Current controversies in early-stage melanoma

Questions on management and surveillance

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Learning objectives
After completing this learning activity, participants should be able to discuss the current controversies associated with staging, treatment and surveillance of early-stage melanoma; describe the therapeutic quandaries relating to melanoma transection at biopsy and how they may be resolved; explain how more extensive sectioning of melanoma biopsy specimens can impact treatment; describe the 31-gene prognostic test and its potential utility; and categorize the evidence to support routine skin examination and surveillance imaging following diagnosis of stage 0, I, and II melanoma.

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There are a number of controversies and uncertainties relating to the management and surveillance of patients with early-stage, localized (ie, stage 0, I, and II) cutaneous melanoma. While tumor stage is a critical predictor of clinical outcome and guides treatment, accurate determination of stage may be affected by the biopsy technique used and the method of sectioning before histologic review. A new molecular prognostic test is available but has not been formally incorporated into staging or treatment guidelines. There are no randomized controlled clinical trials to support guidelines for surveillance following the treatment of early-stage melanoma. In the second article in this continuing medical education series, we review the controversies and uncertainties relating to these issues. The questions we address are controversial because they speak to clinical scenarios for which there are no evidence-based guidelines or randomized clinical trials with the consequence of considerable variability in clinical practice. Our goal is to provide the clinician with up-to-date contextual knowledge to appreciate the multiple sides of each controversy and to suggest pathways to resolution. (J Am Acad Dermatol 2019;80:15-25.)

Key words: imaging; melanoma; staging; surveillance; transection.

This review focuses on controversial questions relating to the staging, treatment, and surveillance of localized, early-stage (ie, stages 0, I, and II) cutaneous melanoma. The questions we address are controversial because they speak to clinical scenarios for which there are

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Abbreviations used:

AJCC:	American Joint Committee on Cancer
CT:	computed tomography
CXR:	chest radiography
GEP:	gene expression profile
LM:	lentigo maligna
MIS:	melanoma in situ
NCCN:	National Comprehensive Cancer Network
PET:	positron emission tomography
SLNB:	sentinel lymph node biopsy
WLE:	wide local excision

no evidence-based guidelines or randomized clinical trials. Tumor staging describes the extent of tumor development and progression, and for early-stage melanoma, this critical information is obtained from histologic assessment of the biopsy, wide local excision (WLE) or sentinel lymph node biopsy (SLNB) specimens. The value of accurate staging is to provide prognostic information, guidance for treatment, and indications for surveillance for tumor recurrence. Several factors, however, may create uncertainty in the accuracy of staging. For example, a key factor in determining melanoma stage is Breslow depth, which may be undefined in biopsy specimens that are transected at the deep margin or vary in magnitude depending on the tissue section examined histologically. A newly developed molecular test has the potential to provide important prognostic information, but its potential use in the current staging system has not been defined. Finally, there are uncertainties relating to the surveillance of patients with early-stage melanoma, given the lack of controlled trials to support the use (and frequency) of imaging and skin examinations. Therefore, there is considerable variability among practitioners in the management of early-stage melanoma,[1-5] and guidelines from organizations such as the American Academy of Dermatology,[6] National Comprehensive Cancer Network (NCCN),[7] and American Joint Committee on Cancer (AJCC)[8] typically provide flexibility to accommodate a range of clinical practices.

WHAT ARE THE CONSEQUENCES OF TRANSECTING A MELANOMA?

Key points

- **Transection prevents precise depth determination**
- **Transection is usually associated with the shave biopsy technique**
- **Transection does not affect survival**
- **May be an indication for SLNB**
- **Considering extent of deep margin involvement and repeat biopsy procedure may be useful**

