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The History and Future of Melanoma Staging

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The evolution and progressive refinement of an internationally accepted melanoma staging system over the last 50 years has resulted in much greater accuracy and increased utility, but the staging process has become more complex and less intuitive. This raises the question of whether melanoma staging should continue to develop with ever-increasing levels of complexity, or whether attempts should be made to produce an alternative system that is simpler and more intuitive. The current, TNM-based American Joint Committee on Cancer (AJCC) staging system for melanoma incorporates only some of the prognostic factors of proven significance. However, the information that is now available about these and other, well-documented prognostic factors allows accurate prediction of an individual melanoma patient's prognosis using a computer-generated estimate. Thus an alternative staging strategy that could be considered in the future would be to use such an estimate to obtain a numerical score for each patient, based on all available information agreed to be of prognostic relevance. A stage grouping could then be assigned on the basis of that score, according to previously determined score ranges for each stage and substage. The advantages of such a system would be that it would allow more reliable comparison of treatment results within and between institutions, and would provide more equivalent stratification groups for patients entering clinical trials of new therapies and those entering adjuvant therapy trials. A further advantage would be that because there would be a direct link between staging and prognostic estimate, such a system would be more readily able to be understood in an intuitive fashion.
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KEY WORDS: melanoma; staging; prognosis; prognostic factors

INTRODUCTION

To understand what may lie ahead, it is always useful and important to consider the past. This is certainly the case when considering melanoma staging, which until recently has provided only a very broad guide to prognosis and has therefore been of limited practical value. It goes without saying that any staging system should reflect prognosis with the greatest possible accuracy, if it is to be of use for clinical and research purposes. The situation is well demonstrated by a consideration of melanoma patients with metastatic involvement of regional lymph nodes. Over a period of many years, such patients were given a prognosis and entered into clinical trials of adjuvant therapy without further sub-staging. However, in an important study initiated and co-ordinated by Dr. Charles Balch on behalf of the Melanoma Staging Committee of the American Joint Committee on Cancer (AJCC), it was clearly demonstrated that within the group of patients with metastatic disease in regional lymph

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nodes, there was a huge variation in prognosis [1]. By analysis of a large, pooled data set of 17,600 patients from 13 melanoma treatment centers around the world, it was found that for a patient with microscopic (not clinically detectable) involvement of a single regional lymph node and with a non-ulcerated primary melanoma, the 5-year survival rate was 69%. On the other hand, for a patient with macroscopic (clinically detectable) involvement of more than three regional lymph nodes and an ulcerated primary tumor (pT), the 5-year survival figure was 13%. In most clinical trials of adjuvant therapies undertaken in the 1970s, the 1980s, and even the early 1990s, patients were entered and stratified simply on the basis of their positive regional lymph node status, with no regard for whether this involvement was microscopic or macroscopic, or whether their pT had been ulcerated or not. It is therefore not surprising that inconclusive results were obtained in these trials, since the mix of patients with an inherently good prognosis and those with an inherently bad prognosis was not considered, and undoubtedly varied both within individual trials and from trial to trial.

Recent advances in our understanding of prognostic factors for melanoma patients, based not only on pathologic features of the pT but also on the location and extent of metastatic disease in regional lymph nodes and at distant sites, have allowed more reliable predictions of outcome to be made, and more useful staging to be achieved. Undoubtedly the most important advance in melanoma staging accuracy over the past decade has resulted from introduction of the sentinel node (SN) biopsy procedure. By detailed histologic examination of a SN (the node most likely to contain micrometastatic melanoma), a highly reliable assessment of regional node status can be achieved. This in turn allows an accurate estimate of prognosis to be made. Indeed, SN status has been shown to be the most powerful prognostic feature of all the features considered to date [2]. A recent review of early experience with the SN biopsy procedure at the Sydney Melanoma Unit (SMU), revealed that, with a median follow-up of 42 months, the actuarial melanoma-specific survival at 5 years was 90% for 836 SN-negative patients compared to 56% for 145 node positive patients (unpublished data). This was despite the fact that complete regional node dissection was routinely performed within 4–6 weeks of the SN biopsy procedure in those found to be SN-positive. The future promises even more accurate and reliable staging, as more precise methods of identifying low-volume metastatic disease in SNs such as reverse transcriptase-polymerase chain reaction (RT-PCR) analysis and magnetic resonance spectroscopy (MRS) are introduced [3], and reliable serum markers of metastatic potential are identified.

HISTORICAL ASPECTS OF MELANOMA STAGING

Earliest Attempts at Melanoma Staging (Pre–1962)

It is important to recognize that the staging systems existing at any particular time were based on variables then known to affect prognosis. Thus the gradual evolution of progressively more sophisticated staging systems has become possible only as new knowledge of prognostic factors has been gained.

Allen and Spitz [4], in their classic paper published in 1953, were the first to report that deeper melanomas had a worse prognosis than more superficial melanomas. However, they did not propose a formal staging system based on this observation.

