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Long-Term Follow-up for Melanoma Patients: Is There Any Evidence of a Benefit?

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SYNOPSIS

As the incidence of melanoma—and therefore the number of melanoma survivors—continues to rise, optimal surveillance strategies are needed that balance the risks and benefits of screening in the context of contemporary resource utilization. Detection of recurrences has important implications for clinical management. Most current surveillance recommendations for melanoma survivors are based on low-level evidence with wide variations in practice patterns and an unknown clinical impact for the melanoma survivor.

Keywords

evidence-based surveillance; cost-effectiveness; melanoma; survivorship; guidelines; diagnostic imaging

INTRODUCTION

Contemporary surveillance guidelines for cancer survivors are low-level, category 2A–2B recommendations (i.e., “based upon lower-level evidence, there is *uniform* consensus [category 2A] or *consensus* [category 2B] that the intervention is appropriate”)¹ and are therefore heavily dependent on expert opinion. Even the handful of tumor types for which

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surveillance recommendations have been rigorously studied lack category 1 (i.e., “based upon high-level evidence, there is uniform consensus that the intervention is appropriate”)¹ surveillance recommendations. As an example, seven clinical trials^{2–8} have evaluated various surveillance regimens for patients with surgically treated colorectal cancer and yielded mixed results. Subsequent meta-analyses of these results^{9,10} have suggested improvements in overall survival (but not disease-specific survival) in the setting of intensive surveillance. In contrast, several well-designed randomized studies evaluating surveillance strategies of varying intensities for women with treated breast cancer have shown no survival benefit for intensive surveillance compared with less intensive strategies.^{11–14} Still, controversy over breast cancer surveillance exists, and surveillance practice patterns vary widely.

From a practical perspective, the frequency and intensity of follow-up for cancer survivors are determined by the resources available and the preferences of the patient in conjunction with a provider’s specific preferences. These factors have increasingly important implications as the number of cancer survivors in the world increases. Owing to improvements in the detection of early-stage melanoma at a time when adequate local treatment is potentially curative, 5-year relative survival rates for patients with melanoma now exceed 90%,¹⁵ which means that more people are living longer after the diagnosis of what was once a frequently deadly cancer.¹⁶ However, in the absence of evidence-based follow-up guidelines, the question is how can clinicians best manage melanoma cases so as to detect disease recurrence while it is still treatable?

As many as half of all patients treated for melanoma will have a recurrence.^{17,18} Of these recurrences, approximately 50% will be in the regional lymph nodes, 20% will be local recurrences, and 30% will arise at distant sites.^{19–21} Although most recurrences will develop in the first 2–3 years after treatment, some late recurrences more than 10 years after treatment are well documented, particularly for patients who initially had early-stage melanoma. In a retrospective study of more than 7100 patients with early-stage melanoma, Crowley and Seigler reported that the overall rate of recurrence 10 years after the diagnosis of the primary was 2.4%.²² Surgical resection is generally performed for local and regional recurrences, with good survival outcome and metastasectomy for distant recurrences in very carefully selected patients has demonstrated survival benefits.^{23–26}

In designing optimal surveillance strategies, clinicians must focus on the risk of early recurrence but must also consider the risk of late recurrences within the context of a patient’s changing risk over time. As an example, in a retrospective study of 340 patients with stage III melanoma, Romano and colleagues²⁷ found that most local and regional recurrences were detected by physical examination alone, whereas patients with distant recurrences most frequently presented with symptoms. Routine computed tomography (CT) imaging detected asymptomatic recurrences in 25% of all patients studied, often within 3 years of **the original** melanoma diagnosis.²⁷ In this study, the incidence of a first-time distant recurrence was 5% or less after 32 months, 40 months, and 21 months for patients with stage IIIA, IIIB, and IIIC disease, respectively, leading the authors to conclude that routine CT imaging as a surveillance method would have low yield beyond those time points.²⁷

Importantly, because cancer survival estimates are heavily influenced by early cancer deaths, the estimates may not accurately reflect long-term outcomes for patients who survive to a certain point after the original diagnosis. As an alternative approach to predicting long-term survival, conditional survival analysis calculates the changing risk of death over time. For patients with all stages of melanoma, conditional survival studies have demonstrated that survival estimates improve dramatically as survival time increases, such that eventually, the original stage at diagnosis is no longer a significant predictor of ongoing survival (Figure 1).^{21,22} These two competing concepts—indolent disease with the potential for late recurrences but in light of known improvements in cancer survival as time from original treatment increases—make optimal melanoma surveillance a complex challenge for patients and clinicians.