Melanoma biopsy specimens often demonstrate lateral transection, but when there is deep transection (ie, involving deep margin), a Breslow thickness cannot be accurately assigned. This is particularly problematic when the extent of deep margin involvement is broad versus focal (Fig 1, *A*). In cases where the biopsy specimen includes a depth of >1 mm, this may not affect treatment. For example, a lesion transected at a depth >1 mm can be treated the same as lesions of known depth of >1 mm (Fig 1, *B*). However, for lesions transected at a depth of <0.8 mm, two aspects of management may be unclear: 1) whether the excisional margins should be 1 cm (invasive melanoma <1 mm depth) or 2 cm (invasive melanoma >1 mm depth); and 2) whether SLNB is indicated (not indicated for lesions <0.8 mm depth unless ulcerated). The latest AJCC guidelines[8] on the management of early-stage melanoma are summarized in Table I. In addition, because Breslow thickness is the most important prognostic factor for early-stage melanoma,[9] it is difficult to estimate the prognosis for deeply transected melanomas.

Factors associated with melanoma transection

Deep transections of melanoma biopsy specimens are not rare phenomena, occurring in 5% to 65% of melanoma biopsy procedures.[10-15] The most commonly associated factor is the shave biopsy technique.[12,14] Shave biopsy procedures are not as deep as saucerization biopsy procedures; however, there is no strict definition as to what anatomic depth is required to classify a biopsy specimen as a "saucerization." While punch biopsy procedures are less likely than shaves to lead to deep transection, the punch will only serve as an excisional biopsy (removing all of the visible tumor) for relatively small diameter lesions (<6 mm). The NCCN guidelines recommend excisional biopsy, but state that full-thickness incisional or punch biopsy of the thickest portion of the lesion is acceptable in certain anatomic areas or for very large lesions.[7] The American Academy of Dermatology guidelines[6] similarly call for an excisional biopsy but also explicitly recognize that a deep shave or saucerization is excisional. However, performing an unanticipated excisional biopsy may not be practical, and for larger diameter lesions the shave biopsy procedure may be appropriate to avoid sampling error associated with partial biopsy specimens. The NCCN guidelines also state that a superficial shave biopsy procedure is appropriate if the index of suspicion for invasive melanoma is low.[7] However, several studies[14,15] found that a lack of clinical concern for melanoma was associated with a higher rate of transection. For shave biopsy

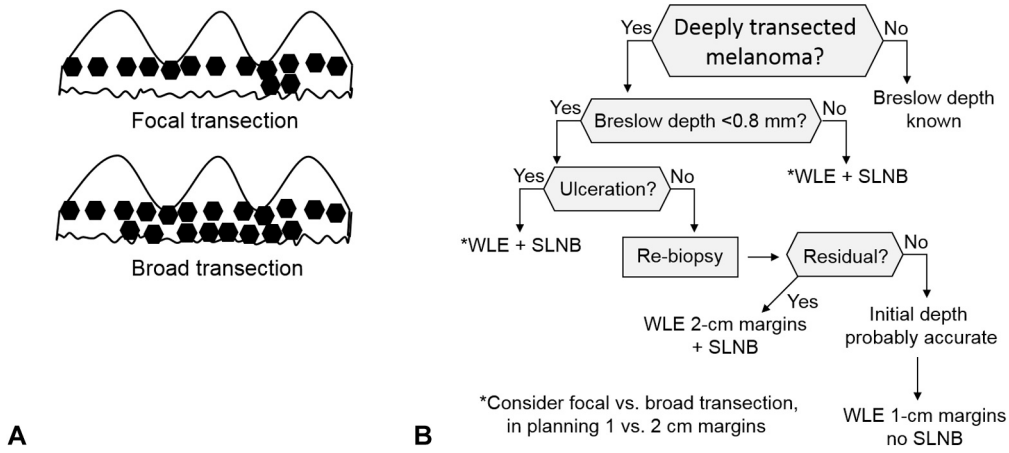

Fig 1. Melanoma transection. **A**, Focal versus broad transection of invasive melanoma. **B**, Decision tree for management of transected melanoma.