One of the first attempts to classify melanoma patients according to the severity of their disease was that of Ackerman and Del Regato in 1954 [5]. They proposed four subgroups: (a) patients with distant metastases, (b) patients with regional lymph node metastases clinically detected and histologically proven, (c) patients with clinically negative but histologically positive regional lymph nodes, and (d) patients with primary disease only, as demonstrated by the clinical and histologic absence of disease either in regional lymph nodes or at distant sites. They established, by use of crude death rates, a clear survival advantage for subgroup (d) over subgroup (a), whilst not demonstrating a particular advantage for subgroup (c) over subgroup (b).

Evolution and Refinement of Melanoma Staging (1962–1992)

The earliest attempts at staging made no attempt to develop a microstaging system based on the features of their primary melanomas for the majority of patients with disease localized to the pT site. This did not occur until 1962, when Petersen et al. [6] suggested a three-stage system based on survival differences in patients with the following primary melanoma histology: Stage I—no dermal invasion, Stage II—invasion of the superficial dermis, and Stage III—tumor formation with or without a ‘‘pigmented flare.’’

By 1964, clear differences in survival had been demonstrated in three groups of patients on the basis of clinical assessment—those with primary disease only, those with regional lymph node metastases, and those with distant disease. Recognition of these categories led to the establishment of a three-stage system by McNeer and Das Gupta [7] from the Memorial Sloan-Kettering Cancer Center. The logical, intuitive nature, and elegant simplicity of this three-stage system made it popular and it is still utilized by some researchers (Table I). It was the

TABLE I. The McNeer and Das Gupta Three Stage System

Stage	Criteria
I	Localized melanoma without metastases to distant or regional lymph nodes
	Primary melanoma untreated or removed by excisional biopsy within 1 month
	Locally metastatic and/or recurrent melanoma
	Multiple primary melanomas
II	Metastases confined to regional lymph nodes
	Primary melanoma present with simultaneous metastases
	Primary melanoma controlled with subsequent metastases
	Locally recurrent melanoma with metastases
	Unknown primary with metastases
III	Disseminated melanoma
	Organic and/or multiple lymphatic metastases and/or
	Multiple cutaneous and/or subcutaneous metastases

TABLE II. The Four Stage MD Anderson Staging System

Stage	Criteria
I	Localized primary melanoma only
II	Local recurrence or satellites (defined as within 3 cm from the primary lesion)
III	Regional disease
	In-transit metastases
	Nodal metastases
	In-transit plus nodal metastases
IV	Distant metastases
	Cutaneous only
	Any visceral site

forerunner of modern tumor-node-metastasis (TNM) staging for melanoma.

In 1965, Mehnert and Heard, building on the work of Petersen et al., proposed another staging system based on primary lesion pathology [8]. Their four prognostic groups, also based on survival differences, were determined by level of invasion, as follows: 0—in situ, I—invading the papillary dermis, II—invading the reticular dermis superficial to the base of the deepest sweat gland, and III—invading the subcutis.

Bodenham, in an appraisal of his own clinical experience up to 1968, came to the conclusion that some melanomas were ''good melanomas,'' i.e. flat ones, and that some melanomas were ''bad melanomas,'' i.e. those that were elevated, non-pigmented, or with satellites [9]. He did not attempt to stage his patients according to these criteria.

In 1969, Clark et al. refined the earlier work of Petersen et al. and Mehnert and Heard by identifying five prognostic categories known now as Clark levels of invasion [10]. The prognostic importance of these categories was corroborated by McGovern in 1970 [11]. Then, also in 1970, Breslow demonstrated that tumor thickness was an important prognostic variable [12]. This factor was later established in 1978 to be prognostically more powerful than Clark level of invasion both by Breslow himself [13] and by Balch et al. [14], and tumor thickness was therefore incorporated into subsequent staging systems.

Less popular than the three-stage system of McNeer and Das Gupta was the four-stage system devised at the MD Anderson Hospital [15] in 1976 to address the substaging of patients with local, in transit, or satellite recurrences who were suitable for isolated limb perfusion, a procedure commonly employed at the MD Anderson Hospital at that time. This MD Anderson staging system had essentially the same shortcomings as the three-stage system. It was primarily clinical and failed to address the prognostic importance of tumor thickness and Clark level for the majority of patients with localized melanoma (Table II).

In 1978, the AJCC [16] and the Union Internationale Contre le Cancer (UICC) [17] incorporated primary melanoma microstaging into their staging systems. They used both Clark level of invasion and tumor thickness in an effort to stage melanoma patients more accurately, but these stages still consigned too many patients to Stage I to make it a useful system. Furthermore, this system was not well accepted because the division between Stages I and II was excessively simplistic and the Stage III category in both the AJCC and UICC systems was poorly defined (Tables III and IV).

In 1983, the Melanoma Subcommittee of the AJCC recommended a modification of its original four-stage 1978 version in order to better discriminate risk both in patients with early melanomas and in those with regional lymph node disease [18]. Patients with localized disease, previously subdivided into two groups (IA and IB) were now subdivided into four subgroups (IA, IB, IIA, and IIB) on the basis of tumor thickness and level of invasion and, for the first time, definitions were inserted for patients with Stage III disease. This staging system, although more comprehensive than the 1978 version, was more complex and many continued to use the more popular three-stage system (Table V).