To address these challenges, current guidelines for surveillance in patients with melanoma published by the National Comprehensive Cancer Network¹ emphasize more frequent visits with more intensive stage-specific surveillance imaging early in the post-treatment phase, when the risk of recurrence is greatest. As the disease-free interval increases, office visits and imaging should become less frequent, but annual skin examinations for all stages of primary disease should continue for the rest of the patient's life. Annual skin examinations for life, particularly for patients with early-stage, low-risk melanoma, are a logical surveillance strategy based on recurrence and survival patterns; however, recommendations become less clear for patients with locally advanced stage III melanoma. Beyond annual skin examinations, the current recommendations for patients with stage III melanoma range from conventional x-ray radiography of the chest to a complex positron emission tomography (PET)/CT scan at time intervals ranging from 3 to 12 months.

The data available to aid in the development of appropriate stage-specific surveillance recommendations are limited in scope and value. The broad generalities in surveillance recommendations very likely reflect uncertainties in modern resource utilization and a limited understanding of the effects of different surveillance strategies on patient quality of life and cancer survival. Toward elucidating these uncertainties and enhancing the understanding of surveillance strategies' effects on melanoma patients' quality of life and survival, this article will review issues key to designing surveillance strategies, including early detection, surveillance evaluation modalities, surveillance effectiveness, variation in current surveillance practices, surveillance costs, and other practice implications.

BENEFITS OF EARLY DETECTION

For patients who have undergone treatment of primary melanoma, early detection of a local recurrence has important implications. An isolated local recurrence in a patient with favorable features can be treated with repeat wide local excision, with good oncologic outcomes. For these patients, long-term prognosis is not adversely affected by the local recurrence if it is detected and treated early, and 5-year survival continues to be a function of primary tumor thickness.^{19,28,29} For those whose disease relapses in the regional lymph node basins, prognosis depends on the tumor burden at the time of detection, but early identification of regional recurrences and subsequent treatment with surgical resection can increase survival time compared with late identification of recurrences that present on

clinical examination or with development of symptoms.²⁸ In the recently published final report from the landmark Multicenter Selective Lymphadenectomy Trial (MSLT-1), Morton and colleagues reported that for patients with intermediate-thickness melanoma, those who underwent nodal observation only and subsequently developed a clinically evident nodal recurrence had 5- and 10-year melanoma-specific survival rates of 57.5% and 41.5%, respectively, whereas patients with positive sentinel lymph node metastases found through biopsy and treated at original presentation had a 10-year melanoma-specific survival of 62.1%.³⁰ The benefit of early detection of regional lymph node recurrences, therefore, highlights the importance of detecting them at a time when appropriate therapy still can be administered with curative intent.

For patients who develop distant melanoma recurrences, the appropriate therapeutic approach is highly debated. Because the lungs are the most common site of distant, metastatic melanoma involvement,³¹ many patients undergo imaging studies aimed at detecting “treatable” distant recurrences. For melanoma patients with pulmonary involvement, the 5-year overall survival is 4%.³² For the 12–25% of patients who are candidates for surgical resection of their metastatic melanoma, 5-year survival may be modestly improved and is as high as 30% in some studies.^{32–34}

In a retrospective analysis of patients enrolled in the Multicenter Selective Lymphadenectomy Trial (MSLT-1), Howard and colleagues²⁴ estimated that as many as 50% of patients with stage IV melanoma may be candidates for surgical treatment of their metastatic disease. In that review, the median survival time was significantly longer for patients undergoing surgical resection of their metastatic disease (15.8 months) with or without systemic medical therapy than for patients who did not undergo surgery (6.9 months). The survival benefit was significantly greater among patients with a longer disease-free interval whose metastatic disease was isolated to one or two organ sites.²⁴ Therefore, although patient selection bias likely plays a large role in retrospective reports of survival after surgery for distant disease recurrence, a carefully selected subset of patients with advanced-stage melanoma would likely benefit from early detection of treatable metastatic disease and subsequent surgical intervention.