Table I. Summary of 2018 American Joint Committee on Cancer staging and management guidelines for early-stage melanoma

Clinical stage	Breslow depth, mm*	Ulceration	Excision margins, cm	SLNB indicated
0 (in situ)	0		0.5-1	No
IA	<0.8	No	1	No
IB	<0.8	Yes	1	Yes
IB	0.8-1.0	Yes or No	1	Yes
IB	1.1-2.0	No	2	Yes
IIA	1.1-2.0	Yes	2	Yes
IIA	2.1-4.0	No	2	Yes
IIB	2.1-4.0	Yes	2	Yes
IIB	>4.0	No	2	Yes
IIC	>4.0	Yes	2	Yes

SLNB, Sentinel lymph node biopsy.
*Rounded to nearest 0.1 mm.

procedures, removing the entire clinical lesion to a depth of 2 mm will usually avoid the conundrum of transection. A useful tip is that palpability of melanoma lesions has been associated with invasion >1 mm.[16,17] Female gender and biopsy sites of ears and digits are reportedly associated with melanoma transection,[15] perhaps reflecting reluctance to inflict deep biopsy scars in females and perceived morbidity as a consequence of biopsy at these sites.

Effect of transection on prognosis

While there are no controlled prospective trials of patients with transected melanomas, several retrospective studies have revealed no survival differences between patients with and without transected melanomas.[10,12-14,18] Similarly, several studies concluded that transected melanomas were not associated with higher rates of lymph node metastasis.[19,20] Approximately 60% of deeply transected melanomas have residual tumor detected in the WLE specimen,[11,13] although only 10% of such cases led to a change in recommendation for SLNB.[10,11]

Resolution: Assess extent of transection and consider rebiopsy

While deep transection has been considered an indication for SLNB,[21] it may not be immediately clear what margins should be taken for the WLE. While excisional margins of 2 cm would be indicated for lesions >1 mm (Table I), for lesions transected at a depth between 0.8 and 1 mm it may be useful to consider whether the lesion is focally or broadly transected (Fig 1, *A*). While there are no studies comparing rates of residual disease in WLE specimens of focally versus broadly transected lesions, the chance of finding more extensive disease is greater if the tumor is broadly transected as opposed to biopsy procedures where the deep margin is only focally involved. Thus, one could consider 1-cm excisional margins for focally transected tumors and 2-cm margins for broadly transected tumors transected at a depth between 0.8 and 1 mm (Fig 1, *B*, Table I). Similarly, for lesions transected at a

Table II. Potential benefits and costs of more extensive analysis of melanoma specimens

Potential benefits	Disadvantages
More accurate staging	Increased cost
Occult invasion detected in 29-33%[25-27]	
Breslow depth increased in 10-100%[28,29]	
Ulceration detected in additional 3%[28]	
May affect treatment	Increased labor
Management changed in 10%[28]	May prompt greater surgical margins*
	May prompt SLNB*
	May exhaust tissue (prevent further use, study)

SLNB, Sentinel lymph node biopsy.
*May be unnecessary (see Table I).

depth <0.8 mm that are ulcerated, one could consider 1-cm excisional margins for focally transected tumors and 2-cm margins for broadly transected tumors (Fig 1, *B*). For nonulcerated tumors transected at a depth <0.8 mm, a reasonable approach would be to perform a repeat biopsy procedure to assess residual disease. If no tumor is found in the subsequent specimen, treatment and staging can be based on the original Breslow depth of the transected biopsy specimen, whereas the presence of residual disease suggests that a 2-cm margin and SLNB would be appropriate (Fig 1, *B*, Table I). For transected melanomas without residual tumor on reexcision, the original Breslow depth accurately predicts survival and prognosis.[13]

WHAT IS THE IMPACT OF MORE EXTENSIVE HISTOLOGIC SECTIONING ON STAGING ACCURACY AND PROGNOSIS?

