This report reflects the best data available at the time the report was prepared, but caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations set forth in this report.

# Guidelines of care for primary cutaneous melanoma

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## DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore these guidelines should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient.

## INTRODUCTION/METHODOLOGY†

A task force of recognized experts was convened to determine the audience for the guideline, define the scope of the guideline, and identify important issues in diagnosis and management. The task force employed an evidence-based model and performed a comprehensive literature search of English- language articles and articles with English-language abstracts. The literature was evaluated and rated on the basis of the strength of the evidence (Table I). The Delphi technique was used to arrive at consensus on the recommendations. Outstanding issues from this process were resolved at a teleconference meeting of the task force. The draft guideline was submitted to an extensive review process, in accordance with the Administrative Regulations for the Guidelines/Outcomes Committee of the American Academy of Dermatology (AAD). This process includes the opportunity for review and comment by the entire AAD membership, followed by final review and approval by the AAD Board of Directors.

†A technical report that provides a complete description of the methodology is available at our Web site, www.aad.org, or by request at reprint request address.

## SCOPE

This guideline addresses the management of those patients with a primary cutaneous melanoma lesion who do not have clinical or histologic evidence of regional or metastatic disease (Fig 1). These patients are frequently diagnosed, treated, and managed by dermatologists without referral to or consultation with specialists. The guideline does not address primary melanomas in less common sites, such as the nail unit and the mucous membranes. The value of sentinel lymph node biopsy is undetermined at this time, and the issue is not addressed in this guideline. For patients who have symptoms of regional or distant metastases, we refer physicians to guidelines for melanoma developed by the Australian Cancer Network and the National Comprehensive Cancer Network.

## DEFINITIONS

*Primary cutaneous melanoma* is defined as any primary melanoma lesion, regardless of tumor thickness, in patients without clinical or histologic evidence of regional or distant metastatic disease.

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**Table I.** Strength of recommendation and level of evidence

| Recommendations | Strength of recommendation* | Level of evidence† | Reference Nos. |
|---|---|---|---|
| Whenever possible, excise the lesion for diagnostic purposes using narrow margins. | Unanimous task force opinion and strong evidence (head and neck only) | L1 (head and neck only) | 3 (head and neck only) |
| Incisional biopsy does not adversely affect survival. An incisional biopsy technique is appropriate when the suspicion for melanoma is low, when the lesion is large, or when it is impractical to perform an excision. | Unanimous task force opinion and strong evidence | L1/2 | 1, 2 |
| Perform a repeat biopsy if the initial biopsy specimen is inadequate for accurate histologic diagnosis or staging. | Unanimous task force opinion | | |
| Fine needle aspiration cytology should not be used to assess the primary tumor. | Unanimous task force opinion | L3—that *can* be used for primary | 4 |
| Histologic interpretation should be performed by a physician experienced in the microscopic diagnosis of pigmented lesions. | Majority task force opinion | | |
| **Pathology report** (see text discussion for explanation) | | | |
| Include in the biopsy report: | | | |
| Patient's age and gender, and the anatomic site of the lesion | Unanimous task force opinion and conflicting evidence | L1/2 | 5-14 |
| Gross description of the specimen | Unanimous task force opinion | | |
| Microscopic description of the specimen (may be contained within a traditional microscopic description, a list format, an image format, or incorporated within the microscopic diagnosis) | Unanimous task force opinion | | |
| Diagnosis | Unanimous task force opinion | | |
| Tumor thickness in millimeters (Breslow's level) | Unanimous task force opinion and strong evidence | L1/2 | 5-17 |
| Ulceration | Unanimous task force opinion and strong evidence | L1 | 10, 13, 17 |
| Margin involvement for surgical excisions | Unanimous task force opinion | | |
| **Reporting of other histologic features is encouraged, but may not be related to prognosis. The following features may be considered optional, but encouraged** | | | |
| Clark's level | Unanimous task force opinion | L1/2 | 12, 15, 16 |

*Recommendations are based on the following: unanimous task force opinion supported by strong to moderate levels of evidence, majority task force opinion supported by strong to moderate levels of evidence, unanimous task force opinion supported by limited or weak scientific evidence, majority task force opinion supported by limited or weak scientific evidence, unanimous task force opinion only, and majority task force opinion only.

