Published in final edited form as:

Surg Clin North Am. 2014 October ; 94(5): 989–1002. doi:10.1016/j.suc.2014.07.003.

Surviving Cutaneous Melanoma: A Clinical Review of Follow-up Practices, Surveillance, and Management of Recurrence

Amy A. Mrazek and Celia Chao

Department of Surgery, University of Texas Medical Branch, Galveston, Texas, USA

Keywords

Melanoma survivorship; Survival prognosis; Surveillance and follow-up; Management of recurrence

Introduction

In the past 10 years, the incidence of melanoma in the U.S. has been increasing an average of 2.6% each year, while the death rates have remained stable over time (1); furthermore, a similar trend has been observed on a global scale within the last two decades, with the highest incidences of melanoma in Australia and New Zealand (2,3). According to the latest report by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, an estimated 921,780 people living in the U.S. have survived melanoma; and their overall five- and ten-year relative survival rates are 91.3% and 89.1%, respectively (1). The majority of melanoma cases are diagnosed at a localized stage, which have more favorable survival rates (98.3%) compared to those with regional (62.4%) or distant metastatic disease (16.0%) (1).

A major component of survivorship involves follow-up and monitoring for recurrence and/or new malignancies. Yang and colleagues (4) reviewed the SEER database from 1988–2007, focusing on the relative risk (RR) of developing a second primary cutaneous melanoma (CM) in 70,819 melanoma survivors, and 6,353 patients with CM subsequent to another primary malignancy. No matter the age of initial melanoma diagnosis, survivors had an increased risk of recurrence: RR 11.89, 95% confidence interval (CI), 10.83–13.03, for patients <45 years old and RR 8.36, 95% CI, 7.93–8.81, for patients ≥45 years of age. Furthermore, the RR remained elevated for the duration of the 15-year study period (4).

© 2014 Elsevier Inc. All rights reserved

Corresponding author: Celia Chao, MD, FACS University of Texas Medical Branch 301 University Blvd., Rte 0737 Galveston, TX 77555 (409) 772-0698, office cechao@utmb.edu.

Amy A. Mrazek, MD University of Texas Medical Branch 301 University Blvd., Rte 0534 Galveston, TX 77555 (409) 789-6994, cell aamrazek@utmb.edu

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: All of the authors have no conflicts of interests to disclose.

These results reinforce the importance of surveillance to identify early and treat new primary CM) in previous melanoma survivors (5).

Prognostic Factors for Melanoma Survival

The American Joint Committee on Cancer (AJCC) Melanoma Task Force has collected data from 30,946 patients, spanning multiple institutions and continents, to develop an evidence-based staging system that helps clinicians evaluate patient prognosis and develop treatment and surveillance plans (6). The 7th edition of the AJCC staging system has incorporated several histologic features of the primary tumor (tumor thickness, mitotic rate, and ulceration), regional and distant metastasis, all of which have been shown to be independent predictors of survival (6).

Survival Related to Localized Melanoma (Stages I and II)

Dr. Andrew Breslow (7) first described the depth of tumor invasion correlating with patient outcomes: 'thin' melanomas (less than 0.76 mm thickness) were low-risk lesions, seldom metastasized, and were considered prognostically favorable; 'thick' melanomas (greater than 4 mm) had a high risk of recurrence or metastasis, and an unfavorable prognosis. The AJCC considers Breslow thickness as the most important prognostic factor of survival in localized melanoma. Increased primary tumor thickness was associated with a significant decrease in 5- and 10-year survival rates ($p < 0.0001$). The 10-year survival rates for each T-stage were 92% for T1 (< 1.0 mm thickness), 80% for T2 (1.01–2.0 mm), 63% for T3 (2.01–4.0 mm), and 50% for T4 melanomas (≥ 4.0 mm) (6).

New to the 7th edition AJCC guidelines, the primary tumor's mitotic rate is considered the second most powerful prognostic factor in localized melanoma survival, replacing the Clark level of invasion. The mitotic rate reflects the tumor's proliferation in the vertical growth phase and is defined as the number of mitotic figures counted over an area of 1 mm² (8). Tumors with increased mitoses over 1/mm² were correlated with worse survival rates ($P < 0.0001$) (6). The 10-year survival rate for tumors with 0 mitosis/mm² was 93% compared to 48% for tumors with ≥ 20 /mm². As expected, thicker or ulcerated tumors were associated with higher mitotic rates (9).

The third most powerful survival predictor was the presence of ulceration of the primary tumor. The incidence of ulceration increases as tumor thickness increases (10). The survival rate of patients with ulcerated tumors was comparable to the rate of the next highest category of a non-ulcerated melanoma with increased thickness (10).

Survival Related to Regional Metastasis (Stage III)

Cox multivariate analysis of the SEER database showed that the total number of nodal metastasis, tumor burden of the metastatic deposits (micro- vs. macro-metastasis), presence of primary tumor ulceration, and Breslow thickness ($p < 0.001$) (6) were all independent predictors of survival in stage III disease, or lymph node-positive melanomas. Survival decreased with increasing nodal involvement (1, 2–3, or 4+ regional nodes), and patients with regional nodal metastasis detected on physical exam (macrometastases) had significantly decreased survival compared to non-palpable metastatic nodes (Table 1) (10).