TABLE III. The 1978 AJCC Staging System

Stage	Criteria
IA	Tumor invading the papillary dermis but not the reticular dermis (levels II and III) and $\leq$1.5 mm thick
IB	Tumor invading the reticular dermis or subcutaneous tissues (levels IV and V) and $>$1.5 mm thick
II	Regional lymph node spread (first station only and non massive or fixed), satellites within 2 cm of the primary melanoma, or in transit metastases
III	Massive or fixed metastatic regional lymph nodes or contralateral, bilateral, primary or secondary echelon nodal involvement
IV	Distant metastases

TABLE IV. The 1978 UICC Staging System

Stage	Criteria
IA	Tumor invading papillary dermis but not reticular dermis (levels II and III) and ≤1.5 mm thick
IB	Tumor invading reticular dermis or subcutaneous tissues (levels IV and V) ≥1.51 mm thick
II	Regional lymph node spread
III	Juxtaregional lymph node spread
IV	Distant metastases

TABLE VI. The 1988 AJCC/UICC Staging System

Stage	Criteria
IA	Primary melanoma ≤0.75 mm thick and/or Clark's level II (pT1); no nodal or systemic metastases
IB	Primary melanoma 0.76–1.50 mm thick and/or Clark's level III
IIA	Primary melanoma 1.51–4.00 mm thick and/or Clark's level IV
IIB	Primary melanoma >4.0 mm thick and/or Clark's level V
III	Regional lymph node and/or in-transit metastases
IV	Systemic metastases

A collaboration between the AJCC and the UICC in 1988 attempted to develop a more internationally acceptable staging system [19]. It had the same tumor thickness cut-offs adopted in the 1983 AJCC staging system but stipulated that when there was a discordance between thickness and level, the measured tumor thickness should take precedence and be used for pT staging. The nodal size cut off was changed from 5 to 3 cm, without any particular justification (Table VI). In a 1992 modification of their 1988 version, the AJCC stated that if there was discrepancy between tumor thickness and level, the pT category should be based on the less favorable finding. The remainder of the staging system was basically unaltered.

Ample data emerged over the next few years demonstrating that, in large patient series, there were additional independent prognostic variables that had not been not used in the 1992 system. These included histologic ulceration, the number of involved lymph nodes, the number and site of distant metastases, and increased serum lactate dehydrogenase (LDH) levels. Consequently, it was proposed that a further revision of the AJCC staging system was necessary [20], and a new Melanoma Staging Committee of the AJCC was formed to undertake this task. At its first meeting in 1999, the Committee unanimously agreed on the need for a new staging system, and set out a number of proposals for a revised system [21].

TABLE V. The 1983 AJCC Staging System

Stage	Criteria
IA	Localized melanoma ≤0.75 mm thick or level II
IB	Localized melanoma 0.76–1.50 mm thick or level III
IIA	Localized melanoma 1.51–4.00 mm thick or level IV
IIB	Localized melanoma >4.00 mm thick or level V
III	Limited nodal metastases involving only one regional lymph node basin or <5 in-transit metastases but without nodal disease
IV	Advanced regional metastases or any patient with distant metastases

THE CURRENT AJCC/UICC STAGING SYSTEM

The Melanoma Staging Committee of the AJCC that was assembled in 1999 included experts from various medical specialties, and representatives from major melanoma treatment centers and cooperative groups from North America, Europe, and Australia. Over a period of 3 years, the Staging Committee considered all the information that was available in the literature, assembled a 17,600 patient database, and analyzed the data that it contained. In this major analysis of prognostic factors, almost half of the patients had at least 10 years of follow up information, and 14% of them had at least 20 years of follow up. Based on the results of analysis of this very large dataset, several major changes from the previous (1997, 5th Edition) staging system were proposed and were ultimately included in the 6th Edition of the AJCC Staging Manual that was published in 2002 [22,23]. Subsequently, it was formally adopted by the UICC TNM Committee, the European Organization for Research and Treatment of Cancer, and the World Health Organization Melanoma Program.

In the new, 6th Edition of the AJCC staging system, the major changes were as follows:

1. Thickness thresholds of 1.0, 2.0, and 4.00 mm were used, replacing the thresholds of 0.75, 1.5, and 4.0 mm in the previous staging system.
2. Ulceration was included as a determinant of prognosis for both the T and the N categories. In the previous system, ulceration was not considered.
3. Clark level of invasion, which had been a primary determinant of T staging, was no longer used except for T1 lesions (i.e. those ≤1.0 mm in thickness).
4. Thick ulcerated melanomas (>4.0 mm) were included as Stage IIc (in the previous system they had been classified as Stage IIIa).
5. The number of involved lymph nodes was taken as the primary determinant of N staging. In the previous system, the maximum dimension of nodal metastases not the number of involved nodes was used for N staging.

6. Tumor burden (assessed as microscopic versus macroscopic disease) was included as a second determinant of N staging. In the previous system, this was not considered.

As well as the above, a clear distinction was drawn for the first time between clinical and pathologic staging. This change was incorporated to allow for the influence of sentinel lymph node biopsy, where micrometastatic disease is identified in patients whose nodes are not clinically abnormal. An outline of the 6th edition of the AJCC/UICC Staging System is given in Table VII. Full details of it are reported elsewhere, together with comprehensive discussion of the rationale for the various changes that were introduced [1,22–26].

