma	
No diagnosis	1	56	2	6	21	86
Benign ¹ /DN ² /MIS ³	3	391	11	23	85	513
Differential diagnosis	1	69	5	3	51	129
Suspected melanoma	2	55	4	16	71	148
Invasive melanoma	0	22	1	2	133	158
Total	7	593	23	50	361	1034

The bold numbers represent those cases for which the diagnostic category of the referring pathologist matched that of the panel.

¹Lesions included: common acquired naevus, Spitz naevus, other special type of naevus.

²DN: dysplastic naevus.

³MIS: melanoma *in situ*.

Lesions classified as 'other' were excluded in this table.

Of the 90 lesions without a referring pathologist's diagnosis the panel made an unequivocal diagnosis in 81 cases, including 21 of invasive melanoma. Of the 131 lesions with a differential diagnosis by the referring pathologist, the panel had an unequivocal diagnosis in 122 cases, including 51 of invasive melanoma. Of the 151 lesions with the referring diagnosis 'suspected melanoma', the panel made an unequivocal diagnosis in 129 cases, including 71 of invasive melanoma.

Overdiagnosis and underdiagnosis were defined and calculated from a perspective of clinical relevance, including therapeutic consequences (see the Materials and Methods section).

Overdiagnosis

Of the 151 lesions classified by the referring pathologist as suspected melanoma, (Table III), 55 lesions were overdiagnosed. Here it was taken into account that lesions classified in a pathology report as 'suspected melanoma' will probably be regarded and treated by clinicians as if they were invasive melanoma. The panel classified 11 cases as common acquired naevus, 25 as Spitz naevus, 8 as other special type of naevus, 8 as dysplastic naevus, and 3 as melanoma *in situ*. Of the 158 lesions classified by the referring pathologist as invasive melanoma, 22 lesions were overdiagnosed. The panel classified 3 cases as common acquired naevus, 10 as Spitz naevus, 4 as other special type of naevus, 2 as dysplastic naevus, and 3 as melanoma *in situ*.

Underdiagnosis

Of the 84 lesions classified by the referring pathologist as common acquired naevus (Table III), 12 were classified by the panel as 'suspected melanoma' or invasive melanoma. The numbers of the other underdiagnosed lesions were Spitz naevus, 25 of 157; other special type of naevus, 7 of 54; dysplastic naevus, 44 of 176; and melanoma *in situ*, 20 of 46.

Table IV presents a summary of the diagnostic categories of referring pathologists versus panel pathologist(s) with the further grouping of diagnoses based on clinical relevance.

DISCUSSION

Although the large majority of melanocytic tumours of the skin do not present significant diagnostic problems, a small minority of lesions are very difficult to diagnose.⁴⁻⁶ An expert pathological diagnosis of such cases may be of great clinical importance. In the present study, in 8 per cent (90) of the lesions submitted, the referring pathologists could not provide a confident diagnosis; in 14 per cent (151) there was suspicion of melanoma, while in a further 12 per cent (131) only a differential diagnosis had been formulated. In these 372 lesions, the panel was able to make an unequivocal diagnosis in 332 cases. It classified 7 per cent (25) as suspected melanoma and 38 per cent (143) as invasive melanoma.

It is unclear how many cases of overdiagnosed invasive melanoma really occur in practice. In the present study, overdiagnosis as 'suspected melanoma' was recorded in 55 of 151 cases and as 'invasive melanoma' in 22 of 158 cases. In the case of a diagnosis of 'suspected melanoma', a second opinion is always likely to be requested, as no certainty is given. In contrast, an incorrect but unequivocal diagnosis of invasive melanoma will not usually be submitted for pathology review, generally leading to overtreatment of the patient. Nevertheless, although an unequivocal diagnosis of invasive melanoma was reported by the referring pathologist in 22 cases, there must have been some element of doubt with regard to the diagnosis, since otherwise, the case would not have been submitted for consultation.

Although the number of discordant diagnoses is quite high, the majority of diagnoses of the referring pathologists matched those of the panel. This might indicate a

proper awareness of difficult cases in practice. The only approach to come up with hard data, however, is a systematic comparison of all diagnoses. In a documentation study of melanomas in one regional Dutch comprehensive cancer centre (Integraal Kankercentrum Oost), all invasive melanomas and melanomas *in situ* are reviewed by a member of the panel (DJR). Of the first 152 lesions, only one case diagnosed as lentigo maligna was classified by the panel member as common acquired naevus and three cases reported as melanoma *in situ* were diagnosed by the panel member as superficial spreading melanoma. These numbers are quite reassuring, regarding the quality of the diagnosis. At the national level, the use of the Dutch PALGA system makes it possible to review, at a later stage, cases of 'thick' invasive melanomas which had not metastasized.⁷ Since most of the metastatic lesions will be verified histologically, a proportion of those thick invasive melanomas without documented metastases may be overdiagnosed naevi. These approaches may become a part of an integrated quality control programme in the future.

