6 Clinical Presentation and Staging of Melanoma

WILLIAM H. WARD[1] • FERNANDO LAMBRETON[1] • NEHA GOEL[1] • JIAN Q. YU[2] • JEFFREY M. FARMA[1]

[1]Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA; [2]Department of Diagnostic Imaging, Fox Chase Cancer Center, Philadelphia, PA, USA

Author for correspondence: William H. Ward, Department of Surgical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA; Email: william.ward@fccc.edu

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Abstract: Cutaneous melanoma is responsible for the vast majority of skin cancer-related deaths in the United States. Known risk factors include genetic defects, environmental exposures, and a combination of both. Among environmental risks, exposure to ultraviolet rays is the most important and the most modifiable risk factor. Several genetic syndromes involve increased risk of melanoma, including xeroderma pigmentosum, familial atypical multiple moles and melanoma syndrome, BRCA2 mutation, and congenital melanocytic nevi. Although the necessity of implementation remains controversial, the most effective melanoma screening technique is the whole-body skin examination. Typically, melanoma lesions are incidentally discovered during routine skin examination using the "ABCDE" mnemonic. Once suspected, questions pertaining to the sites of potential metastasis should be asked and excisional or partial biopsy should be considered. The primary histologic subtypes of melanoma include superficial spreading, lentigo maligna, nodular, acral lentiginous, desmoplastic, and amelanotic. Melanoma staging is completed via clinical and histologic assessment using the American Joint Committee on Cancer TNM system. Delayed or deficient elements of initial melanoma evaluation can limit patient outcomes and increase

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disease-related mortality. Clinicians involved in the diagnosis or treatment of cutaneous melanoma must be familiar with the available screening options, key steps of diagnosis, and the staging ramifications of disease discovery.

Key words: ABCDE system; Clinical presentation; Diagnostic strategies; Melanoma; Staging

Introduction

Despite the important progress seen in the treatment of oncologic diseases over the past few decades, the incidence and mortality associated with malignant melanoma continues to increase (1). Among the most common malignancies in the United States, the incidence of melanoma currently ranks fifth overall when compared to other common cancers (2). As a result of its aggressive behavior and diagnostic challenges, it is responsible for the vast majority of skin cancer-related deaths. This chapter will focus on appropriate screening considerations for melanoma, clinical approaches to diagnosis and confirmation, and updated staging guidelines to facilitate subsequent therapy (1).

Screening Considerations

ETIOLOGY OF DISEASE DEVELOPMENT

Cutaneous melanoma evolves from aberrant melanocytes located within the basal layer of the epidermis. These melanocytes are responsible for the production of melanin, a substance which absorbs potentially harmful ultraviolet (UV) radiation. Left unchecked, UV radiation affects integumentary cells by causing direct damage to individual DNA strands. Although UV-induced DNA damage is normally repaired by specific DNA repair mechanisms, genetic or environmentally derived errors within this repair complex can lead to the formation of an invasive melanoma (3, 4).

GENERAL RISK FACTORS

Like most other neoplastic conditions, known risk factors of melanoma include genetic defects, environmental exposure, and a combination of both (5). Although multiple genetic syndromes incur a significantly increased risk for the development of cutaneous malignancy (discussed later), inherited phenotypic traits associated with melanoma include fair skin, light hair, red hair, freckles, and light eye color. Unsurprisingly, a positive family history is a strong risk factor for the evolution of this disease. As the number of first-degree relatives with melanoma increases, so does the risk of developing the disease (6). Patients with one first-degree relative with melanoma are 1.7 times more likely to be diagnosed with melanoma, whereas two first-degree relatives incur a nine-fold increase in risk. In addition, as patients with a positive family history grow older, the cumulative risk of melanoma also increases (7).

Regarding environmental risks, UV exposure is the most important and the most potentially modifiable risk factor contributing to the development of melanoma. Compared with those with chronic and continuous exposure, patients with intermittent, more intense exposure to the sun are at much higher risk (4). A history of sunburns, specifically blistering sunburns in childhood and adulthood, can be associated with approximately twice the baseline risk of melanoma development (5). Significant UV radiation exposure before the age of 35 significantly increases the risk of melanoma (7). Although UV-A sunlight has certainly been implicated as a cause of melanoma (e.g., tanning salon-related UV radiation), most skin damage is actually caused by UV-B rays (4).