The 6th edition AJCC staging system for melanoma was evidence-based, and clearly provided more comprehensive and accurate staging than any previous system. However, two important criticisms of it have been raised. Firstly, it increased the tumor thickness cut off for T1 tumors from $\leq$0.76 mm to $\leq$1.0 mm. This has resulted in more tumors being assigned to this category and has resulted in a reduction in the overall survival estimate for T1 tumors in the new staging system compared with that for TI tumors in the previous system. Hence patients with tumors $\leq$0.76 mm are now given a more pessimistic prognosis than they were according to the previous staging system, and this is probably inappropriate [27]. Secondly, inclusion of ulceration as a determinant of prognosis in the 6th edition without an unambiguous definition of ''ulceration'' has caused concern [28,29]. However, a recent SMU study found good interobserver reproducibility between pathologists in the assessment of ulceration [30].

OTHER PROGNOSTIC FACTORS OF RELEVANCE TO STAGING

Many studies that have sought to define prognostic factors for patients with melanoma have indicated that parameters not included in the current AJCC staging system may have an influence on outcome. In the AJCC database analysis, for example, the most important determinants of prognosis were found to be pT thickness and ulceration [1], but patient age, primary site, Clark level, and gender all had a statistically significant bearing on outcome as well. The relevance of patient age to staging is supported by the finding that it not only influences the thickness and ulcerative state of the melanoma, [31] but it also influences the likelihood of SN positivity, and therefore has a bearing on prognosis [32,33]. Recent studies, discussed in the next section, have shown that tumor mitotic rate (TMR) is an important independent prognostic indicator, but information about TMR was not included in the AJCC database. It must also be borne in mind that the information in the AJCC database used to determine new TNM categories was largely based on melanomas with superficial spreading and nodular growth patterns. However, as the authors of the article outlining the new staging system acknowledged [22], other growth patterns may have a different etiology and prognosis [34,35].

STAGING BASED ON HISTOLOGY

Histologic assessment of the pT and of regional lymph nodes (when available for evaluation) currently forms the basis of staging for all melanoma patients who do not have evidence of locoregional or distant disease either on clinical examination or using conventional imaging techniques. The addition of immunohistochemical staining to routine hematoxylin and eosin (H&E) examination, first described by Cochran et al. in 1982 [36], makes it possible to recognize metastatic melanoma cells in lymph nodes with greater confidence and results in the ''upstaging'' of up to 20% of patients [36–39]. Use of a panel of immunohistochemical markers, typically including markers for S100 and HMB 45, has therefore become routine in many institutions. As a consequence, a proportion of patients who would have been designated as

TABLE VII. The 2002 AJCC Staging System

Stage	Criteria
0	Melanoma in situ
IA	Tumor thickness $\leq$1.0 mm without ulceration and level II/III
IB	Tumor thickness $\leq$1.0 mm with ulceration or level IV/V, or tumor thickness 1.01–2.0 mm without ulceration
IIA	Tumor thickness 1.01–2.0 mm with ulceration or tumor thickness 2.01–4.0 mm without ulceration
IIB	Tumor thickness 2.01–4.0 mm with ulceration or tumor thickness >4.0 mm without ulceration
IIC	Tumor thickness >4.0 mm with ulceration
IIIA	Any tumor thickness with no ulceration 1–3 microscopic nodes
IIIB	Any tumor thickness with ulceration and 1–3 microscopic nodes or any tumor thickness without ulceration and 1–3 macroscopic nodes or any tumor thickness with or without ulceration and either satellite(s)/in transit metastasis(es) without metastatic node(s)
IIIC	Any tumor thickness with ulceration and either 1–3 macroscopic node(s) or satellite(s)/in transit metastasis(es) without metastatic node(s) or any tumor thickness with four or more metastatic nodes or satellite(s)/in transit metastasis(es) with metastatic node(s)
IV	Any tumor thickness, any number of nodes and any distant skin, subcutaneous nodal or visceral metastases

having AJCC Stage I or Stage II disease on the basis of H&E staining alone are assigned to the Stage III category.

The major limitation imposed on staging using these methods is that logistic and financial considerations make it possible to examine only a few histologic sections of each lymph node. It is conservatively estimated that complete examination of a single, entire lymph node of average size requires cutting, staining and examining at least 600 standard sections, each 4–5 microns in thickness. Such a process is clearly not a realistic possibility in routine practice, and even in a research setting the cost and manpower requirements mean that it is rarely able to be performed.

Alternative ways of assessing lymph nodes for the presence of melanoma cells have therefore been explored. The most promising approach to date has been the use of RT-PCR technology. Originally undertaken using only tyrosinase as a marker, it has now been shown that better discrimination is achieved using a panel of markers, including MAGE-3 and MART-1 (Melan A) [40,41]. Analysis of patient survival data has shown that the prognosis for those who have nodes that are RT-PCR positive but histologically negative (by both H&E and immunohistochemical staining) is worse than the prognosis for those who are both histologically and RT-PCR negative—but better than the patient group that is both RT-PCR positive and histologically positive. Recent results from the Florida Melanoma Trial [42], for example, indicated that patients whose SNs were both histologically and RT-PCR negative had a recurrence rate of only 6.6% at 3 years whereas those with histologically negative but RT-PCR positive SNs had a recurrence rate of 22%. The group with histologically and RT-PCR positive SNs had a 3-year recurrence rate of 42%. Thus it appears clear that more accurate staging of melanoma patients can be achieved by supplementing standard histologic lymph node assessment with RT-PCR testing.