Unlike breast cancer, evaluation of the sentinel lymph node (SLN) for melanoma requires immunohistochemical staining. The AJCC defines micrometastasis as the presence of cells staining positive for one melanoma-associated marker (i.e., S-100, Melan-A/MART1, HMB-45) and evidence of malignant morphology on hematoxylin and eosin staining (6,11). Similar to the prognosis for stages I and II, the presence of primary tumor ulceration and increased thickness was associated with lower survival rates.

Survival Related to Distant Metastasis (Stage IV)

Patients with stage IV disease, who have distant metastases, have poor overall survival; however, the specific site of metastasis and serum lactate dehydrogenase (LDH) level can help stratify patients by prognosis and for enrollment into clinical trials. The one-year survival rate differs depending on the metastatic site: 62% for metastasis to the skin, subcutaneous tissue, or distant lymph nodes (M1a); 53% for pulmonary metastasis (M1b); and 33% for other visceral sites (M1c) (6). Elevated serum LDH levels, in combination with distant metastasis to any site, upstages the patient's classification to M1c, which has the worst prognosis.

Additional Prognostic Survival Factors

Although not identified as independent prognostic factors in the AJCC staging and classification guidelines, several additional risk factors have been reported to be associated with melanoma survival. Female patients seem to have a survival advantage with cutaneous melanoma; more men die of the disease than women in the U.S. (4.1 versus 1.7 deaths per 100,000 persons) (1). In a German study, the gender-associated advantage was lost by the age of 60 (12). Review of the AJCC Melanoma Database and the Sunbelt Melanoma Trial revealed that increasing age correlates with worse prognosis and a decline in survival (10,13). Garbe and colleagues (14) evaluated the relationship between the primary CM's anatomic site and survival rates. Melanoma located in TANS regions (thorax, upper arm, neck and scalp) had a less favorable prognosis than those located on the lower trunk, thigh, lower leg, foot, lower arms, hands, and face. CM are more common in fair-skinned races; yet, African Americans, who have overall lower incidence of melanoma, have a lower 10-year survival rate and higher risk of recurrence after surgical treatment than Caucasians and other races with comparable stage of disease (15). Lastly, several other tumor-related factors discussed in the literature may have prognostic value and require future studies: route of invasion (local spread versus lymphatic, hematogenous, perivascular, or distant metastasis), tumor-infiltrating lymphocytes, tumor regression, mutations in molecular markers (N-RAS, Raf, c-Kit, G proteins), alterations in cell-signaling pathways (MAPK, ATP/PI3K, cell cycle, and p53-regulated cell death), and serum markers like S100 and melanoma-inhibiting activity, a protein secreted by melanoma cells (11). However, their value remains controversial, and further studies are needed to determine clinical utility.

On-line Melanoma Prognosis Calculators

On-line computer models have been developed to determine a melanoma patient's prognosis based on the AJCC guidelines (www.melanomaprognosis.org) (16). Callender and colleagues (17) improved the prognostic accuracy of the computer model by incorporating sentinel lymph node biopsy (SLNB) results (melanomacalculator.com); they validated their

prognostic model using known data from 1,001 patients and showed a concordance correlation coefficient (CCC) of 0.984 compared to the AJCC model CCC of 0.784 (17). These computer calculators may be useful tools for physicians to develop individualized care plans and facilitate patient education.

Melanoma Surveillance

Despite the variability in recommended melanoma surveillance practice patterns, the purpose is universally identical: early detection of recurrent disease or a new second primary melanoma. Surveillance includes patient education with instructions for self-examination, reassurance, promotion of patient well-being, and monitoring the patient for the development of side effects or toxicity due to previous therapies. When recurrent or new lesions are recognized early, appropriate treatment can be initiated expediently, which is believed to improve overall survival outcomes (18).

Surveillance can be the responsibility of many types of health care providers: primary care physicians (PCPs), nurse practitioners, physician assistants, dermatologists, oncologists, general and plastic surgeons, as well as a multi-disciplinary team for more advanced cases (19). Also, patient preference and access to care influence who provides surveillance care. McKenna *et al* (20) performed a retrospective observational study of melanoma surveillance provided by dermatologists, PCPs, and surgical specialists; they found that patients followed by dermatologists had better overall survival, disease-free survival, and recurrence-free survival at 5 years. However, these results may be due to selection bias since patients treated by dermatologists often had thinner melanomas with better prognostic features.

The majority of primary melanomas, as well as their recurrences, are first detected by the patient and/or family member, rather than a physician. Recurrences are often identified within the first two years after primary tumor diagnosis (21–23). A recent retrospective study by Salama and colleagues (24) showed that among 11,615 patients originally diagnosed with stage I and II melanomas, the overall risk of initial recurrence peaked at 12 months. They found that for this population, recurrence involving the skin, both local and distant, as well as the regional nodal basin peaked at 8 months, whereas pulmonary and distant metastatic recurrence peaked at 24 months. Once recurrence was found, the interval to discovery of a second recurrence shortened to 6 months, and the third recurrence to 2.6 months (24).