Key points

- **No standards exist for sectioning technique of suspected melanoma biopsy specimens**
- **Upstaging could potentially affect treatment and prognosis**
- **Invasive melanoma: may change Breslow depth**
- **Melanoma in situ: may detect occult invasion**
- **Extensive sectioning may increase staging accuracy, but is unlikely to affect outcome**

There are no universally applied standards for how biopsy specimens that are suspicious for melanoma are rendered for histologic evaluation, including how the specimen is grossed, thickness of sections cut, and how many sections are examined per tissue block.[22,23] Sampling error is an inherent risk in the microscopic examination of tissues where a 3-dimensional specimen is rendered into 2-dimensional specimens on glass slides.[24] If 600 sections are cut in 5- μm increments from a 3-mm skin biopsy specimen, well below 1% of the entire specimen volume is represented on the slides. While more extensive sectioning and examination of the tissue block has the potential to provide a more accurate rendering of diagnostic and prognostic histologic features (depth of invasion, ulceration, and mitoses), there are commensurate increases in cost, workload, and potential exhaustion of remaining tissue for future uses (Table II). While upstaging a melanoma may have therapeutic and prognostic implications, such as larger excision margins or SLNB, the majority of suspicious lesions from which a biopsy specimen is obtained prove not to be melanoma.[30] Therefore, an optimal balance needs to be sought between diagnostic accuracy and practicality.

Changing Breslow depth in invasive melanoma

It is not uncommon for a greater Breslow depth to be observed in the WLE specimen compared to the original melanoma biopsy specimen, potentially leading to upstaging. Comparisons of matched excisional and biopsy specimens found that final depth increased in 4% to 22% of cases.[10,11,31-34] Consequently, several studies have demonstrated that more extensive sectioning of invasive melanoma biopsy specimens can result in a deeper Breslow depth reported.[28,29]

Detecting occult invasion in melanoma in situ

Previous studies found that approximately 12% to 20% of patients with lentigo maligna had invasive disease in their excision specimens,[35-38] but many of these cases were large lesions on the head or neck diagnosed by incisional (or partial) biopsy. A fraction of patients diagnosed with melanoma in situ (MIS) have occult invasion that can be demonstrated by more extensive sectioning coupled with immunohistochemical analysis.[25-27,39] While the detection of occult invasion is the likely basis for

occasional metastasis after a diagnosis of MIS,[27,40] the relatively high rate of invasion reported[25-27] seems at odds with the prognosis associated with MIS—which carries a life expectancy equivalent to that of the general population.[41] It has been suggested that in some cases the appearance of melanocytic cells in the dermis may result from tangential sectioning of surrounding rete ridges or follicular infundibula.[42] Moreover, identifying melanoma cells in the dermis is problematic given that immunohistochemical markers routinely used do not discriminate between malignant and nonmalignant melanocytes.

Increased tumor invasion revealed by more extensive sectioning and immunostaining is unlikely to affect clinical outcome

The high survival associated with MIS suggests that the presence of occult invasive melanoma cells has limited prognostic significance and an exhaustive search for microinvasion in MIS specimens[43] may have no practical value. A similar scenario has been reported in the detection of micrometastatic disease in sentinel lymph nodes with immunohistochemistry (and not seen on routine hematoxylin–eosin staining), which appears to have limited prognostic significance.[44] Therefore, while more extensive sectioning or use of immunohistochemical stains may enable detection of invasive disease in MIS lesions or increased Breslow depth in invasive melanoma lesions, such upstaging is unlikely to affect prognosis. However, the detection of increased lesion depth leads to more accurate staging with consequences for treatment planning (surgical margins or consideration of SLNB [Table I]). Prospective studies are needed to determine whether focal invasive melanoma cells detected with immunohistochemical staining, or increased Breslow thickness found with extensive sectioning, are clinically significant.

WHAT IS THE ROLE OF THE 31-GENE PROGNOSTIC TEST?