†The criteria for rating the level of evidence of a particular article is dependent on whether the study and/or the research question relates to diagnosis, prognosis, or treatment and prevention.

The rating criteria for studies on diagnosis are (1) it is a good diagnostic test, (2) there are good diagnostic criteria, (3) the test and criteria are reproducible, (4) there is proper patient selection, and (5) there are at least 50 cases and 50 controls.[43] Studies that meet at least 4 of these 5 criteria are rated level 1 (all 5 criteria) or level 2 (4 of the 5 criteria) and are considered strong evidence. Studies that meet 3 of the 5 criteria are rated level 3 and are considered moderate evidence. Studies that meet fewer than 3 criteria are rated level 4 (2 criteria) or level 5 (one criterion) and are considered limited or weak evidence.

The rating criteria for studies on prognosis are as follows: (1) it is a cohort study, (2) with good inclusion/exclusion criteria, (3) with follow-up of at least 80% of the cohort, (4) with adjustment for confounders, and (5) with reproducible outcome measures.[43] Cohort studies that meet all of the remaining 4 remaining criteria are rated level 1, and cohort studies that meet any 3 of the remaining 4 criteria are rated level 2. Level 1 and level 2 ratings are considered strong evidence. Level 3 ratings (cohort studies that meet any 2 of the remaining 4 criteria) and level 4 ratings (cohort studies that meet any one of the remaining 4 criteria) are considered moderate evidence. A study is rated level 5 if it is a cohort study that does not meet any of the remaining 4 criteria. Level 5 is considered limited or weak evidence. Level 6 ratings are given when there is no cohort study, for example, case reports or case series. Level 6 is considered weak evidence.

Studies on treatment and prevention are rated level 1 if there are several randomized controlled trials (RCTs) that demonstrate a significant difference, level 2 if there is an RCT that demonstrates a significant difference, and level 3 if there is an RCT showing some difference.[44] Levels 1, 2, and 3 are considered strong evidence. A nonrandomized controlled trial or subgroup analysis of an RCT is rated level 4 and a comparison study with some kind of control/comparison is rated level 5.[44] Levels 4 and 5 are considered moderate evidence. Case series without controls are rated level 6, and case reports with fewer than 10 patients are rated level 7.[44] Levels 6 and 7 are considered limited or weak evidence.

**Table I.** Cont'd

| Recommendations | Strength of recommendation* | Level of evidence† | Reference Nos. |
|---|---|---|---|
| Growth phase | Unanimous task force opinion | L2 | 5, 11, 15 |
| Tumor infiltrating lymphocytes | Unanimous task force opinion | L1/2 | 5, 8, 11 |
| Mitotic rate | Unanimous task force opinion | L1/2 | 5, 7, 11 |
| Regression | Unanimous task force opinion | L1/2 | 5, 11, 12 |
| Angiolymphatic invasion, microsatellitosis, neurotropism, histologic subtype | Unanimous task force opinion | | |
| **Clinical surgical margins based on tumor thickness and histologic confirmation that margins are tumor free** (see text for rationale) | | | |
| In situ, 0.5 cm | Unanimous task force opinion | L6 | 28 |
| <2 mm, 1 cm | Majority task force opinion and strong evidence | L2 | 20-22, 24 |
| ≥2 mm, 2 cm | Majority task force opinion and strong evidence | L1/2 | 23, 25-27 |
| **Diagnostic work-up of asymptomatic patients and on-going follow-up** | | | |
| Routine laboratory tests and imaging studies are not required in asymptomatic patients with primary cutaneous melanoma ≤4 mm for initial staging or routine follow-up. Indications for such studies are directed by a thorough medical history and thorough physical examination. Chest x-ray and LDH are optional. | Unanimous task force opinion and strong evidence | L1/2 | 29-36, 42 |
| Patient education on self-examination of the skin and lymph nodes is recommended. | Unanimous task force opinion and moderate evidence | L3 | 38 |
| Routine interval follow-up physical examinations are recommended at least annually. | Unanimous task force opinion and strong/moderate evidence | L1/2 | 34-37, 40, 41 |
| Results of routine interval history and physical examination should direct the need for laboratory tests and imaging studies. | Unanimous task force opinion | L3 | 39 |

*Excision* is defined as complete removal of the lesion.

*Incisional biopsy* is defined as partial removal of the lesion for diagnostic purposes.