Because the early detection of melanoma recurrences has a potential survival benefit for a select population of patients, optimal surveillance strategies that can impact clinical care must be defined. The primary objective of surveillance should be to detect local, regional, and distant recurrences at a time when intervention can still improve survival. It is important to note, however, that for the increasing numbers of melanoma survivors in the United States, no available data suggest that disease control, survival, or quality of life is significantly improved with routine surveillance imaging studies. Patients with local and regional recurrences, a majority of whom are diagnosed clinically, have favorable 5-year survival, as high as 80%.²² Distant metastatic disease, on the other hand, which is usually diagnosed with routine oncologic surveillance imaging or imaging ordered as a result of symptom presentation, has uniformly poor 5-year survival once diagnosed (20% or less³⁵). These data lead to the question of whether more intensive surveillance to detect recurrences before distant disease develops would translate to improved patient survival.

SURVEILLANCE EVALUATION MODALITIES

Clinical examination effectively diagnoses local recurrences in more than 50% of patients with treated melanoma in whom recurrent melanoma or second primary tumors develop.^{28,36} In a study of 1062 patients with early-stage melanoma (I/II), self-detection and clinical physical examination identified 95% of all recurrences at a median of 17 months following a sentinel lymph node biopsy with negative results.³⁷ A prospective database analysis of 118 patients with stage II or III melanoma found that 67% of recurrences were diagnosed through self-detection or symptomatic presentation. An additional 26% of recurrences were found by clinical examination on routine follow-up.³⁸ A review found that 18% of 38 patients with stage III melanoma developed a recurrence at a median disease free interval of 25 months; the majority of these recurrences (57%) were identified by the patient or physician in a clinical examination.³⁹

Regional lymph node basins can be effectively evaluated using non-invasive ultrasonography. Studies have demonstrated that the sensitivity of ultrasonographic evaluation of the lymph node basins is 87–99%, with a specificity of 74–99%^{39,40} when the tumors within the lymph node are greater than 1 mm.^{41,42} To determine the effect of ultrasonographic surveillance in the detection of regional recurrences in patients with treated melanoma, a meta-analysis using data from a systematic review of four major medical indices was completed by Xing and colleagues.⁴³ For this analysis, patient-level data were extracted from the 74 studies deemed eligible using quality assessment and were subsequently modeled using Bayesian statistics to yield findings related to the sensitivity, specificity, and diagnostic odds ratio for imaging of the regional lymph nodes and of distant metastases using ultrasonography, CT, PET, and PET/CT, with credible intervals to define the posterior probability distribution for interval estimation. Ultrasonography had the highest sensitivity (60%, 95% credible interval [CI]: 33–83%), specificity (97%, 95% CI 88–99%), and diagnostic odds ratio (42, 95% CI: 8.08–249.8) for the surveillance of regional lymph nodes.⁴³ Therefore, ultrasonography is superior to physical examination alone for the detection of regional lymph node recurrences^{44,45}; as such, ultrasonography has been incorporated into many international guidelines for the follow-up of melanoma patients.⁴⁶ The same study found that for the surveillance of distant metastases, PET/CT had the highest sensitivity (80%, 95% CI: 53–93%), specificity (87%, 95% CI: 54–97%), and diagnostic odds ratio (1675, 95% CI: 226.5–15,920). Summary findings for this study appear in Table 1.