Key points

- **Limitations of SLNB as a prognostic test in patients with thin melanoma**
- **Gene expression panel segregates lesions into 2 classes to predict metastatic risk**
- **Not a substitute for SLNB**
- **Resolution: more data needed to incorporate into staging schemes**

While the prognosis for patients with early-stage melanoma is excellent, ≤5% of patients with minimally invasive (<0.8 mm) stage I disease will ultimately develop distant metastatic disease,[8] and such cases are responsible for the majority of deaths from melanoma.[45-47] As a prognostic test, the SLNB identifies patients with a higher risk of death from thin melanoma.[48-50] However, SLNB may not be predictive for patients who develop metastasis through hematogenous spread not involving the regional lymph nodes. Earlier detection of metastases in lower-risk patients may lead to better clinical outcomes.[51,52] Therefore, there would be considerable value in a prognostic test (particularly one that is noninvasive) that would improve staging accuracy for patients at greater risk for metastasis who would be potential candidates for closer follow-up or adjuvant therapy after surgical resection.

Development of the GEP test

Previous studies identified patterns of gene expression (ie, gene signatures) associated with melanoma tumor progression and metastasis.[53-55] Building on these data and a previously developed prognostic test for uveal melanoma,[56] Castle Biosciences Inc (Friendswood, TX) developed a panel of 31 genes (28 signature plus 3 control genes) based on their differential expression in "low risk" and "high risk" primary melanoma tumors.[57] Expression of individual genes is assessed from messenger RNA extracted from formalin-fixed paraffin-embedded tumor tissue slides and amplified by reverse transcription polymerase chain reaction. A training set of melanoma cases collected from multiple centers with clinical follow-up information was used to develop a binary algorithm that designates the gene expression profile (GEP) in a given tumor as either class 1 (low risk) or class 2 (high risk). The DecisionDx-Melanoma test (Castle Biosciences Inc) is designed to identify which patients with early-stage primary melanoma are at high risk of metastasis. The GEP test is ordered by downloading a form from the company's website. Archival tissue with sufficient tumor remaining to cut multiple slides is required.

Clinical validation studies

In the initial clinical validation study, which included 78 cases of AJCC 7th edition–classified stage I or II melanoma associated with either a metastatic event or >5 years of follow-up without metastasis, distant metastasis-free survival and recurrence-free survival at 5 years for the class 1 GEP cases was 98% and 100%, respectively, while that for the class 2 GEP cases was 37% and 68%.[57] Comparing the prognostic accuracy of the

GEP signature to AJCC tumor factors and stage, multivariate analyses characterized the GEP signature as an independent risk factor for metastasis, and GEP class assignment was associated with a greater hazard ratio for metastasis than AJCC staging.[57] For the 164 stage I and IIA cases included in the training and validation cohorts, the GEP predictor identified 90% of cases without metastasis as class 1 and 80% of cases with documented metastasis as class 2.[57] These results were further substantiated in a second clinical validation study, in which combining GEP classification and SLNB status further improved predictive accuracy for distant metastasis risk.[58] In a separate study, identification of high-risk tumors was improved by combining the GEP test with the AJCC Outcome Prediction Tool[59] (http://melanomaprognosis.net). On the other hand, an interim multivariate analysis of the GEP test in patients enrolled in the EXPAND and INTEGRATE trial registries showed that thickness, mitotic rate, and GEP class significantly predicted recurrence, while only tumor thickness significantly predicted distant metastasis and overall survival.[60]

Utility of the GEP test

The GEP test appears to identify a subset of patients with a higher risk of distant metastasis than indicated by conventional staging parameters. However, it is important to recognize that the GEP test is not a substitute for SLNB—while both tests are predictive of survival, they are not designed to measure the same things. While SLNB directly tests lymph node involvement, the GEP test predicts risk of distant metastasis. Failure to stage a patient with SLNB introduces the risk of not identifying a stage III patient with occult nodal metastases who would otherwise be eligible for adjuvant therapy with agents approved by the US Food and Drug Administration in that setting.[61,62] The GEP test may be more likely to predict the risk of distant metastasis via hematogenous spread independent of regional lymph node involvement. The NCCN Guidelines Committee for melanoma does not currently recommend the test outside of a clinical trial, stating that the validation studies were performed on a training set from relatively high-risk melanomas and it has not been prospectively evaluated for its independent prognostic value in a large population of patients with average- to low-risk melanoma.[63] With the newly released 8th edition of the AJCC staging system for melanoma,[8] it is not clear what additional prognostic information can be gleaned from a class 2 designation from the GEP test. While the GEP test results may provide reassurance or affect lifestyle planning decisions, there are no adjuvant therapies approved by the US Food and Drug Administration that are available for a node-negative class 2 GEP-tested patient. Only a prospective clinical trial on GEP class 2 patients with long-term clinical follow-up can determine if adjuvant therapy will be of any clinical benefit to such patients.