Chronic immunosuppression represents another exposure-related risk factor for melanoma development. Such immunosuppression may be the result of an existing neoplastic condition. For example, approximately 5% of patients with a personal history of melanoma will be diagnosed with a second melanoma (6). In addition, patients with a personal history of nonmelanoma skin cancer have more than a fourfold relative risk of developing melanoma. Other causes of chronic immunosuppression may result from pharmaceutical agents used in the treatment of AIDS, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, or patients with organ transplantation (7).

POPULATIONS AT INCREASED RISK

As discussed previously, several genetic syndromes involve a significantly increased risk of melanoma development. These conditions include xeroderma pigmentosum (XP), familial atypical multiple moles and melanoma (FAMMM) syndrome, BRCA2 mutation, and congenital melanocytic nevi (7, 8). XP, an autosomal recessive condition in which UV-related DNA repair mechanisms are deficient, carries an approximately 1000-fold increase in the risk of melanoma. Sun avoidance and regular self-skin examinations are mandatory, as is frequent surveillance by a dermatologist with extensive XP experience (6, 7).

FAMMM syndrome, also known as the B-K mole syndrome, is caused by germline mutations in CDKN2A (6). An autosomal dominant condition, FAMMM syndrome has incomplete penetrance. Diagnosis is determined through family history and is confirmed when at least two first-degree relatives have both melanoma and multiple dysplastic nevi. Interestingly, overall survival is similar to that of sporadic melanoma (7). Families with a suspected diagnosis of FAMMM should undergo frequent skin examinations and should complete a genetics consultation to evaluate for CDKN2A mutation. As CDKN2A mutations are also associated with pancreatic cancer, extensive documentation of the family history is mandatory in these patients, and screening for other associated malignancies should occur (6).

More widely associated with inherited breast and ovarian carcinomas, a BRCA2 mutation nearly triples the risk of cutaneous melanoma development. A tumor suppressor gene, mutations in BRCA2 also degrade cellular DNA repair mechanisms. As BRCA2 mutations can also lead to prostate and pancreatic cancers, potential patients should similarly undergo genetics or risk assessment evaluations following the documentation of a thorough family history (8).

The presence of congenital melanocytic nevi also increases the risk of melanoma development, with larger lesions having the highest risk. These lesions can

be either followed closely or removed prophylactically. Since melanomas that occur within congenital melanocytic nevi usually develop before the age of 10, prophylactic removal of these lesions should be considered early in life (7).

SCREENING RECOMMENDATIONS

The most effective melanoma screening technique is the whole-body skin examination (WBE). WBE involves a review of the entire cutaneous surface of a disrobed patient by the treating provider. Despite the proven efficacy of this approach, completion of this screening technique is less common than preventative screening modalities used in the early detection of other malignancies. The implementation of the WBE as an annual melanoma screening tool in the United States has been controversial (1, 9). Although many within the dermatology and oncology communities have called for the institution of routine melanoma screening recommendations, the United States Preventative Service Task Force (USPSTF) stopped short of endorsing annual screening WBEs as an effective prevention measure in 2016 due to insufficient evidence. Because of the paucity of data examining potential screening-related harms or program feasibility concerns in the United States, the USPSTF limited its support for WBE as a recommended intervention for patients at particularly high risk of cutaneous malignancy (10).

Despite the recommendations issued by the USPSTF, evidence does exist which supports the concept of widespread screening to facilitate early melanoma detection and decreased mortality (11). One of the most cited study examining the feasibility and efficacy of a population-based melanoma screening program is the SCREEN project in Northern Germany. Begun in 2003, this program involved the screening of over 360,000 patients by physicians of various specialties who had completed an 8 h WBE training course. The SCREEN project resulted in a 30% increase of melanoma detection within the study population and an approximately 50% decrease in melanoma-related mortality compared with the rest of Germany (12). Another study with similar findings was performed in Australia in 2008. This case-control study demonstrated a 38% increase in the probability of a thin melanoma (<0.75 mm) being identified and that pre-diagnosis WBE screening leads to a 14% risk reduction of thick melanoma (>0.75 mm) diagnosis (5).