In the only prospective study evaluating surveillance for patients with melanoma according to stage, Garbe and colleagues²⁸ followed a cohort of 3008 patients with stage I–IV melanoma over a 2-year period. Patients were evaluated according to German surveillance guidelines, with frequent physical examinations (every 3 months) and routine ultrasonographic evaluation of the tumor scar and draining lymph node basins (annually for patients with stage I disease, every 6 months for those with stage II disease, and every 3–6 months for those with stage III disease). Cross-sectional imaging using CT scan or MRI was used only to evaluate suspicious clinical or ultrasonographic findings. Nearly 50% of recurrences were detected with clinical examination alone, even in patients with stage III

disease. The addition of CT performed on the basis of clinical suspicion detected an additional 27.7% of recurrences.²⁸

SURVEILLANCE EFFECTIVENESS

To understand the extent to which surveillance imaging translates to a survival benefit for patients with treated melanoma, Rueth and colleagues⁴⁷ developed a decision-support model designed to evaluate the effectiveness of routine CT and PET/CT surveillance of patients with stage I-III melanoma. In this study, a probabilistic Markov model representing the stage-specific natural history of surgically treated melanoma was developed (Figure 2). The model estimates were derived from 1600 patients with melanoma who were evaluated and surgically treated at a single institution. Patient-level time-to-event data were used to determine the monthly transition probabilities, which were estimated using parametric survival models from the time of definitive local/regional treatment. The study evaluated the ability of various surveillance imaging modalities and timelines (CT or PET/CT performed every 6 or 12 months for 5 years) to detect regional or distant recurrences that could be treated with surgical resection with curative intent, using established sensitivity and specificity data for contemporary diagnostic imaging modalities including CT, PET/CT, MRI and US.⁴⁷

For patients with stage I melanoma, in whom recurrence rates are low, the authors calculated that if routine surveillance imaging were performed at 12-month intervals, 362 CT scans or 249 PET/CT scans would have to be performed over the course of 5 years to diagnose one treatable recurrence in a patient with stage I disease.⁴⁷ Furthermore, they reported that routine annual surveillance imaging for patients with stage I melanoma would result in a 5-year total of 45,296 CT scans or 45,314 PET/CT scans per 10,000 patients to detect one treatable recurrence.

In contrast, as the incidence of regional or distant recurrence increased with disease stage, so too did the number of surgically treatable recurrences detected with routine surveillance imaging increase with stage. Among the highest-risk patients—those with stage IIIC disease—the authors calculated that routine surveillance CT or PET/CT performed every 12 months would detect surgically treatable regional and distant recurrence in 6.4% and 8.4% more patients, respectively, than would annual physical examination alone. In this population, one of every 34 CT scans and one of every 26 PET/CT scans would detect a treatable recurrence.

According to these identification estimations, although more treatable recurrences were detected with the use of routine PET/CT than with CT alone, there were no differences between CT and PET/CT in the calculated 5-year disease-specific survival, regardless of disease stage. Similarly, more frequent imaging (every 6 months versus every 12 months) did not substantially increase the 5-year disease-specific survival, regardless of disease stage (Table 2). The greatest survival benefit from more frequent imaging was seen for patients with stage IIIB or IIIC disease. Even in these groups, however, the difference between a less rigorous imaging strategy of CT every 12 months and a more rigorous imaging strategy of PET/CT every 6 months in terms of 5-year disease-specific survival was minimal.

Notably, routine surveillance imaging did not substantially increase life expectancy for any subgroup of melanoma patients regardless of imaging modality or frequency (Figure 3). For patients with stage I melanoma, in whom the average life expectancy was 51.6 months without surveillance imaging, the increase in life expectancy that resulted from the addition of rigorous, routine surveillance PET/CT imaging every 6 months was only 0.4 months. This translated to an increase in relative survival time (relative to the survival of patients who underwent clinical examination alone) of only 0.7%. Even for patients with stage IIIC disease who underwent the most aggressive imaging strategy of PET/CT surveillance imaging every 6 months and in whom treatable recurrence rates exceeded 20%, the mean increase in life expectancy was only 2 months—from 30.0 to 32.0 months—which translated to a relative survival time increase of 6.8%.