## ISSUES

The task force identified the following as issues of primary importance in the management of primary cutaneous melanoma: the preferred biopsy technique for histologic evaluation, the information provided in the biopsy report for therapeutic and prognostic importance, the effect of the size of surgical margins on recurrence and survival, the value of diagnostic tests for initial staging of asymptomatic patients, and the value of routine interval follow-up and diagnostic tests for asymptomatic patients.

### Biopsy technique and histologic evaluation

#### Recommendations

1. Whenever possible, excise the lesion with narrow margins for diagnostic purposes.
2. An incisional biopsy technique is appropriate when the suspicion for melanoma is low, when the lesion is large, or when it is impractical to perform an excision.
3. Perform a repeat biopsy if the initial biopsy specimen is inadequate for accurate histologic diagnosis or staging.
4. Fine needle aspiration cytology should not be used to assess the primary tumor.
5. Histologic interpretation should be performed by a physician experienced in the microscopic diagnosis of pigmented lesions.

#### Discussion

Melanoma may be difficult to diagnose accurately on a clinical basis alone, and patients presenting with a lesion that is clinically suspect for melanoma should undergo a biopsy. Although there is strong evidence that an incisional biopsy does not adversely affect survival,[1,2] the task force recommends excision of the lesion with narrow margins, while ensur-