Although broad consensus is lacking regarding routine melanoma screening in the United States, many dermatologists, oncologists, and primary care providers have incorporated annual WBEs into their practices and institutional preventative care programs. In addition, there is uniform agreement that patients at increased risk of melanoma should absolutely undergo yearly WBE, ideally at the hands of a dermatologist. Such patients include those with albinism, XP, a family history of melanoma, a personal history of skin cancer and individuals on chronic immunosuppressive medications (7).

Clinical Diagnosis

PATIENT HISTORY

Typically, melanoma lesions are incidentally discovered during routine skin examination (5). Occasionally, patients may be alerted to the presence of a concerning

TABLE 1 Fitzpatrick Classification of Skin Types I through VI

Type I	Type II	Type III	Type IV	Type V	Type VI
White skin. Always burns, never tans.	Fair skin. Always burns, tans with difficulty.	Average skin color. Sometimes mild burn, tan about average.	Light-brown skin. Rarely burns. Tans easily.	Brown skin. Never burns. Tans very easily.	Black skin. Heavily pigmented. Never burns, tans very easily.

nodule by persistent itching, bleeding, or crusting of a pigmented lesion. Unfortunately, most melanomas are asymptomatic and may only cause the aforementioned symptoms of local inflammation after growth progression has occurred (7). Once the diagnosis is suspected, questions pertaining to sites of potential metastasis should be included in the history. Potential indicators of metastatic spread may include seizures, headaches, vision changes, coughing, hemoptysis, shortness of breath, dyspnea, changes in bowel habits, new-onset back pain, or any systemic symptoms (fevers, chills, night sweats, weight loss, etc.). Other concerning items within a patient's history that should alert the examining physician include a past medical history of cutaneous malignancy, chronic sun exposure, history of blistering sun burns, use of tanning salons, family history of melanoma, pancreatic cancer, other familial syndromes, or a procedural history of prior skin biopsies. Finally, it should be noted that patients with fair skin (Fitzpatrick type I) are at increased risk of melanoma compared with those with darker skin (Fitzpatrick type VI) (Table 1) (13–15).

PHYSICAL EXAMINATION FINDINGS

During a clinical examination, any pigmented lesion with features contained within the "ABCDE" mnemonic should be considered suspicious for melanoma (Figure 1). Developed for both physicians and patients to recognize characteristics often associated with melanoma, the ABCDE system includes **A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter larger than 6 mm, and **E**volution or timing of the lesion's growth. Should such a lesion be identified, the surrounding area should be assessed for possible satellite lesions or in-transit metastatic foci (7). Once a concerning lesion is thoroughly assessed, the remaining cutaneous surfaces (i.e., scalp, perineum, interdigital space, genitalia, and subungual regions) should be closely inspected for the presence of any additional lesions of suspicion. All lesions with a benign appearance should be documented and all lymph node basins should be palpated for lymphadenopathy (14).

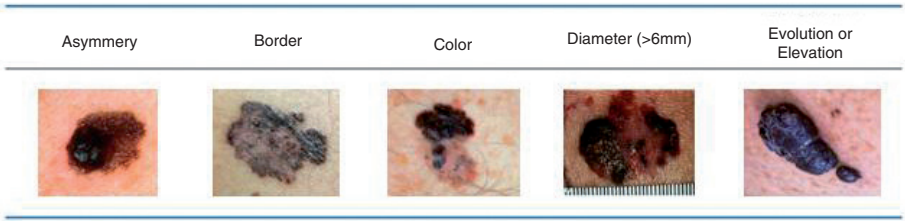

Figure 1 **ABCDE System for Diagnosis of Melanoma.**

Diagnostic Strategies

Once a suspicious lesion is assessed and properly documented, biopsy and histologic review should be considered. Sampling of the lesion in question can be performed through several methods, including excisional biopsy and partial biopsy. As previously discussed, vertical depth of invasion is among the most important prognostic factors in melanoma diagnosis. Thus, excisional biopsy of the entire specimen with narrow margins is the most effective way to facilitate proper diagnosis and treatment planning. This approach is supported by the American Academy of Dermatology and has long been preferred as the biopsy technique of choice by surgical oncologists involved in the definitive treatment of this disease process.