Underdiagnosis of invasive melanoma as a benign lesion was noted in this study in 13–25 per cent of the cases: 12 of 84 common acquired naevus; 25 of 157 Spitz naevus; 7 of 54 other special type of naevus; 44 of 176 dysplastic naevus; and 20 of 46 melanoma *in situ*. Again, although these figures on discordant cases are quite high, the majority of the cases were concordant. This probably reflects a low threshold to submit cases to the panel and a proper identification of the group of difficult lesions.

A major problem in estimating the true number of underdiagnosed melanocytic lesions in general practice is the fact that most thin misdiagnosed invasive melanomas will not metastasize and will remain undetected as misclassified lesions. In a recent search for underdiagnosed cases covering about 10 years in The Netherlands, using the PALGA system, only a few cases of truly proven invasive melanoma 'misdiagnosed' as Spitz naevus were uncovered.⁸ However, it remains unclear how many cases may have been given another key diagnosis in the computerized system, after a case being recognized as a 'misdiagnosis', e.g., after metastasis.

Many lesions were diagnosed by the panel as Spitz naevus or as another special type of naevus. In addition, of the 23 lesions with a differential diagnosis given by the panel, seven lesions concerned the diagnosis Spitz naevus versus invasive melanoma, six lesions the diagnosis (dysplastic) naevus versus invasive melanoma, and five lesions the diagnosis other special type of naevus versus invasive melanoma. Obviously, both referring pathologists and panel pathologists have difficulties in diagnosing such lesions.^{4–6,9,10} In terms of improving the general level of accuracy in melanoma diagnosis, it would appear to be most effective to concentrate postgraduate education on the specific problems concerning dysplastic naevus and Spitz naevus. A teaching slide set composed of difficult cases could be circulated among laboratories and discussed with an expert. During such discussions, the technical quality of histological slides could also be addressed. At a later stage, test slide sets could be

circulated in order to evaluate the diagnostic skill of the participating pathologists. Also, quality monitoring may focus on the problems mentioned. Local laboratories, in consultation with more experienced colleagues in difficult cases, can select representative lesions (i.e., not classical, but without a reason for consultation) for a second opinion (intra- or inter-institutional).

The procedure of consultation by individual panel members only is a result of the relatively large number of cases submitted and the need for a rapid response. A prompt response is greatly appreciated by both the referring pathologist and the clinician. For this reason, an independent opinion by all panel members on all cases is not feasible. As a compromise, only selected cases, which are considered difficult by the reviewing panel member, are sent to the other members for further evaluation. In addition, the regular panel meetings prove very useful in fine-tuning the histopathological criteria and their interpretation. In almost every case a consensus could be reached, although this does not always mean an unequivocal diagnosis. In fact, the panel, for mainly technical reasons, was not able to make a diagnosis in seven cases and could make only a differential diagnosis in 23 cases and a diagnosis of 'suspected melanoma' in 50 cases. Here, molecular techniques may provide relevant additional diagnostic information.

In this article, the diagnosis of the panel is assumed to be the correct diagnosis. We realize that the panel too is susceptible to misinterpretation or observer bias. However, based on the specific experience acquired in this particular field of pathology, the panel is more likely to change wrong diagnoses into correct ones than the other way around. Cases diagnosed as melanoma *in situ* or invasive melanoma are monitored through the cancer registry, which will enable clinical validation of the panel diagnosis. In addition, cases diagnosed as benign with a later presentation of melanoma metastasis can be traced systematically through the pathology databank PALGA.

So far, there has been no opportunity to perform an inter-observer study among all panel members on submitted, or otherwise selected, difficult cases. However, in a recent extended inter-observer study on melanocytic lesions among ten (dermato)pathologists in the melanocytic field in Europe, the best overall inter-observer agreement was between two members of the panel who participated in that study.¹¹ Furthermore, in an earlier independent review of a set of 104 melanocytic lesions (not especially difficult cases), the pair-wise inter-observer agreement among the three panel members was good (agreement >95 per cent and kappa >0.80, unpublished results, PEJ dW) compared with other studies. Even so, an inter-observer study on the lesions received for consultation as described here needs to be performed, as this is a specific subgroup of cases. The lesions are difficult to diagnose, more often located in the head and neck region, and the patients tend to be younger. Such a study may yield more specific information on the problems encountered in this area of pathology.

In this article, the diagnoses of referring pathologists and the Pathology Panel of the Dutch Melanoma

Working Party were compared. The rates of overdiagnosis and underdiagnosis (together with incorrect treatment) are shown to be quite high. There is no reason to believe that such rates of diagnostic problems exist only in The Netherlands. Difficulties in diagnosing melanocytic lesions are well known in the international literature,^{4-6,9,10} but they are described in a more qualitative manner. In the 3 years analysed, the panel received some requests from pathologists abroad, amongst which misdiagnoses were also found.

In summary, our data indicate that a second opinion given by pathologists experienced in the diagnosis of cutaneous melanocytic lesions is useful for diagnostic quality assurance. Uncertainty in the assessment of diagnoses and over- or under-diagnosis are serious problems that deserve to receive continuous attention. The quality of melanoma pathology can be improved by expert review and by continuing education targeted at the specific problems signalled.

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