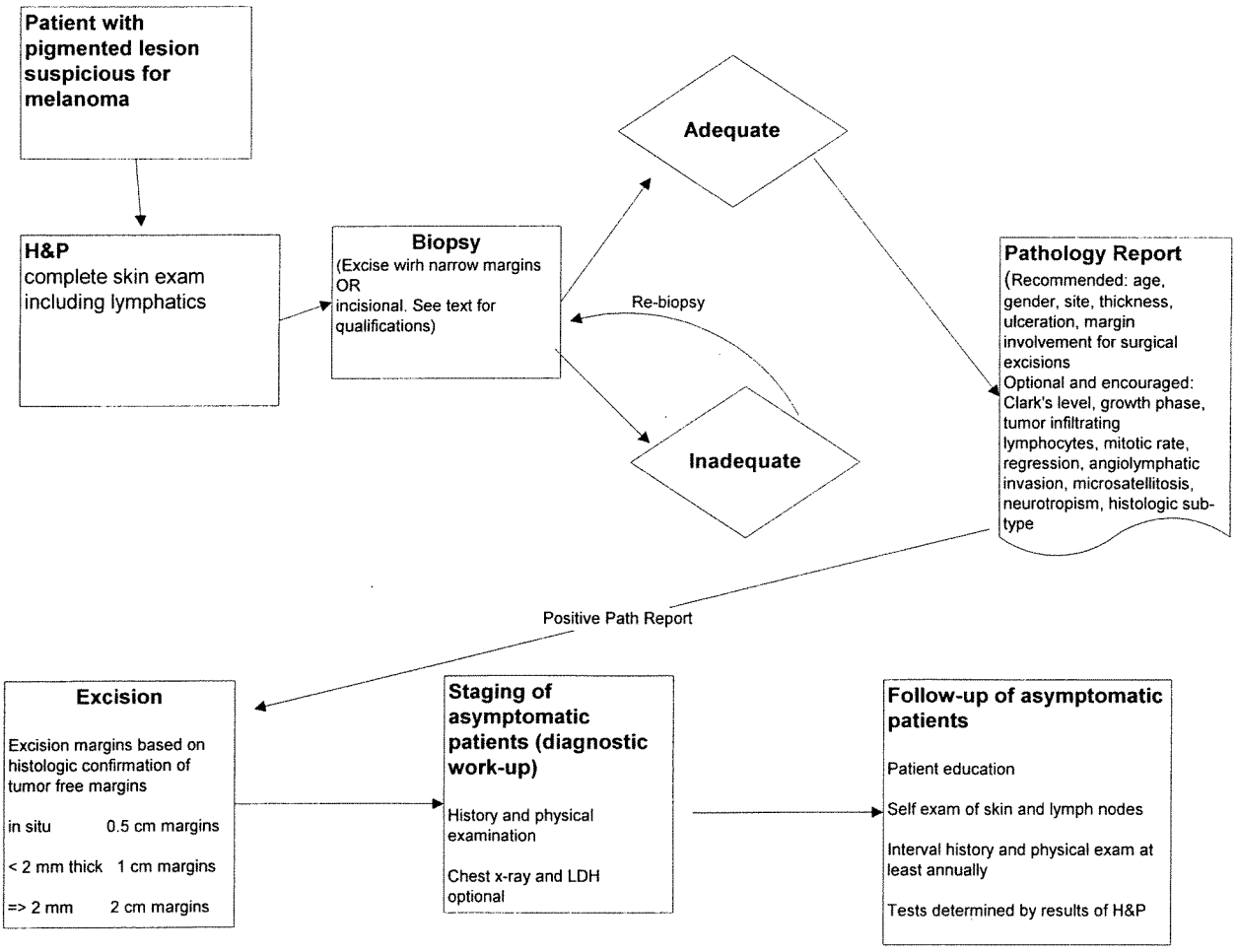


**Fig 1.** Algorithm of recommendations for the diagnosis, treatment, and management of primary cutaneous melanoma.

ing that the specimen is adequate for histologic evaluation.[3] There may be situations in which the clinical suspicion for melanoma is low, the lesion is too large, or when it is impractical to perform an excision (eg, of the nail unit). In these situations an incisional biopsy is appropriate so long as the sample is representative of the entire process. If, on histologic evaluation, the specimen is believed to be inadequate for accurate histologic diagnosis or staging, a repeat biopsy would be appropriate. Fine needle aspiration cytology should not be used to assess the primary tumor.[4]

Because melanoma can be difficult to diagnose both clinically and histopathologically, the task force recommends that the biopsy be interpreted by a physician experienced in the microscopic diagnosis of pigmented lesions.

## Pathology report

### Recommendations

1. Include in the biopsy report:
   a. Patient's age
   b. Gender
   c. Anatomic site of the lesion
   d. Gross and microscopic description of the specimen (see discussion for explanation)
   e. Diagnosis
   f. Tumor thickness in millimeters (Breslow's level)
   g. Ulceration (see discussion for explanation)
   h. Margin involvement for surgical excisions (see discussion for explanation)
2. Reporting of the following histologic features is encouraged, but optional: Clark's level, growth phase, tumor infiltrating lymphocytes, mitotic

rate, regression, angiolymphatic invasion, microsatellitosis, neurotropism, and histologic subtype. (See discussion for explanation.)

**Discussion**

There is conflicting evidence on the value of age, gender, and anatomic site for prognostic purposes.[5-14] The task force recommends including these factors in the pathology report for identification purposes. A gross description is used to record the details of the material received. The information usually contained within a microscopic description may be contained within a traditional microscopic description, a list format or an image format, or incorporated within the microscopic diagnosis. There is strong evidence of the value of reporting Breslow thickness[5-17] and ulceration in lesions in which the dermis is involved[10,13,17] for prognostic purposes. The task force recommends inclusion of these elements in the biopsy report. In the pathology report, the task force also recommends inclusion of the presence or absence of margin involvement by the tumor in surgical excisions as an indication of the completeness of the tumor that was available for histologic evaluation and as a guide to additional therapy.

There is strong evidence that Clark's level,[12,15,16] growth phase,[5,11,15] tumor-infiltrating lymphocytes,[5,8,11] mitotic rate,[5,7,11] and regression[5,11,12] have prognostic value. However, the task force questions the consistency in the application of these measurements and in the definition of these attributes among pathologists. Accordingly, the task force recommends these attributes as optional elements in the biopsy report. Optional elements may be useful to gain further evidence and to better understand the disease process.

Although there is evidence that the presence of satellite and other types of melanoma metastases is associated with a poor prognosis, there is no compelling evidence on the prognostic value of reporting angiolymphatic invasion, microsatellitosis, neurotropism, and histologic subtype. The task force recommends these attributes as optional elements in the biopsy report. Optional elements may be useful to gain further evidence and to better understand the disease process.

One high-quality study reported absence of inflammatory response and tumor thickness plus tumor regression as independent predictors of progression in tumors 1.5 mm or less in thickness.[18] Another high-quality study reported the type of invasive front as an independent prognosticator for melanomas more than 3 mm in thickness.[17] The task force has no recommendation on the significance of these factors in the prognosis of thin and thick melanomas, pending confirmation by other researchers.