If an appropriate panel of markers can be identified and its reliability validated, RT-PCR examination of lymph nodes therefore has the potential to make an important contribution to routine staging for melanoma patients. However, pathologists have generally been reluctant to submit half of each lymph node for RT-PCR testing because conventional histologic examination of that tissue is then no longer possible, and also because of concerns about the accuracy of RT-PCR assessment (the PCR technique is so sensitive that scrupulous laboratory technique is required to minimize the occurrence of false positive results). In addition, the requirement that RT-PCR analysis of lymph nodes be performed on fresh or frozen tissue, prior to fixation for standard histologic assessment, causes a major logistic difficulty. This problem may have been overcome recently by investigators at the John Wayne Cancer Institute, who have used a technique that allows RT-PCR testing of conventionally processed tissue sections [41]. The potential therefore now exists to perform routine staging using RT-PCR for all melanoma patients, by sending their slides or formalin-fixed tissue blocks to central processing laboratories for assessment. This may improve the accuracy of the procedure.

Even fundamental features of the primary melanoma, as assessed by conventional H&E staining, may be useful in further refining melanoma staging and making it more accurate and prognostically relevant. For example, it has recently been reported that TMR is a better indicator of prognosis than ulceration, second in importance only to pT thickness as a prognostic indicator [43,44] and that TMR assessment is reproducible amongst pathologists [30]. The 2002 (6th Edition) AJCC/UICC staging system is based primarily on pT thickness and ulceration, and it is therefore possible the TMR may be a valuable parameter to be incorporated in future systems, to further improve the accuracy and usefulness of staging. The AJCC database analysis confirmed that Clark level of invasion had independent prognostic significance, but its power as a prognostic indicator was much less than that of ulceration, except in thin melanomas ($\leq$1.0 mm in thickness). Clark level was therefore not included in the revised staging system, except for thin pTs.

STAGING BASED ON ANATOMIC IMAGING

At the time a patient presents with a primary melanoma conventional radiologic imaging with plain X-rays and computerized tomographic (CT) scans rarely reveals evidence of metastatic disease [45,46]. Similarly, magnetic resonance (MR) imaging and even whole body positron emission tomography (PET) at this time is very infrequently of value. Nor is high resolution ultrasound (US) examination of the regional lymph nodes at the time of presentation likely to reveal metastatic disease in them, because we have found in SMU patients that tumor deposits less than 4 mm in diameter cannot be reliably detected by US (unpublished data), and very few patients who present with a primary melanoma and clinically normal regional nodes have tumor foci greater than 4 mm in diameter in their SNs.

The value of routine imaging to re-stage patients as part of routine melanoma follow up is also not established [45,47]. Even when clinically detectable metastatic disease is present in regional lymph nodes, the likelihood of detecting systemic metastasis using conventional imaging methods is low [48]. The greater sensitivity of PET scanning becomes valuable in this situation, and undoubtedly improves staging accuracy by detecting some patients with AJCC Stage IV disease who would otherwise have been assigned to the Stage III category.

For those patients who develop symptoms possibly attributable to their melanoma in the course of follow up, however, conventional imaging and PET scanning will provide valuable staging information, and may identify potentially resectable disease, either in regional lymph nodes or in systemic sites. The ability to perform co-registered PET/CT scans has improved the accuracy of localization of metastatic disease, although the practical value of this recently introduced modality has yet to be fully assessed.

STAGING USING PROTON MAGNETIC RESONANCE SPECTROSCOPY

Recent reports of the use of proton MR spectroscopy (MRS) to determine whether or not metastatic melanoma is present in sentinel lymph nodes [49,50] suggest that increased staging accuracy may be possible using this technique. MRS can be used to examine either whole lymph nodes (in vivo or ex vivo) or fine needle aspiration biopsy material obtained from nodes. When metastatic melanoma is present, characteristic spectra are observed, with prominent peaks for specific metabolites such as choline compounds and taurine (Fig. 1). These MRS peaks are not apparent when benign tissues are examined [49,50]. Validation studies are currently in progress at our own institution and at other centers, and the results of these studies will determine the general applicability of MRS to achieving more accurate staging of melanoma patients. If its accuracy and reliability is confirmed, widespread implementation of this method of assessment should not be difficult, because conventional MR imaging machines can be used to generate spectral rather than anatomic images if appropriate software is installed. Clearly, it would be of enormous benefit to be able to stage patients by lymph node assessment without the need for surgical SN removal. MRS examination of fine needle aspirates from SNs, or of intact SNs in situ, offers this possibility.