With a negative predictive value nearing 100%, routine imaging can effectively rule out melanoma recurrence; however, the high rate of false-positive studies and the low positive predictive value associated with imaging mean that many studies must be performed to detect a small number of treatable recurrences, likely with little impact on patient survival.⁴⁸ Even the identification of treatable recurrent disease by means of routine surveillance imaging using the most sensitive tests available would likely result in only a minimal increase in life expectancy compared with results for routine clinical examination alone. For patients with stage III melanoma, the average gain in absolute life expectancy as a result of routine surveillance imaging is only a few months. These data solidify the point that for the majority of patients with surgically treated melanoma, routine imaging is not likely to offer a substantial long-term survival benefit; however, a subset of stage III patients may obtain a modest survival benefit from routine surveillance imaging.

VARIATION IN CURRENT SURVEILLANCE PRACTICES

In the absence of evidence-based guidelines, many clinicians use practice patterns that they or their patients are most comfortable with. To identify the most commonly used frequency, duration, and type of follow-up for patients with melanoma, Cromwell and colleagues⁴⁹ completed a systematic review of three medical indices and found significant variability in surveillance practices depending on the country in which the study was conducted and the background of the treating clinician. A total of 104 studies were eligible for inclusion in that review, encompassing studies done in seven countries (Australia/New Zealand, Canada, Germany, the United Kingdom, the United States, the Netherlands, and Switzerland (Table 3)) and studies with treating clinicians in four medical specialties (general practitioner, dermatologist, medical oncologist, and surgical oncologist (Table 4)). Practices varied between

In the review of Cromwell et al.,⁴⁹ among patients with stage I melanoma, intervals between visits during the first 2 years after treatment ranged from every 2 months to every 12 months, with routine imaging that often included lymph node ultrasonography and chest x-ray radiography. Thereafter, in the absence of recurrence, visit intervals decreased to 3–12 months for years 3–5 after treatment. The highest frequencies of visits were seen in the United Kingdom and the Netherlands.⁴⁹ General practitioners evaluated patients more frequently than clinicians in any other specialty.

As reported in Cromwell et al.,⁴⁹ for patients with stage II melanoma, clinical examination frequency was less varied, with clinicians in the majority of countries screening these patients at least every 3 months. Clinicians in Canada, the United States, and Switzerland reported common use of CT scans of the chest, abdomen, and pelvis area, and clinicians in Germany frequently used magnetic resonance imaging in addition to CT. All specialists routinely evaluated patients every 3 months for the first 3 years after diagnosis. After 3 years of disease-free survival, surgical oncologists tended to decrease patients' clinical visits to every 6 months, whereas other specialists continued with visits at 3-month intervals through year 5.⁴⁹

For patients with stage III melanoma, in whom the risk of recurrence is considerably higher than in those with earlier-stage disease, variation in type and frequency of follow-up remains high. Among most specialties and countries, the use of diagnostic imaging tools was much more widespread, with ultrasonography being the most commonly used strategy, followed by PET/CT and CT alone (Tables 3–5).⁴⁹

COSTS OF SURVEILLANCE

Such extreme variations in clinical practice and resource utilization when these variations likely have a minimal impact on life expectancy have important implications for clinical care, particularly in the contemporary era of increasing cost-consciousness in healthcare. Hofmann and colleagues⁵⁰ reported that in Germany, imaging studies detected 25% of melanoma recurrences but accounted for 50% of follow-up costs. The cost per detected first recurrence in patients with stage I disease was as high as €35,900 (\$32,310 according to 2002 conversion data) for aggressive imaging regimens whereas the cost per detected, treatable metastases using clinical examination alone ranged from €2800 (\$2520) for patients with stage III disease to €13,300 (\$11,970) in patients with stage I/II recurrence in 2002.⁵⁰ Importantly, in this study, there was no survival difference between patients with recurrences detected by clinical examination and patients with asymptomatic recurrences detected with imaging.⁴⁸ Similarly, Basseres and colleagues⁵¹ concluded that for patients with stage I melanoma treated in France, clinical examination was the only cost-effective surveillance modality. Hengge and colleagues⁵² calculated that for patients with stage II disease, the median cost to detect a recurrence with clinical examination was €2,715 (\$2,444); this cost increased to €32,007 (\$28,806) when surveillance imaging was added. All of these investigators concluded that routine surveillance imaging for patients with surgically treated stage I or II melanoma is not cost-effective.