Approximately 1–8% of melanoma survivors will develop a second primary melanoma in their lifetime, which is often thinner than the first primary (25). Physicians, more often than patients, detect the second primary melanoma. The literature is controversial regarding the specific time frame for subsequent melanoma development, and therefore so are the recommendations for the optimal duration of follow-up (26). Some have reported that the second primary melanoma develops within the first few months to 2 years after initial diagnosis, while others found that 40% of new primaries were detected more than 7 years later (22).

Variation in Follow-up Practices

Despite the controversies, some consensus exists amongst surveillance practices: initial follow-up frequency should be increased in patients with higher AJCC stages of melanoma, and follow-up visits can be less frequent as the patient remains disease-free over time (19). Also, it is important to note that the vast majority of studies analyzing follow-up patterns are retrospective in nature. Cromwell *et al.* (25) recently performed a systemic review of published surveillance strategies from 1970 to 2011; they found significant variation in follow-up relative to disease state, country of origin, and physician specialty. Greatest variation in surveillance frequency was noted in stage I patients, which ranged from 1–6 visits/year for the first 2 years of treatment, and with regard to the use of routine diagnostic imaging and laboratory evaluations. Universal agreement was reached for all patients to perform self-examinations and to decrease visits to annual surveillance after 5 years of disease-free follow-up (25).

Turner and colleagues (27) studied the delay of diagnosis based on two different surveillance schedules in stage I and II melanoma patients. They found that the less frequent monitoring strategy (two visits per year followed by annual visits through 10 years) only delayed diagnosis by a little over 2 months in an extra 44.9 and 9.6 patients per 1,000 for recurrence and new primary tumors, respectively. The duration of follow-up continues to be debated, and ranges from years to a lifetime of surveillance. Table 2 compares surveillance recommendations by the National Comprehensive Cancer Network® (NCCN®) and other organizations with published guidelines (19,25,28).

NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) for Melanoma: Follow-up

The NCCN Guidelines® for Melanoma, Version 3.2014, are an up-to-date set of evidence-based clinical care guidelines established by experts from 25 major cancer centers across the U.S. Algorithms for suggested follow-up are based on the clinical/pathological AJCC stage of disease (26). For stage 0 (in situ) disease, the NCCN® recommends “common follow-up recommendations for all patients,” which include a minimum of annual skin exams for life accompanied by patient education on skin and lymph node self-exams. For patients with stage IA-IIA with no evidence of disease (NED), a history and physical (H&P) should be performed every 6–12 months for 5 years, after which annual visits are sufficient. The surveillance schedule of stage IIB-IV patients with NED should include a more frequent interval of visits, which can be lengthened over time as the chance of recurrence decreases: H&P every 3–6 months for 2 years, every 3–12 months for 3 years, and annually thereafter. Also, within this 5-year time period after the diagnosis of a primary melanoma, physicians should consider incorporating radiologic imaging (CT, PET, and/or MRI) every 4–12 months for metastatic surveillance (26).

Tailoring Surveillance Schedules to Individual Patient Needs

An individual patient's surveillance strategy must account for multiple factors: benefit in outcome improvement, clinical relapse risk profile, coordination of shared care in follow-up, patient's preference, psychosocial needs, access to a support system, and cost effectiveness of surveillance intensity (29). A thorough risk profile assessment includes review of a

patient's family history of melanoma, presence, extent, and quantity of dysplastic nevi, skin phenotype, risk of nodal recurrence, whether the patient elected for a complete lymphadenectomy (CLND) after a positive SLNB, and history of ultraviolet exposure and skin cancer prevention behavior (26,30). The practitioner must also take into account how the schedule affects patient convenience, travel time, cost burden, and patient satisfaction—since all of these factors will directly influence patient compliance. Standard follow-up visits must include patient education, which involves the review of surveillance strategies, prognosis, and counseling on disease prevention.

H&P examination is among the best screening tools for detection of recurrence or new primaries (22,31). At each visit, the practitioner should ask about new or changing cutaneous or subcutaneous lesions, masses, or pain. The review of systems should inquire about the presence of constitutional symptoms like weight loss, neurologic changes, pain, gastrointestinal or pulmonary complaints—all of which are clues for metastatic disease. The physical exam must include a complete head-to-toe skin exam of sun-exposed and non-sun-exposed sites, including the scalp, conjunctiva, oral mucosa, nails, palms, soles, inter-digital web spaces, and genitalia/perianal area (30), as well as thorough lymph node examination, with attention directed toward primary echelon nodes and interval nodes. These practices enable early identification of local/regional/in-transit recurrence or the development of new primary lesions.

Patient Education and Risk Factor Modification

Patients should be instructed on how to perform skin self-examinations (SSE) and lymph node exams; yet, studies have shown that most melanoma survivors neither consistently nor comprehensively conduct SSE (32). These cost-effective SSE should be conducted on all skin surfaces in a well-lit area, monthly. If patients have multiple dysplastic nevi, baseline digital photography of lesions can be employed to improve the sensitivity of SSE detecting new lesions (33). When patients identify new or changing lesions that last more than 2 weeks, they should be advised to report the changes to the practitioner overseeing their surveillance; the 2-week window is suggested since the majority of acute inflammatory or ecchymotic lesions will resolve within this time frame (34).