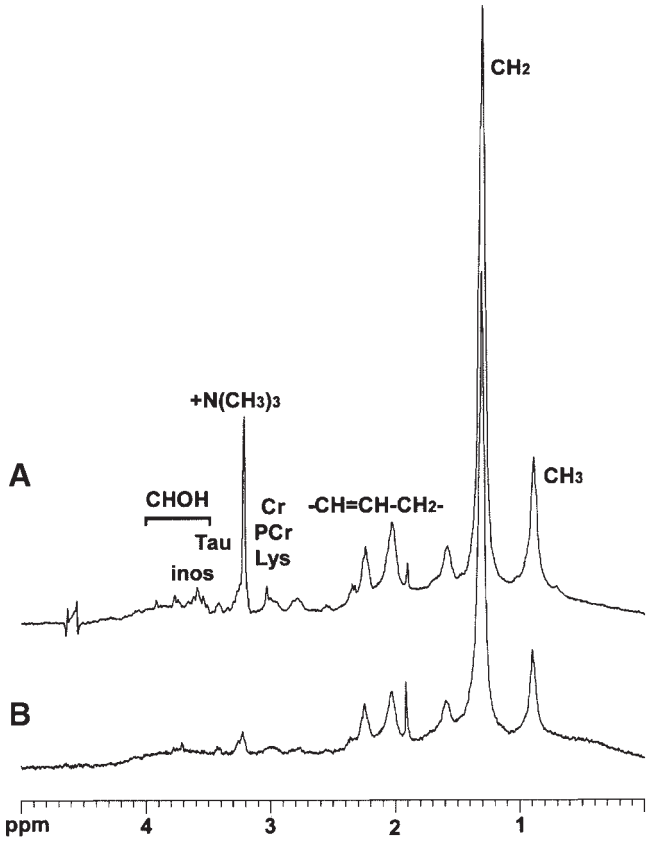

Fig. 1. One-dimensional proton magnetic resonance spectra (8.5 T) of FNABs of regional lymph nodes from melanoma patients. (**A**) Node containing metastatic melanoma; and (**B**) benign node. CH_3, methyl; CH_2, methylene; $+N(CH_3)_3$, *N*-trimethyl of choline and choline-based metabolites; $–CH=CH–CH_2–$, acyl chain protons, N- or O-acetyl groups at 2.0 ppm; Cr, creatine; PCr, phosphocreatine; Lys, lysine; Tau, taurine; inos, inositol; CHOH, carbohydrate residues.

STAGING USING MARKERS IN THE BLOOD

Circulating Melanoma Cells

Following studies by Smith et al. [51] showing that melanoma cells could be detected in the circulation of patients using RT-PCR methodology, a number of studies have been carried out to evaluate the utility of such assays in the management of melanoma [51–72]. The aims of these studies in patients with AJCC Stages I, II, and III disease have been largely to evaluate correlations between test results and risk of relapse or time to relapse and death, whereas in patients with clinically evident disease correlations were sought with overall survival. Several studies have also examined whether the tests could be used to assess response to treatment.

Results of the studies have been controversial and complicated by variations in the test procedures [73], the number of blood samples tested, the number of markers used, and over-interpretation of results from small numbers of patients. The use of markers that were not specific for melanoma has been perhaps the most important confounding factor. Careful studies by Curry et al. [67] demonstrated that p97, gp100, and Muc-1 could be detected by PCR tests on blood samples from normal subjects and were therefore not suitable for tests on melanoma patients because of their lack of specificity for melanoma. Review of studies that exclude these less reliable markers indicates wide agreement that detection of circulating melanoma cells (CMCs) in systemic blood samples shows a general correlation with stage of the disease. More importantly, detection of CMCs was shown to be an indicator of early relapse and poor survival from melanoma [64,66–68,70–72,74]. Multiple tests were shown to increase the sensitivity of detection of CMCs

[75–77] and tests carried out up to 6 months after surgical removal of localized melanoma were still shown to be associated with an adverse prognosis [70]. Curry et al. [75] found that tests on three blood samples taken in the first 3 months after surgical removal of melanoma provided the highest sensitivity for detection of CMCs.

Two issues impact on whether the association with prognosis shown in these studies indicates a useful role for PCR tests in management. One is whether the tests add additional information to staging by the usual clinical and pathologic procedures. Several studies have shown that positive PCR tests for tyrosinase were an independent predictor of recurrence from melanoma, suggesting that they might therefore be a useful addition to standard staging methods [55,57,64,66,70–72,74]. Studies by Palmieri et al. [78] on 200 patients, however, failed to show that PCR tests (for tyrosinase, MART-1, and p97) added additional information from that provided by standard staging procedures. Once again, differences in test protocols and sampling times may account for the differences between the studies. A second issue in assessing utility of the tests relates to their sensitivity for predicting clinical recurrence of melanoma. Curry et al. [67,68,75] found that the false negative rate for prediction of melanoma recurrence using PCR tests for CMCs was approximately 30%. This result implies that should the tests be used to select patients for adjuvant therapy, 30% of those patients at risk would not receive treatment.

Thus, available evidence suggests that the detection of CMCs in melanoma patients provides additional prognostic information but utility of the assays is limited by high false negative rates for identifying patients who subsequently relapse from melanoma. Their use in staging melanoma patients therefore cannot be recommended until these problems are overcome.