**Surgical management (margins)**

**Recommendations (see discussion for rationale)**

| Tumor thickness | Clinical excision margins* (cm) |
|---|---|
| In situ | 0.5 |
| <2 mm | 1 |
| ≥2 mm | 2 |

*Based on histologic confirmation of tumor-free margins.

**Discussion**

Individual melanoma cells have the capacity to locally migrate away from the tumor origin. Melanoma may extend wider or deeper than is visible to the eye. Therefore the task force recommends that a margin of clinically normal-appearing skin be removed around the tumor site to ensure complete removal of the tumor. The goal of surgery for melanoma of any thickness is to assure complete excision confirmed by histologically negative margins.

Mohs surgery has been advocated for the treatment of primary cutaneous melanoma.[19] Mohs surgery may prove useful for excision of melanoma, especially those located on the head, neck, hands, and feet. The task force has no recommendation on Mohs surgery for the treatment of melanoma pending additional studies.

There are several high-quality trials that provide information regarding the effect of excision margins of melanomas on recurrence and survival. One long-term follow-up study showed no statistically significant difference in survival or recurrence with excision margins of 2 cm versus 5 cm for lesions that are between 0.8 mm and 2 mm or less in thickness.[20] Two studies showed no statistically significant difference in survival or recurrence with 10-mm margins[21] or with 1- versus 3-cm margins[22] for lesions 2 mm or less in thickness. In these studies the anatomic location of the lesions was limited to the trunk and proximal extremities,[20] had a majority of lesions on the trunk and extremities,[21] or did not identify the anatomic location.[22]

A trial of lesions on the trunk and extremities 1 to 4 mm thick with excision margins of 2 versus 4 cm showed no statistically significant effect of surgical margin on disease-free and overall survival.[23] One study of stage I melanomas originating on the face showed no statistically significant difference in survival or recurrence among patients having excision margins of less than 1 cm, 1 to 2 cm, or more than 2 cm.[24]

**Table II.** Review of systems for visceral melanoma metastases

| | |
|---|---|
| *Constitutional* | *Neurologic* cont'd |
| Weight loss | Balance problems |
| Malaise | Blackouts |
| Decreased appetite | Numbness |
| Weakness | Local weakness |
| Fatigue | Paralysis |
| Fever | Mood swings |
| *Respiratory* | *Musculoskeletal* |
| Cough | Bone pain (eg, rib, spine, hip) |
| Hemoptysis | *Gastrointestinal* |
| Pneumonia | Cramping |
| Pleurisy | Abdominal pain |
| Chest pain | Bleeding |
| Dyspnea | Nausea |
| *Hepatic* | Anorexia |
| Abdominal pain | Vomiting |
| Jaundice | Constipation |
| *Neurologic* | *Skin/lymphatics* |
| Headache | Color change |
| Memory disturbance | "Swollen glands" |
| Depression | Nonhealing/bleeding skin lesion(s) |
| Focal central nervous system symptoms | Lumps |
| Visual disturbances | New pigmented skin lesion(s) |
| Seizures | Easy bruising |

Adapted from Johnson TM, Chang A, Redman B, Rees R, Bradford C, Riba M, et al. Management of melanoma with a multidisciplinary melanoma clinic model. J Am Acad Dermatol 2000;42:820-6.

Two trials involved patients with lesions in categories ranging from 0.75 mm or less in thickness to a few lesions more than 4 mm thick (5%-6% of the study populations) and resection margins in categories ranging from 1 mm to more than 20 mm.[25,26] The extent of surgical excision had no statistically significant effect on survival or recurrence. One study of patients with lesions thicker than 4 mm showed that surgical margins of 2 cm or less versus more than 2 cm had no statistically significant effect on survival or recurrence.[27]

There are no prospective controlled trials for excision margins for in situ melanomas. For in situ tumors, 5 mm has been recommended by others.[28] Clearly an in situ melanoma may extend widely beyond its visible margin. On the basis of case series, one author advocates wider margins for larger in situ tumors, noting that histologically melanoma cells may have wider clinical extensions around large-diameter tumors than around smaller tumors.[19] Thus it is possible that margins of re-excision for an in situ tumor should be based on primary tumor diameter. The task force emphasizes the importance of careful histologic examination of surgical margins. However, there are no prospective controlled trials evaluating this concept of larger margins for in situ tumors with larger surface dimension. Thus in light of the evidence based on the available data that wider margins are not correlated with improvement in survival, the most important concept is that complete surgical removal of the entire neoplasm be accomplished with histologic verification of removal.