Ultraviolet radiation exposure is a well-established modifiable risk factor; however, studies have shown that although the knowledge about the impact of sun-related behaviors and practice are improved in melanoma patients, there remains an unchanged attitude toward the “healthy” appearance of tans (35). Recommended sun behavior counseling should include: using sun protection (sunscreen and protective clothing), reducing ambient and recreational sun exposure, seeking shade when possible, and avoiding sunburns and tanning bed usage (36).

Evaluation of Psychosocial Distress and Coping Mechanisms

The psychosocial impact of melanoma can be profound. Anxiety and depression are the most commonly reported emotions experienced by melanoma patients, which can be manifested in a variety of ways: delay in seeking medical care, poor compliance, a lower quality of life (QoL), increased medical visits and cost, and reduced participation in

surveillance programs (37,38). Validated instruments available for QoL assessment include the Functional Assessment of Cancer Therapy Scale-Melanoma questionnaire (39), and the Malignant Melanoma Module, which is currently being updated in collaboration with the European Organization for Research and Treatment of Cancer Quality of Life Group (40,41).

Reassessment of the psychosocial impact of melanoma is necessary as patients experience different reactions to their disease over the course of survivorship: problems moving past the cancer diagnosis, feelings of abandonment as visits become less frequent over time, a sense of “watchful waiting” for recurrence, difficulty living with on-going physical limitations and a distorted body image after surgery, and struggling to find positive meaning in life (42). Coping mechanisms of patients can significantly impact his or her quality of life; more functional styles like problem-focused coping should be promoted over avoidance or denial (43). In a randomized controlled trial of melanoma patients during various stages of survivorship, Fawzy *et al* (44) found that psychiatric interventions incorporating education, stress management, enhancement of coping skills, and psychological support were associated with greater disease-free intervals and survival than the control group.

Some patients think that regular clinic visits evoke a sense of safety and reassurance; however, others may perceive frequent follow-up as a source of anxiety, fear, and a repeated reminder of the possibility of cancer recurrence and mortality. The physician can help develop a tailored supportive care program in the form of educational techniques, behavioral or skill training, social support, and psychotherapy; referrals to psychologists, counselors, or group programs may also benefit the patient or caregiver (42). Patient satisfaction with follow-up visits is improved with practitioner accessibility, and continuity of care provides patients with a sense of confidence in the clinical care provided (37). Lastly, education and support can help alleviate the burden of disease on caregivers.

Diagnosis and Management of Melanoma Recurrence

Melanoma recurrence can be divided into several categories: local, in-transit/satellite, regional, or distant. Moreover, local recurrence is subdivided into local scar and true local recurrence. The first recurrence of melanoma most often involves the regional lymph nodes (50%), and less commonly, local/in-transit/satellite disease (20%), and distant metastasis (30%) (25,34); these statistics are likely to change as SLNB with completion nodal basin dissection for positive nodal disease are now utilized routinely, identifying micrometastasis earlier.

Local Scar Recurrence

Local scar recurrence is due to persistent disease and is defined by the presence of *in situ* and/or a radial growth phase. Local recurrence occurs within a 2 cm radius of the scar or skin graft. The work-up of melanoma recurrence should parallel how primary tumors are managed (26). Local scar recurrence is confirmed by biopsy/fine needle aspiration (FNA), and its management is comparable to that of primary tumors with the same stage. Wide local re-excision should be performed based on the primary tumor's characteristics, and lymphatic mapping/SLNB or adjuvant therapy may be considered.

Local, Satellite, and In-transit Recurrence

True local recurrence develops after an initial adequate primary tumor excision, and its incidence increases with primary melanoma thickness and ulceration (45). Local recurrence commonly develops from dermal lymphatic disease in close proximity to the scar; whereas, satellite and in-transit disease results from endolymphatic spread. Locoregional disease manifests as cutaneous or subcutaneous nodules between the primary tumor site and the regional nodal basin, and should be considered recurrence until proven otherwise (26,45). These tumors may or may not be palpable, and when visible, are often pink or flesh colored rather than hyper-pigmented like a traditional melanoma tumor.

Local, satellite, or in-transit lesions should be confirmed pathologically by biopsy or cytology from FNA. Chest radiographs, computed tomography (CT) scan, positron emission tomography (PET) scan, magnetic resonance imaging (MRI), or lymph node ultrasonography may be used to investigate signs and symptoms concerning for metastasis. The standard of care for resectable locoregional recurrence is surgical resection with negative margins. Depending on the size and anatomic location of the tumor, skin grafting or flap closure may be employed for wound coverage.

Additional treatment options for locoregional disease include enrollment in a clinical trial, non-surgical local therapies like intralesional injections of the bacillus Calmette-Guérin (BCG) or granulocyte-macrophage colony stimulating factor, phototherapy with a pulsed dye or carbon dioxide laser, topical agents like imiquimod (immunomodulator and toll-like receptor agonist), diphencyprone (a contact sensitizer, for superficial dermal lesions), regional therapies like isolated limb infusion (ILI)/hyperthermic isolated limb perfusion (HILP) with melphalan, systemic therapies like interferon alpha (IFN- α) or interleukin-2 (IL-2), electrochemotherapy (which involves the delivery of high-intensity electrical pulses to cause cell membrane poration and increase chemotherapeutic delivery), and palliative radiation therapy for unresectable disease (26,31,46). Adjuvant therapeutic options for locoregional recurrence include joining a clinical trial, observation, or initiation of high-dose IFN- α therapy.