Serum Lactate Dehydrogenase (LDH)

Until now, it has been unusual for a serum measurement to be incorporated in a staging system. However, multivariate analyses in a number of studies provided compelling evidence that an elevated serum LDH concentration was a powerful independent predictor of outcome in patients with metastatic melanoma [79,80]. For this reason, the AJCC Melanoma Staging Committee proposed that patients with Stage IV disease who had a raised serum LDH concentration should be assigned to a separate, worse prognosis category (M1c).

Markers of Endogenous Immune Response

Despite careful analysis of known prognostic factors, some patients with early stage melanoma who have no adverse prognostic features that can be identified will metastasize. In an attempt to more accurately predict the likelihood of metastasis, Morton's group in Santa Monica has assessed the endogenous immune responses to early and intermediate stage melanoma, and found a correlation with occult nodal disease and survival. In an important study designed to test the hypothesis that this response might have prognostic significance independent of standard prognostic factors, the immune response to a 90-kDa tumor-associated antigen (TA90) was assessed [81]. It was determined that the presence of an immune complex to TA90 and the absence of an anti-TA90 IgM response correlated with metastasis in patients judged to be at low or intermediate risk of such metastasis according to standard prognostic indices. Ten year survival figures for patients with AJCC Stage Ib or IIa melanoma were approximately 80% for those whose anti-TA90 IgM titers were $\geq$800, and only approximately 25% in patients whose anti-TA90 IgM titers were $<$800 ($P < 0.0001$). TA90 is a melanoma-expressed glycoprotein antigen that elicits a specific immune response in the sera of melanoma patients [82–85]. The clear-cut demonstration of a correlation between the presence of TA90 immune complex and the subsequent development of distant metastases in patients with AJCC Stage Ib or IIa melanoma suggests that this is a potentially valuable staging tool. In the same study, it was shown that there was a correlation between the absence of an endogenous anti-TA90 IgM response and the development of distant metastases in such melanoma patients. These correlations were found to be independent of locoregional relapse, tumor thickness, level of invasion, ulceration, anatomic site, gender, and age. A positive TA90 immune complex result was obtained in 41 of 50 patients with metastases, but in only 9 of 50 patients with no metastases, which suggests that this assay is sensitive and specific for the detection of occult metastases. It is well-documented that melanoma can induce both cellular and humoral immune responses (the latter forms the basis for the production of the TA90 immune complex), and this has been the basis for the development of anti-melanoma vaccines.

RT-PCR assays and other assays for antigens expressed on melanoma cells, including S100 protein, neuron-specific enolase, melanoma-inhibiting activity (MIA), and 5-S-cysteinyldopa, have been used in attempts to detect occult melanoma. It is possible that a battery of assays may provide the most accurate prognostic estimate, with measurement of serum levels of TA90 immune complex and assays of melanoma-expressed antigens in sentinel lymph nodes, peripheral blood, and perhaps bone marrow. It is of interest that Litvak et al. found that anti-TA90 IgG antibodies did not appear to correlate with the hematogenous dissemination of melanoma cells. Available data suggest that the specific stimulation of an immune response to melanoma, e.g.

anti-TA90 IgM antibodies, correlates with survival, but that anti-TA90 IgG antibodies are not protective. Litvak et al. concluded that assays for TA90 immune complex and anti-TA90 IgM may potentially help to identify patients whose early stage melanoma is likely to spread to regional or distant sites. It was proposed that these assays might complement emerging RT-PCR-based detection assays. The eventual development of an immunologic or molecular-based detection system might allow clinicians to identify with increased accuracy those patients most likely to benefit from adjuvant therapy after surgical resection of a thick primary melanoma or locoregionally recurrent disease. Serum levels of MIA protein have recently been found to provide important prognostic information early in the course of Stage III melanoma, and rising levels often indicate melanoma recurrence before there is clinical evidence of disease [86]. Prospective studies to further examine these new concepts in staging and determination of prognosis are already in progress. In parallel, clinical trials of promising adjuvant therapies are proceeding, in the hope that effective agents with acceptably low toxicity will be found.

AN ALTERNATIVE MELANOMA STAGING STRATEGY

It is generally acknowledged that a staging system should be simple and practical, and that its fundamental purpose should be to group patients in a way that reflects the biology and natural history of the disease process [25,26,87]. This is best achieved by estimating prognosis on the basis of information that is as accurate as possible. This is necessary not only so that patients can be reliably informed of their prognosis but also so that they can be staged in a way that permits valid comparison of treatment outcomes within and between institutions, and of clinical trial stratification groups. If these objectives of a staging system are accepted, it does not seem logical to assign staging on the basis of selected parameters, as in the current AJCC/UICC melanoma staging system, whilst not considering other well documented and statistically confirmed parameters of prognostic significance.