HOW (AND HOW OFTEN) SHOULD PATIENTS WITH EARLY-STAGE MELANOMA BE SCREENED?

Key points

- **Lack of controlled studies on the frequency of complete skin examination**
- **No imaging indications for stage 0 or I disease**
- **Imaging can detect recurrence in patients with stage II disease, but is unlikely to affect survival**
- **Some imaging may be indicated in stage IIB and IIC disease, but only for several years after diagnosis**

There are no prospective studies on the optimal frequency of screening patients after a diagnosis of early-stage melanoma. Imaging is expensive and associated with a risk of false-positive findings leading to further unnecessary testing. In addition, there are risks of cumulative radiation exposure —one standard computed tomography (CT) scan is equivalent to 400 chest radiograph (CXR) exposures,[64] and CT scans have been associated with an increased risk of cancer.[65] While negative imaging studies may be reassuring, it is not well established that treatment of occult metastatic disease (before symptoms arise) improves survival. While several studies have documented better outcomes in patients with isolated lung or soft tissue metastases,[51,66,67] others found that survival was not significantly different for patients whose metastases were detected by routine imaging compared with those whose detection by imaging was prompted by symptoms.[68,69]

Skin examination frequency should depend on risk of next occurrence, but may be tailored to patient-specific factors

A recent survey of dermatologists found that 49% recommended 6-month follow-up intervals within 5 years of melanoma diagnosis while 63% recommended 12-month intervals after 5 years.[2] Skin examination frequency should reflect a patient's likelihood of developing a subsequent melanoma,

Table III. Recommendations for screening patients after a diagnosis of early-stage melanoma

	Skin screening*		Routine imaging†	
Stage	**Years 1-5**	**Years 5+**	**Years 1-5**	**Years 5+**
0	6 months	Annual	None	None
IA	3-6 months	Annual	None	None
IB	3-6 months	Annual	None	None
			0.3% rate of metastatic detection[74]	
			60-89% rate of false-positives[74]	
			Ultrasound monitoring does not affect survival[75]	
IIA	3-6 months	Annual	None	None
	Recurrences in stage I/II patients more likely to be detected by skin examination than imaging[76]			
	Relapses in stage II patients most likely to be patient-detected[77]			
	Imaging in stage II patients unlikely to affect survival[78,79]			
IIB	3-6 months	Annual	6-12 months‡	None
IIC	3-6 months	Annual	6-12 months§	None
			52% of recurrences are locoregional[80]	

*No prospective trials to inform. May increase frequency for younger patients, those with family history, patients with numerous or atypical nevi being monitored by photography or digital dermoscopy, or those not regularly performing skin self-examination.
†Not recommended in National Comprehensive Cancer Network guidelines.[7]
‡Regional ultrasound only.
§Regional ultrasound, or more intense surveillance (computed tomography, or positron emission tomography/computed tomography scans every 3-12 months, and annual magnetic resonance imaging of the brain) if required for an adjuvant clinical trial.

which may not be the same for all patients. The cumulative probability of having a second primary melanoma is estimated at 0.99% at 1 year after initial diagnosis, 2.06% at 5 years, 3.17% at 10 years, and 5.34% at 20 years.[70] One study found that hazard rates for subsequent melanoma did not differ between stage I and stage II patients,[71] while another reported that subsequent melanomas were more likely in patients with MIS than those with invasive melanoma.[72] Overall risk is higher in patients with multiple primary melanomas and those with familial melanoma diagnosed with their first melanoma before 40 years of age.[73]

The NCCN guidelines recommend physical examination every 6 to 12 months for 5 years after the diagnosis of early-stage melanoma and then annually for life.[21] Higher frequency screening could perhaps be considered in younger patients or those with positive family history (Table III). Frequency of follow-up may also be tailored to perceived difficulty of examination. For example, patients with numerous atypical nevi being monitored by photography or digital dermoscopy may benefit from more frequent monitoring.[81] Patient adherence to skin self-examination may be equally important, because multiple studies have shown that approximately 50% to 60% of melanomas are detected by patients between office visits.[82,83] It follows that patients not routinely performing skin self-examination should be seen more often.