Regional Recurrence

Regional recurrence directly involves the lymph nodes. Romano *et al* (47) found that the first recurrence amongst stage III patients was more often systemic (51%) rather than local/in-transit (28%) or regional (21%). This is speculated to be occult nodal micro-metastases that, over time, develop into palpable nodal metastasis and spread to distant sites (34). Recurrent regional malignancies are more likely to develop after unfavorable primary tumor characteristics (increased Breslow thickness, mitoses, ulceration), lesions of the head and neck, and an initially (false) negative SLNB (46).

Regional recurrence should be confirmed pathologically by FNA (preferred) or lymph node biopsy, and work-up is similar to that of primary stage III tumors. Patients without previous nodal dissection or history of an incomplete resection should undergo CLND (26). If the patient had a prior CLND, the recurrence should be excised to negative margins. As shown in the international Multicenter Selective Lymphadenectomy Trial (MSLT-1), delayed

CLND is a morbid procedure significantly associated chronic lymphedema (48). Treatment options for unresectable locoregional or systemic disease include enrollment in a clinical trial, radiation therapy, systemic therapy, IFN- α , or supportive care.

Metastatic Recurrence

Lastly, the presentation of distant recurrence can vary, manifesting as a single lesion or as multifocal disease. The most common sites of metastasis are brain, lung, and liver; less common sites include the skin, distant lymph nodes, bone, adrenal glands, or gastrointestinal tract (31,34).

The work-up and treatment of distant metastatic disease is similar to that of primary stage IV melanoma. Pathologic diagnosis is required, preferably by FNA rather than biopsy. The extent of baseline disease should be characterized with serum LDH levels and CT of the chest/abdomen/pelvis, MRI, and/or PET scan. Treatment options depend on whether the distant metastasis is limited and resectable versus disseminated and unresectable (26).

If feasible, surgical resection of solitary metastatic lesions is recommended; but patients can be offered the alternatives of observation or systemic therapy followed by repeat scans to measure disease progression. Management options for patients with disseminated disease include systemic therapy, clinical trial, palliative resection and/or RT for symptomatic patients, or supportive care. Current preferred systemic therapy regimens include ipilimumab, vemurafenib for melanomas with BRAF mutations, and high-dose IL-2 (26). Additional options include dacarbazine and/or temozolomide, imatinib for tumors with c-KIT mutations, cisplatin and vinblastine with/without IL-2, IFN- α , paclitaxel alone or in combination with carboplatin (26). As with any systemic therapy, patients should be monitored closely for side effects and toxicity. When patients have brain metastasis, surgical intervention and/or radiation is recommended to minimize or delay central nervous system morbidity, and such therapies include stereotactic radiosurgery or whole brain radiotherapy.

Conclusion

The incidence of melanoma continues to rise while mortality rates remain stable, resulting in a growing population of melanoma survivors. The development of surveillance strategies must be tailored to each individual patient, taking into consideration tumor stage, prognosis relative to the initial primary tumor characteristics, and risk factors for recurrence or a second primary. General agreement exists regarding frequent follow-up visits for advanced stages of melanoma initially, and as the patient's disease-free interval increases, visits can be less frequent. Critical components of each follow-up visit include an H&P, reinforcement of skin and lymph node self-examination, sun behavior counseling, evaluation of patient well-being, and development of coping skills.

Surgical resection with negative margins is the treatment of choice for operable local, satellite, and in-transit regional recurrence; additional therapeutic options for locoregional recurrence vary from intralesional injections of BCG to regional ILI/HILP, immunomodulators, systemic therapies, and enrollment in clinical trials. Regional nodal recurrence should be excised and CLND performed if not completed previously.

Management of metastatic recurrence is dependent on whether distant metastasis is limited or disseminated. For complex cases, melanoma survivorship may best be managed by a multidisciplinary team of specialists, each of whom are experts in their respective fields.