Alternatively, partial biopsy may be performed and is typically completed via a punch or shave technique. A punch biopsy, if properly positioned, may be advantageous since the provision of a full-thickness sample is possible (14). However, this technique often requires suture-based closure, which lengthens the encounter. Despite its frequent use among dermatologists and primary care physicians, partial biopsy performed via the shave technique has previously raised doubts regarding staging accuracy and histologic interpretation due to its ability to transect a segment of the lesion in question. Despite historical resistance, a properly performed shave biopsy is easy to execute, typically does not require cutaneous suturing, and can be quickly completed in a busy outpatient setting (14, 16). A recently published, multi-institutional, retrospective study of 600 patients challenged decades of surgical dogma. This study demonstrates that partial biopsy for melanoma does not adversely affect disease-free survival or overall survival and rarely results in the need for repeat biopsy. The authors conclude that partial biopsy is safe and should be performed by primary care providers and specialists alike. Therefore, it is reasonable to complete either excisional or partial biopsy when concerning lesions are encountered (16).

HISTOLOGIC CONFIRMATION

Diagnostic confirmation involves routine histologic analysis by the receiving pathology department (14). Microscopic findings including cytologic atypia, amplified cellularity, and the number of dermal mitotic figures should be noted in

an effort to distinguish benign disease from malignant melanoma. Established guidelines recommend the formal reporting of Breslow thickness (mm), histologic subtype; dermal mitotic rate; peripheral margin status; deep margin status; and the presence or absence of histologic ulceration, microsatellitosis, tumor infiltrating lymphocytes, cellular regression, angiolymphatic invasion, vertical growth phase, neurotropism, and pure desmoplasia. In addition, Clark's levels of anatomic staging should be reported for lesions <1 mm in thickness. By combining the reported histologic features with a patient's gross clinical findings, the proper diagnosis can be achieved and ambiguity avoided (13).

DISEASE TYPES AND PROGNOSTIC FACTORS

The primary histologic subtypes of melanoma include superficial spreading, lentigo maligna, nodular, acral lentiginous, desmoplastic, and amelanotic (Table 2) (17). *In situ* melanoma is considered Stage 0 and occurs when tumor cells are microscopically identified but have not penetrated the epidermis (18). Comprising approximately 70% of confirmed melanomas, the superficial spreading subtype is the most common type and arises from an existing nevus. The lentigo maligna subtype is less common, typically demonstrates slow progression, and frequently appears in sun-exposed areas (face, head, etc.). Nodular melanomas are characterized by the absence of a radial growth phase, variable presentation, and robust vertical invasion. Acral lentiginous melanomas have a higher incidence in patients with darker skin pigmentation and frequently occur on the palms, soles, and subungual spaces. Desmoplastic melanomas are uncommon lesions that are typically seen in elderly patients and feature limited spindle or atypical cells. Possibly the most challenging subtype in terms of diagnosis, amelanotic melanomas have a characteristic absence of pigmentation and are considered rare (14).

TABLE 2 Melanoma Subtypes

Subtype	Frequency	Characteristic
Superficial spreading	70%	Arises from existing nevus.
Nodular	5%	Absence of a radial growth phase, variable presentation, and robust vertical invasion.
Lentigo Maligna	4–15%	Typically demonstrates slow progression, and frequently appears in sun-exposed areas (i.e., face, head, etc.)
Acral lentiginous	5%	Has higher incidence in patients with darker skin pigmentation and frequently occur on the palms, soles, and subungual spaces.
Amelanotic	4%	Characteristic absence of pigmentation and are considered rare.
Desmoplastic	Less than 4%	Rare melanoma seen in older adults that is characterized by scant spindle cells and minimal cellular atypia.

Melanoma Staging

Initially, the proper staging of melanoma is the result of clinical assessment and histologic confirmation. The American Joint Committee on Cancer TNM system is used with resultant clinical and pathologic staging assignment (Table 3) (18). Once the index lesion has been histologically confirmed as melanoma, additional characteristics that contribute to the T (tumor) stage include overall tumor thickness, presence of ulceration, and the presence of mitosis in lesions <1 mm in thickness (T1)(14, 19).