Factors to consider when determining the re-excision margin:

- Is there any evidence of metastatic disease?
- Given tumor location, what is the risk of disfigurement compared with the potential melanoma recurrence for a given margin of skin?
- Where are the melanoma cells? Excising to fascia may not be necessary for melanoma tumors confined to the upper levels of the skin, while wider cutaneous margins may be appropriate for large in situ tumors.

## Initial diagnostic work-up and on-going follow-up

### Recommendations

1. Routine laboratory tests and imaging studies are not required in asymptomatic patients with primary cutaneous melanoma 4 mm or less in thickness for initial staging or routine follow-up. Indications for such studies are directed by a thorough medical history and thorough physical examination.
2. Patient education on self-examination of the skin and lymph nodes is recommended.

3. Routine interval follow-up physical examinations are recommended at least annually.
4. The results of routine interval history and physical examination should direct the need for laboratory tests and imaging studies.

## Discussion

***Work-up.*** There is strong evidence that routine imaging studies including chest x-ray and blood work have limited, if any, value in the initial work-up of asymptomatic patients with primary cutaneous melanoma 4 mm or less in thickness.[29-33] The task force recommends that the indications for initial imaging studies and blood work are most appropriately directed based on findings from a thorough medical history and thorough physical examination. (Table II).

Some studies have suggested that chest x-ray and serum lactate dehydrogenase (LDH) may be helpful in detecting occult metastases and may alter clinical management.[30,32] However, in a study involving more than 800 asymptomatic patients with localized melanomas initially examined with chest x-ray, unsuspected metastasis was demonstrated in only 1 patient.[29] The false-positive rate was approximately 15% and led to costly and unnecessary investigations that may have contributed to an increase in patient anxiety. On the other hand, negative results may alleviate patient anxiety. Recognizing that initial imaging studies and/or LDH are very insensitive and nonspecific means of detecting clinically occult distant disease, as well as the psychologic impact that the initial diagnosis of melanoma may have on some patients, the task force recommends that these tests be optional for asymptomatic patients with melanoma 4 mm or less in thickness.

***Follow-up.*** The goal of follow-up of patients with melanoma is to reduce morbidity and mortality through the detection of asymptomatic metastases and additional primary melanomas. There is no evidence to support a specific follow-up interval, but the task force recommends follow-up 1 to 4 times per year, depending on the thickness of the lesion and other risk factors, for 2 years after diagnosis and one to two times per year thereafter. Factors that may be considered in instituting the frequency and content of a follow-up protocol for an individual patient include (1) tumor thickness, (2) patient with multiple melanomas, (3) presence of clinically atypical nevi, (4) family history of melanoma, (5) patient anxiety, and (6) patient awareness/ability to recognize signs and symptoms of disease.

Follow-up interventions may include patient education, patient self-examination of the skin and the lymph nodes, physician interval examination, and laboratory/radiologic examination.

There is strong evidence that the majority of metastases and recurrences are discovered by the patient or a family member.[34-37] A single retrospective study provides moderate evidence that skin self-examination may result in the earlier detection of primary cutaneous melanoma in a still surgically curable stage.[38] Accordingly, the task force recommends educating patients with melanoma to perform self-examination of the skin and lymph nodes and to bring new or changing skin lesions and unusual constitutional symptoms to medical attention.

Melanoma metastases, local recurrences, and second primary melanomas have been detected by physicians at routine interval examinations.[34-37,39] Accordingly, the task force recommends routine interval examinations with a thorough history and thorough physical examination, as outlined in Table II. No direct data are available to assess the impact of the frequency of interval follow-up examination on outcome.[39-41] Recommendations are predicated on the association of the thickness of the primary tumor with the probability of metastases and the observation that the majority of metastases manifest in the first few years after diagnosis. Patients also typically require the most psychologic support in the initial follow-up period.

As in the case of initial work-up, imaging studies and blood work during follow-up are most appropriately directed based on findings from a thorough medical history and thorough physical examination. There is strong evidence that routine imaging studies including chest x-ray and blood work have limited, if any, value in the follow-up of asymptomatic patients.[34-36,42] On the rare occasions that laboratory and imaging studies do find asymptomatic metastases, it is hard to evaluate the impact of therapy on outcome.

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