References

1. Howlader, N.; Noone, AM.; Krapcho, M., et al. [Accessed March 6, 2014] Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review, 1975–2010. Available at: http://seer.cancer.gov/csr/1975_2010/
2. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. *Ann Oncol.* 2009; 20(Suppl 6):vi1–7. [PubMed: 19617292]
3. Garbe C, Leiter U. Melanoma epidemiology and trends. *Clin Dermatol.* 2009; 27:3–9. [PubMed: 19095149]
4. Yang GB, Barnholtz-Sloan JS, Chen Y, et al. Risk and survival of cutaneous melanoma diagnosed subsequent to a previous cancer. *Arch Dermatol.* 2011; 147:1395–402. [PubMed: 22184761]
5. Freedman, DM.; Miller, BA.; Tucker, MA. New malignancies following melanoma of the skin, eye melanoma, and non-melanoma eye cancer. In: Curtis, RE.; Freedman, DM.; Ron, E., et al., editors. *New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973–2000*. National Cancer Institute; Bethesda, MD: 2006. p. 339–62.
6. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol.* 2009; 27:6199–206. [PubMed: 19917835]
7. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. *Ann Surg.* 1970; 172:902–8. [PubMed: 5477666]
8. Mervic L. Prognostic factors in patients with localized primary cutaneous melanoma. *Acta Dermatovenerol Alp Panonica Adriat.* 2012; 21:27–31.
9. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol.* 2011; 29:2199–205. [PubMed: 21519009]
10. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol.* 2001; 19:3622–34. [PubMed: 11504744]
11. Fernandez-Flores A. Prognostic factors for melanoma progression and metastasis: from hematoxylin-eosin to genetics. *Rom J Morphol Embryol.* 2012; 53:449–59. [PubMed: 22990532]
12. Mervic L, Leiter U, Meier F, et al. Sex differences in survival of cutaneous melanoma are age dependent: an analysis of 7338 patients. *Melanoma Res.* 2011; 21:244–52. [PubMed: 21540649]
13. Chao C, Martin RC 2nd, Ross MI, et al. Correlation between prognostic factors and increasing age in melanoma. *Ann Surg Oncol.* 2004; 11:259–64. [PubMed: 14993020]
14. Garbe C, Buttner P, Bertz J, et al. Primary cutaneous melanoma. Prognostic classification of anatomic location. *Cancer.* 1995; 75:2492–8. [PubMed: 7736393]
15. Collins KK, Fields RC, Baptiste D, et al. Racial differences in survival after surgical treatment for melanoma. *Ann Surg Oncol.* 2011; 18:2925–36. [PubMed: 21479687]
16. Soong, SJ.; Ding, S.; Coit, DG., et al. [Accessed March 16, 2014] Individualized melanoma patient outcome prediction tools. Developed based on the American Joint Committee on Cancer Melanoma Database. Available at: www.melanomaprognosis.org
17. Callender GG, Gershenwald JE, Egger ME, et al. A novel and accurate computer model of melanoma prognosis for patients staged by sentinel lymph node biopsy: comparison with the American Joint Committee on Cancer model. *J Am Coll Surg.* 2012; 214:608–19. [PubMed: 22342785]
18. Garbe C, Paul A, Kohler-Spath H, et al. Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: recommendations for an effective follow-up strategy. *J Clin Oncol.* 2003; 21:520–9. [PubMed: 12560444]

19. Trotter SC, Sroa N, Winkelmann RR, et al. A global review of melanoma follow-up guidelines. *J Clin Aesthet Dermatol*. 2013; 6:18–26. [PubMed: 24062870]
20. McKenna DB, Marioni JC, Lee RJ, et al. A comparison of dermatologists', surgeons' and general practitioners' surgical management of cutaneous melanoma. *Br J Dermatol*. 2004; 151:636–44. [PubMed: 15377351]
21. Epstein DS, Lange JR, Gruber SB, et al. Is physician detection associated with thinner melanomas? *JAMA*. 1999; 281:640–3. [PubMed: 10029126]
22. Francken AB, Bastiaannet E, Hoekstra HJ. Follow-up in patients with localised primary cutaneous melanoma. *Lancet Oncol*. 2005; 6:608–21. [PubMed: 16054572]
23. Francken AB, Shaw HM, Accortt NA, et al. Detection of first relapse in cutaneous melanoma patients: implications for the formulation of evidence-based follow-up guidelines. *Ann Surg Oncol*. 2007; 14:1924–33. [PubMed: 17357855]
24. Salama AK, de Rosa N, Scheri RP, et al. Hazard-rate analysis and patterns of recurrence in early stage melanoma: moving towards a rationally designed surveillance strategy. *PLoS One*. 2013; 8:e57665. [PubMed: 23516415]
25. Cromwell KD, Ross MI, Xing Y, et al. Variability in melanoma post-treatment surveillance practices by country and physician specialty: a systematic review. *Melanoma Res*. 2012; 22:376–85. [PubMed: 22914178]
26. Coit, DG.; Thompson, JA.; Andtbacka, R., et al. [Accessed March 9, 2014] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines^(R)) For Melanoma (version 3.2014). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
27. Turner RM, Bell KJ, Morton RL, et al. Optimizing the frequency of follow-up visits for patients treated for localized primary cutaneous melanoma. *J Clin Oncol*. 2011; 29:4641–6. [PubMed: 22067399]
28. Fong ZV, Tanabe KK. Comparison of melanoma guidelines in the U.S.A., Canada, Europe, Australia and New Zealand: a critical appraisal and comprehensive review. *Br J Dermatol*. 2014; 170:20–30. [PubMed: 24116870]
29. Rychetnik L, McCaffery K, Morton RL, et al. Follow-up of early stage melanoma: specialist clinician perspectives on the functions of follow-up and implications for extending follow-up intervals. *J Surg Oncol*. 2013; 107:463–8. [PubMed: 23090908]
30. Brown MD. Office management of melanoma patients. *Semin Cutan Med Surg*. 2010; 29:232–7. [PubMed: 21277536]
31. Dunki-Jacobs EM, Callender GG, McMasters KM. Current management of melanoma. *Curr Probl Surg*. 2013; 50:351–82. [PubMed: 23849560]
32. Mujumdar UJ, Hay JL, Monroe-Hinds YC, et al. Sun protection and skin self-examination in melanoma survivors. *Psychooncology*. 2009; 18:1106–15. [PubMed: 19142859]
33. Oliveria SA, Chau D, Christos PJ, et al. Diagnostic accuracy of patients in performing skin self-examination and the impact of photography. *Arch Dermatol*. 2004; 140:57–62. [PubMed: 14732661]
34. Benvenuto-Andrade C, Oseitutu A, Agero AL, et al. Cutaneous melanoma: surveillance of patients for recurrence and new primary melanomas. *Dermatol Ther*. 2005; 18:423–35. [PubMed: 16297018]
35. Lee TK, Brazier AS, Shoveller JA, et al. Sun-related behavior after a diagnosis of cutaneous malignant melanoma. *Melanoma Res*. 2007; 17:51–5. [PubMed: 17235242]
36. Geller AC, O'Riordan DL, Oliveria SA, et al. Overcoming obstacles to skin cancer examinations and prevention counseling for high-risk patients: results of a national survey of primary care physicians. *J Am Board Fam Pract*. 2004; 17:416–23. [PubMed: 15575033]
37. McLoone JK, Watts KJ, Menzies SW, et al. Melanoma survivors at high risk of developing new primary disease: a qualitative examination of the factors that contribute to patient satisfaction with clinical care. *Psychooncology*. 2013; 22:1994–2000. [PubMed: 23382138]
38. Kasparian NA. Psychological stress and melanoma: are we meeting our patients' psychological needs? *Clin Dermatol*. 2013; 31:41–6. [PubMed: 23245972]

39. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993; 11:570–9. [PubMed: 8445433]
40. Sigurdardottir V, Bolund C, Brandberg Y, et al. The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique. *Qual Life Res.* 1993; 2:193–203. [PubMed: 8401455]
41. Winstanley JB, White EG, Boyle FM, et al. What are the pertinent quality-of-life issues for melanoma cancer patients? Aiming for the development of a new module to accompany the EORTC core questionnaire. *Melanoma Res.* 2013; 23:167–74. [PubMed: 23358427]
42. Tan JD, Butow PN, Boyle FM, et al. A qualitative assessment of psychosocial impact, coping and adjustment in high-risk melanoma patients and caregivers. *Melanoma Res.* 2014
43. Vurnek M, Buljan M, Situm M. Psychological status and coping with illness in patients with malignant melanoma. *Coll Antropol.* 2007; 31(Suppl 1):53–6. [PubMed: 17469751]
44. Fawzy FI, Fawzy NW, Hyun CS, et al. Malignant melanoma. Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch Gen Psychiatry.* 1993; 50:681–9. [PubMed: 8357293]
45. Levine SM, Shapiro RL. Surgical treatment of malignant melanoma: practical guidelines. *Dermatol Clin.* 2012; 30:487–501. [PubMed: 22800553]
46. Squires MH 3rd, Delman KA. Current treatment of locoregional recurrence of melanoma. *Curr Oncol Rep.* 2013; 15:465–72. [PubMed: 23907518]
47. Romano E, Scordo M, Dusza SW, et al. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. *J Clin Oncol.* 2010; 28:3042–7. [PubMed: 20479405]
48. Morton DL. Overview and update of the phase III Multicenter Selective Lymphadenectomy Trials (MSLT-I and MSLT-II) in melanoma. *Clin Exp Metastasis.* 2012; 29:699–706. [PubMed: 22729520]
49. Australian Cancer Network Melanoma Guidelines Revision Working Party. Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Cancer Council Australia and Australian Cancer Network; Sydney and New Zealand Guidelines Group; Available at: <https://www.nhmrc.gov.au/guidelines/publications/cp111> [Accessed March 6, 2014]
50. British Columbia Cancer Agency. [Accessed March 6, 2014] Melanoma follow-up. Available at: <http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Skin/Melanoma/ManagementPolicies/Follow-up.htm>
51. Alberta Cutaneous Tumor Team. [Accessed March 6, 2014] Referral and follow-up surveillance of cutaneous melanoma. Available at: <http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-cu001-followup-surveillance.pdf>.
52. Dummer R, Hauschild A, Guggenheim M, et al. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012; 23(Suppl 7):vii86–91. [PubMed: 22997461]
53. Pflugfelder A, Kochs C, Blum A, et al. S3-guideline “diagnosis, therapy and follow-up of melanoma” -- short version. *J Dtsch Dermatol Ges.* 2013; 11:563–602. [PubMed: 23721604]
54. Marsden JR, Newton-Bishop JA, Burrows L, et al. Revised UK guidelines for the management of cutaneous melanoma 2010. *J Plast Reconstr Aesthet Surg.* 2010; 63:1401–19. [PubMed: 20728418]
55. Dummer R, Guggenheim M, Arnold AW, et al. Updated Swiss guidelines for the treatment and follow-up of cutaneous melanoma. *Swiss Med Wkly.* 2011; 141:w13320. [PubMed: 22180245]

Key points

- Surveillance strategies should be more frequent for patients with advanced stages of melanoma, and visit frequency can later decrease over time as the disease-free interval increases.
- Important components of follow-up exams include history and physical exams, patient education, risk-factor modification, assessment of the psychosocial impact of disease, and counseling on healthy coping mechanisms.
- The work-up of melanoma recurrence is based on the type of recurrence: local, satellite/in-transit, regional, or distant metastatic disease.
- The treatment of melanoma recurrence parallels how primary tumors, nodal, and distant metastases are managed.