No imaging indications for stage 0, stage I or stage IIA disease

A CXR after the diagnosis of early-stage melanoma is inexpensive and provides a baseline for comparison should future CXRs be prompted by symptoms. However, studies of 1100 patients with stage I and II melanoma who had a CXR within 6 months of diagnosis revealed false-positive findings in 7% to 15% and pulmonary metastasis in only 1 patient.[84,85] Rates of false-positivity in such patients are even higher with CT scanning.[74] In patients with stage IB or IIA disease who were monitored by ultrasound of regional lymph node basins compared to those with only clinical follow-up, there was no difference in either progression pattern or survival.[75] In 1 study of 87 patients with stage IB disease seen every 6 months for 5 years followed by 1 annual visit, 10 patients had symptoms or physical findings leading to a negative workup, while there were 3 true recurrences with distant metastases that presented symptomatically between scheduled follow-up visits.[86] Taken together, these data suggest that routine imaging of patients with low-risk localized melanoma (stages 0-IIA) is not warranted, either at diagnosis or during follow-up (Table III).

Detection of recurrence in stage II disease

While magnetic resonance imaging is optimal for detection of brain metastases,[87] ultrasound is superior for detection of lymph node metastases, and positron emission tomography/CT is superior for detection of distant metastases.[88] Several studies have described the circumstances of recurrence in patients with stage II disease undergoing routine imaging surveillance. A substantial fraction (50-70%) of recurrences were symptomatic or detected by patients and relatively few (3-26%) were detected by imaging.[76-78,89,90] While several studies of stage II patients found higher rates of recurrence detected by imaging,[80,91] this did not appear to differ substantially by substage.[90,91] The highest yield for routine imaging in stage IIC patients is during the first 4 years after diagnosis, and physician examination is unlikely to detect relapses beyond 3 years for stage IIA and IIB and beyond 2 years for stage IIC patients.[77]

Imaging surveillance unlikely to improve survival in stage II patients

Does imaging detection improve survival in stage II patients? Several studies have failed to demonstrate a statistically significant difference in survival for patients who detected recurrence themselves compared with those whose recurrence was physician detected or detected on routine imaging.[78,79,89]

Indications for imaging tests for patients with stage II disease

For patients with stage IIB and IIC disease, NCCN guidelines recommend physical examination every 6 months, but no recommendations are given for routine imaging.[21] Because most recurrences manifest within the first 3 years,[21] routine imaging to screen for asymptomatic recurrence beyond 3 to 5 years is not recommended (Table III). Stage IIB and IIC patients may benefit from routine regional ultrasound in the first few years after diagnosis (Table III) given the prevalence of regional nodal recurrences in these substage groups, which carry recurrence risks similar to stage III patients.[77,90,91] This modality carries the advantage of low expense and no ionizing radiation and may be more sensitive than direct palpation or more costly radiation-intense CT scans.[92] Surveillance for stage IIC patients in the first few years after diagnosis may also include more intense surveillance if required for an adjuvant clinical trial (Table III).

Questions regarding the most appropriate frequency and methods of surveillance imaging for patients with early-stage melanoma are likely to remain unsettled given the improbability of developing a controlled prospective randomized trial for patients at each substage. It is important to recognize that essentially all of the surveillance imaging studies referenced above primarily involved patients whose recurrences occurred before the advent of targeted and immunotherapies. It is possible that future studies in patients with access to these therapies may show more substantial benefit from earlier detection of disease recurrence.

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