Although the current TNM-based AJCC/UICC melanoma staging system is much more accurate, clinically relevant and useful than previous systems, it has become very complex and is difficult to understand intuitively. A patient with melanoma can be assigned to one of 22 TNM staging categories, and the system that is used has diverged markedly from basic TNM staging concepts. T staging, for example, spans two AJCC stages (Stages I and II), and parameters completely unrelated to the TNM system have been included, such as serum LDH measurement to categorize patients with Stage IV disease. Another reason that the system is no longer intuitive is because prognosis and stage grouping are not always directly linked. It is anomalous, for example, that the prognosis for some patients with AJCC Stage II disease is worse than for others with Stage III disease. For example, Stage IIc disease has a worse prognosis than Stage IIIa and Stage IIIb disease, and the prognosis for patients with Stage IIb disease is no better than the prognosis for patients with Stage IIIa disease [1]. An intuitive TNM-based system would require that the prognosis for all N0 patients (i.e., those with tumor-free regional nodes) would be better that that of patients with N1 or N2 disease, regardless of T stage. Furthermore, as previously mentioned, the AJCC prognostic factors analysis demonstrated that identifying patients with Stage III disease indicated that they had a 5 year survival probability ranging from 13 to 69%—hardly a useful grouping for informing patients of their prognosis or for providing meaningful stratification in clinical trials.

Parameters used to determine staging according to the current AJCC melanoma staging system are tumor thickness, ulceration, Clark level (for T1 tumors only), number of metastatic nodes, extent of metastatic involvement of nodes (microscopic versus macroscopic), presence or absence of in transit or satellite metastases, sites of distant metastases, and serum LDH (for patients with systemic metastases only). However, several parameters of proven prognostic significance are not considered in the staging system; these include TMR, site of pT, age, gender, and tumor growth pattern. Nor are more recently demonstrated serum markers of prognosis, such as TA90, MIA, and S 100, included.

The important question that must be considered is whether the melanoma staging system should continue to develop along existing lines, with ever-increasing levels of complexity and progressive loss of the ability to use and interpret it intuitively, or whether attempts should be made to produce a system that is simpler to use and more intuitive, so that it has greater practical applicability. One possible solution would be to abandon the present expanded and heavily modified TNM system as the basis for melanoma staging and instead to use the information that is now available about prognostic factors to accurately predict each patient's prognosis using an appropriately constructed and validated computer-generated estimate of prognosis, such as that described by Cochran et al. [88]. It would be possible, using such a computer software program, perhaps developed, officially sanctioned, and distributed by the AJCC and the UICC, to obtain a numerical prognostic score for each patient, based on all available information of statistically confirmed relevance to prognosis. The patient could then be assigned to a stage group on the basis of that score, according to previously agreed score ranges for each stage.

The advantages of such a system would be that it was intuitive, would allow reliable comparison of treatment results within and between institutions, and would provide a more uniform composition of stratification groups for patients entering clinical trials of new treatment strategies and those entering adjuvant therapy trials. As new information about prognostic factors became available and was statistically validated, the program generating the computer estimates (and thus the staging system) could be updated, with the possibility of retrospective adjustment of the staging for patients previously staged according to the scoring system that was in use at the time. The great attractions of such a system would be (i) that it used all parameters available for a given patient to determine staging, and (ii) that it assigned stage on the basis of a score determined from a continuous range, rather than on the basis of placement in a category selected from an arbitrary series of discontinuous variables. If it was thought necessary, an additional staging category could be added to indicate whether the patient had developed in transit or regional node disease (N) or distant metastasis (M), or both (NM). This might be important when stratifying patients for clinical trials, because the responses to some forms of treatment might depend on the type of metastatic disease, and not just on the calculated prognosis without that treatment.

It is useful to consider a specific example of how such a numerical staging system could work. If it was agreed that 5-year survival, expressed as a percentage, was an appropriate value to be determined for every patient, this would give a possible range of scores from 0 to 100. It could then be agreed, say, to use a 10 stage system. Patients determined by the computer program to have a score of 90–100 could be classified as having Stage I disease, those with a score of 80–90 as having Stage II disease, those with a score of 70–80 as having Stage III disease, and so on. Alternatively, other stage groupings could be selected, not necessarily distributed evenly across the numerical score range, in such a way that staging of greater practical relevance was achieved. It might, for example, be considered appropriate to designate Stage I disease as a score of 90–100, Stage II disease as 65–90, Stage III disease as 25–65, and Stage IV disease as 0–25. These stages would correspond quite closely to the 5-year survival probabilities for patients with Stage I, Stage II, Stage III, and Stage IV disease according to the current AJCC/UICC staging system. It would also be possible to allocate patients to substages, if this was considered necessary, by specifying score ranges for each substage.

SUMMARY AND CONCLUSIONS

The evolution and progressive refinement of an internationally accepted melanoma staging system has resulted in greatly improved accuracy, but more complex and less intuitive staging. This raises the question of whether the present, TNM-based system should continue to develop with ever-increasing levels of complexity, or whether attempts should be made to produce an alternative system that is simpler and more intuitive, so that it has greater practical applicability. The information that is now available about prognostic factors in patients with melanoma allows accurate, computer-assisted prediction of an individual patient's prognosis. An alternative staging strategy that could be considered in the future would be to use such a prognostic estimate to obtain a numerical score for each patient, based on all available information of known prognostic relevance, and then to assign that patient to a stage group on the basis of that score, according to previously agreed score ranges for each stage and substage. Such a system would allow reliable comparison of results within and between institutions, and provide more equivalent stratification groups for patients entering clinical trials of new treatment strategies and those entering adjuvant therapy trials. As new prognostic factors were identified and validated, they could be incorporated into the standard computer program used to determine prognosis, making staging progressively more accurate without the need for periodic major revisions of the entire staging system.

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