N (nodal) stage is determined by the number of involved lymph nodes. As previously discussed, nodal status should be initially assessed at the time of preoperative clinical examination. If palpable lymphadenopathy is encountered, nodal status should be confirmed via ultrasound-guided fine needle aspiration. If no clinical evidence of nodal involvement is present preoperatively, sentinel lymph node biopsy (SLB) should be performed at the time of surgery for all

TABLE 3 Melanoma Staging

Stage	Classification	5-year survival
Stage 0	Tis: Melanoma *in situ*	>98%
Stage I (A/B)	T1a: <0.8 mm and nonulcerated T1b: ≥0.8 mm or <0.8 mm with ulceration T2a: >1.0–2.0 mm without ulceration	97–92%
Stage II (A, B, C)	T2b: >1.0–2.0 mm with ulceration T3a: >2.0–4.0 mm without ulceration T3b: >2.0–4.0 mm with ulceration T4a: >4.0 mm without ulceration T4b: >4.0 mm with ulceration	81–53%
Stage III (A, B, C, D)	N1a: 1 clinically occult (in SLN biopsy) N1b: 1 clinically detected N1c: Presence of in-transit, satellite, and/or microsatellite mets N2a: 2–3 clinically occult (in SLN biopsy) N2b: 2–3, at least 1 clinically detected N2c: 1 clinically occult or detected, with in-transit, satellite, and/or microsatellite mets N3a: 4 or more clinically occult (in SLN biopsy) N3b: 4 or more, at least 1 of which clinically detected, or presence of any number of matted nodes N3c: 2 or more clinically occult or clinically detected with in-transit, satellite, and/or microsatellite mets	78–40%

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TABLE 3 Melanoma Staging

Stage	Classification	5-year survival
Stage IV	M1a: Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph nodes. LDH not recorded or unspecified M1a(0): LDH not elevated M1a(1): LDH elevated M1b: Distant metastasis to lung with or without M1a sites of disease. LDH not recorded or unspecified M1b(0): LDH not elevated M1b(1): LDH elevated M1c: Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease. LDH not recorded or unspecified M1c(0): LDH not elevated M1c(1): LDH elevated M1d: Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease. LDH not recorded or unspecified M1d(0): LDH not elevated M1d(1) LDH elevated	20–15%

Adapted from Gershenwald JE et al. AJCC cancer staging manual. 8th ed. Amin MB, editors. Chicago, IL: American Joint Committee on Cancer; 2017. p. 563.

lesions >1 mm in thickness. In addition, SLB should be considered for lesions between 0.76 and 1.0 mm thickness when high-risk features are present (lymphovascular invasion, high mitotic count, ulceration, etc.). Current guidelines do not recommend SLB for lesions ≤0.75 mm thick (20).

M (metastatic) stage is assigned based on the presence or absence of metastatic disease and, if present, is further classified by the location (skin, lymph nodes, viscera, lungs, or increased serum lactate dehydrogenase). Melanoma without nodal or distant metastases is classified as Stage I or Stage II, depending on the depth of vertical invasion. Stage III disease includes patients with either gross or microscopic lymph node metastasis and Stage IV disease includes patients with evidence of distant metastasis (13, 14, 19, 21).

Unlike other solid malignancies, the use of cross-sectional imaging and serum laboratory analysis to facilitate initial clinical staging is not routinely recommended outside of Stage IV disease (22). However, computed tomography (CT) (with or without positron emission tomography [PET]) and magnetic resonance imaging (MRI) should be considered for all patients with specific symptoms, Stage III disease, or even Stage II melanoma with high-risk features. In the setting of Stage IV melanoma, CT imaging of the chest, abdomen, and pelvis should be obtained, and a brain MRI can be considered (13, 21).

Conclusion

As discussed in the subsequent sections of this book, treatment options for advanced stages of cutaneous melanoma have significantly expanded in recent years. Although many of these new interventional approaches have injected much prognostic optimism into the field as a whole, it must be emphasized that delayed or deficient elements of the initial melanoma evaluation process can limit patient outcomes and increase disease-related mortality. Clinicians involved in the diagnosis or treatment of cutaneous melanoma must be familiar with the importance of available screening options, the key steps of clinical and histologic diagnosis, and the staging ramifications of disease discovery. Improvement in these areas will reduce disease incidence and progression, and may afford increased hope to patients afflicted with cutaneous melanoma.