Synopsis

The number of melanoma survivors in the United States (U.S.) continues to steadily increase 2.6% per year, while death rates have remained stable over time. Although controversy exists regarding optimal surveillance strategies, recommendations for clinical monitoring are based on tumor stage, tumor phenotype, likelihood of recurrence, prognosis, risk factors, psychosocial impact of disease, and patient well-being. Management guidelines for recurrent disease depend on the type of recurrence: local, satellite/in-transit, regional, or distant metastasis. This article is a current review of the literature concerning melanoma survivorship.

Table 1

Five-Year Survival Rates for Stage III Patients with Micro- vs. Macro-metastases.

No. of Positive Nodes	<u>Microscopic + Nodes</u>		<u>Macroscopic + Nodes</u>		<i>P</i> *
	Survival % $\pm$ SE	No.	Survival % $\pm$ SE	No.	
1	61 $\pm$ 2.8	469	46 $\pm$ 3.6	220	< .0001
2	56 $\pm$ 4.6	172	37 $\pm$ 4.4	139	< .0001
3	56 $\pm$ 8.5	69	27 $\pm$ 6.0	63	< .001
4	36 $\pm$ 8.7	40	24 $\pm$ 4.4	106	.1034
>4	35 $\pm$ 8.7	73	24 $\pm$ 3.5	175	.0011

From: Balch et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001; 19:3622-34.

* *P* value based on the comparison of survival curves using the log-rank test.

Table 2

Summary of Melanoma Surveillance Guidelines by Country.

AJCC Staging	Australia/New Zealand (49)	Canada (BCCA, AHS) (50,51)	Europe (ESMO) (52)	Germany (S3 Guidelines) (53)	United Kingdom (BAD, BAPRAS) (54)	United States (NCCN) (26)	Switzerland (55)
<i>Recommended Number of Visits Per Year (Includes ROS and H&P)</i>							
Stage 0	1	1	No consensus	--	0	1	--
Stage 1							
Years 1–2	2	1–2	No consensus	2–4	2–4	1–2	2–4
Year 3	2	1–2		2–4	2–4	1–2	2–4
Year 4–5	2	1		1–2	2	1–2	1–2
Year > 5	1	1		1–2, up to 10 yr	--	1	1–2, up to 10 yr
Stage II							
Years 1–2	3–4	2–4	No consensus	4	4	2–4	4
Year 3	3–4	2		4	4	1–4	4
Year 4–5	3–4	1–2		2–4	2	1–4	2–4
Year > 5	1	1		1–2 up to 10 yr	--	1	1–2, up to 10 yr
Stage III–IV							
Years 1–2	3–4	2–4	No consensus	4	4	2–4	4
Year 3	3–4	2–4		4	4	1–4	2
Year 4–5	3–4	1–3		4	2	1–4	2
Year > 5	1	1		2, up to 10 yr	1, up to 10 yr	1	--
<i>Recommended Self-Exams</i>							
	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<i>Routine Diagnostic Testing and Frequency (Number of Times Per Year)</i>							
Stage 0	No	No	--	--	No	No	--
Stage I	No	No	--	LNS for Stage 1B (2)	No	No	No
Stage II	LNS (3–4)	No	--	LNS for Stage IIC (2–4); CT (2)	No	Consider brain MRI, CXR, CT, or PET/CT for Stage IIB*	LNS, CT, MRI, PET, or PET/CT for Stage IIC (1–2)
Stage III	LNS (3–4)	No	Consider LNS, CT, or PET/CT	LNS (2–4); CT(2)	Based on clinical need	Consider brain MRI, CXR, CT, or PET/CT *	LNS, CT, MRI, PET, or PET/CT (1–2)

AJCC Staging	Australia/New Zealand (49)	Canada (BCCA, AHS) (50,51)	Europe (ESMO) (52)	Germany (S3 Guidelines) (53)	United Kingdom (BAD, BAPRAS) (54)	United States (NCCN) (26)	Switzerland (55)
Stage IV	LNS (3–4)	No	Consider LNS, CT, or PET/CT	LNS (2–4); CT(2)	Based on clinical need	Consider brain MRI, CXR, CT, or PET/CT *	Individualize care
Symptom Initiated	--	CXR, CT	--	--	LNS, CT, OR PET/CT	Consider CXR, CT, PET/CT, or MRI	--
<i>Routine Laboratory Tests and Frequency (Number of Times Per Year)</i>							
	No	No	No	S-100 for Stage IB (2–4)	LDH for Stage IV	No	S-100 (1–2)

Abbreviations from Table 2:

AHS: Alberta Health Services; BAD: British Association of Dermatologists; BAPRAS: British Association of Plastic, Reconstructive, and Aesthetic Surgeons; BCCA: British Columbia Cancer Agency; CCO: Cancer Care Ontario; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network, *Category 2B recommendation; routine imaging not recommended after first 5 years; CT: Computed tomography; CXR: Chest x-ray; H&P: History and physical; LDH: Lactate dehydrogenase; LNS: Lymph node sonography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; ROS: Review of systems