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References

1. Shellenberger R, Nabhan M, Kakaraparthi S. Melanoma screening: A plan for improving early detection. Ann Med. 2016;48(3):142–8. http://dx.doi.org/10.3109/07853890.2016.1145795
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
3. Perlis C, Herlyn M. Recent advances in melanoma biology. Oncologist. 2004;9(2):182–7. http://dx.doi.org/10.1634/theoncologist.9-2-182
4. Garibyan L, Fisher DE. How sunlight causes melanoma. Curr Oncol Rep. 2010;12(5):319–26. http://dx.doi.org/10.1007/s11912-010-0119-y
5. Aitken JF, Elwood M, Baade PD, Youl P, English D, *Clinical whole-body skin examination reduces the incidence of thick melanomas.* Int J Cancer, 2010. 126(2): p. 450–8.
6. Leachman SA, Carucci J, Kohlmann W, Banks KC, Asgari MM, Bergman W, et al., *Selection criteria for genetic assessment of patients with familial melanoma.* J Am Acad Dermatol, 2009. 61(4): p. 677.e1-14.
7. Psaty EL, Scope A, Halpern AC, Marghoob AA, *Defining the patient at high risk for melanoma.* Int J Dermatol, 2010. 49(4): p. 362–76.
8. Gumaste PV, Penn LA, Cymerman RM, Kirchhoff T, Polsky D, McLellan B, *Skin cancer risk in BRCA1/2 mutation carriers.* Br J Dermatol, 2015. 172(6): p. 1498–506.
9. Sondak VK, Glass LF, Geller AC. Risk-stratified screening for detection of melanoma. JAMA. 2015;313(6):616–17. http://dx.doi.org/10.1001/jama.2014.13813
10. Wernli KJ, Henrikson NB, Morrison CC, Nguyen M, Pocobelli G, Whitlock, EP, *U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews*, in *Screening for Skin Cancer in Adults: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force*. 2016, Agency for Healthcare Research and Quality (US): Rockville (MD).

11. Weinstock MA, Ferris LK, Saul MI, Geller AC, Risica PM, Siegel JA, et al., *Downstream consequences of melanoma screening in a community practice setting: First results.* Cancer, 2016. 122(20): p. 3152–3156.
12. Breitbart EW, Waldmann A, Nolte S, Capellaro M, Greinert R, Volkmer B, et al., *Systematic skin cancer screening in Northern Germany.* J Am Acad Dermatol, 2012. **66**(2): p. 201–11.
13. Coit DG, Andtbacka R, Anker CJ, Bichakjian, CK, Carson WE, Daud A, et al., *Melanoma, version 2.2013: featured updates to the NCCN guidelines.* J Natl Compr Canc Netw, 2013. 11(4): p. 395–407.
14. Kauffmann RM, Chen SL. Workup and staging of malignant melanoma. Surg Clin North Am. 2014;94(5):963–72, vii. http://dx.doi.org/10.1016/j.suc.2014.07.001
15. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124(6):869–71. http://dx.doi.org/10.1001/archderm.1988.01670060015008
16. Zager JS, Hochwald SN, Marzban SS, Francois R, Law KM, Davis AH, et al., *Shave biopsy is a safe and accurate method for the initial evaluation of melanoma.* J Am Coll Surg, 2011. 212(4): p. 454–60; discussion 460-2.
17. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Bardia A, et al., *Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis.* Mayo Clin Proc, 2007. 82(3): p. 364–80.
18. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al., editors. *AJCC Cancer staging manual.* 8th ed. New York: Springer; 2017.
19. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al., *Final version of 2009 AJCC melanoma staging and classification.* J Clin Oncol, 2009. 27(36): p. 6199–206.
20. Coit DG, Thompson JA, Algazi A, Andtbacka R, Bichakjian CK, Carson WE, et al., *Melanoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology.* J Natl Compr Canc Netw, 2016. 14(4): p. 450–73.
21. NCCN. NCCN clinical practice guidelines in oncology. Melanoma V. 1.2017. Fort Washington, PA: NCCN; 2016.
22. Pandalai PK, Dominguez FJ, Michaelson J, Tanabe KK, *Clinical value of radiographic staging in patients diagnosed with AJCC stage III melanoma.* Ann Surg Oncol, 2011. 18(2): p. 506–13.