To understand the potential role of imaging for patients with more advanced disease, Bastiaannet and colleagues⁵³ conducted a multi-institutional, multinational cost analysis exploring the utility of cross-sectional imaging for *preoperative* staging for patients presenting with clinically detectable nodal disease. In their study, the addition of CT decreased the cost of staging and subsequent treatment by 5.5% compared with chest radiography and clinical examination alone, whereas the addition of PET/CT to chest radiography and clinical examination increased these costs by 15.1%.⁵¹ This cost difference was due to the fact that PET/CT, which has a slightly higher diagnostic accuracy than CT, upstaged disease, which led to higher adjuvant treatment costs despite lower surgical

treatment costs. The authors concluded that routine preoperative imaging in patients with melanoma presenting with clinically detectable regional metastases (stage III) is cost-effective. However, they could not make inferences about postoperative surveillance imaging because of the study design.⁵¹ In fact, the cost-effectiveness and clinical impact of routine *postoperative* surveillance imaging for patients with stage III disease has not been well evaluated in any contemporary studies; an analysis that critically explores the diagnostic and survival benefits of postoperative surveillance imaging in these patients in the context of resource utilization and medical costs is needed.

Clearly, investigations designed to develop standardized follow-up protocols for melanoma cancer survivors that balance cost, resource utilization, and patient outcomes are very much needed; such studies are currently ongoing.

OTHER PRACTICE IMPLICATIONS

Although the early detection of a surgically resectable recurrence may be the primary reason for performing routine surveillance imaging, other ramifications of surveillance must be considered. Surveillance also can lead to reassurance or confirmation of an ongoing disease-free interval, which could not only guide future surveillance but also benefit quality of life; the initiation of systemic treatment for non-surgical candidates or early enrollment into clinical trials; and the detection of new primary malignancies or second primary melanomas.^{47,49,50}

In a recent meta-analysis of 15 survey-based studies evaluating the psychosocial response to melanoma, Rychetnik and colleagues⁵⁴ reported that despite increasing evidence refuting the benefits of routine surveillance imaging for patients with early-stage disease, clinicians continue to order surveillance imaging studies for patients with stage I and II disease to provide reassurance. Nearly 75% of such patients in that study underwent a wide range of diagnostic imaging studies (conventional chest radiography, CT, or ultrasonography) that are not currently recommended by published guidelines; the authors noted that one of the primary reasons that physicians ordered diagnostic tests was patient anxiety or patient request.⁵² This aggressive use of surveillance imaging suggests a need for ongoing, data-driven initiatives that aim to mitigate anxiety and improve survivor quality of life by delineating when surveillance imaging can provide actual survival benefit while reducing potentially unnecessary cost.

Less aggressive surveillance also may reduce adverse effects due to imaging procedures. Imaging studies are not without risk to the patient, with the potential for contrast dye reactions, renal injury, and harmful radiation exposure. Radiation exposure is a potential consideration for clinicians ordering surveillance imaging studies for melanoma survivors. Mathews and colleagues recently estimated that radiation exposure is associated with an excess incidence rate of 9.38 cancers per 100,000 person-years at risk.⁵⁵ Similarly, Miglioretti and colleagues studied radiation exposure resulting from CT imaging in children and projected that the 4 million pediatric CT scans performed annually in the United States would result in 4,870 future malignancies.⁵⁶ Although the risks of radiation exposure are less well studied in adults, the American College of Radiology has developed a series of

guidelines to help identify the clinical conditions in which imaging is most appropriate,⁵⁷ and the National Institute of Biomedical Imaging and Bioengineering is challenging investigators to develop new technology that will drastically reduce radiation exposure resulting from radiographic imaging.⁵⁸

Once patients are diagnosed with disease recurrence, the limited ability of systemic therapy to offer a long-term survival benefit for patients has been a vexing challenge for melanoma care providers, resulting in a heavy reliance on surgical treatment. Recent studies have shown promising results using targeted systemic therapies and combination therapies in the treatment of unresectable stage III and stage IV disease.^{59,60} The promising early results seen for patients treated with novel targeted agents like vemurafenib and ipilimumab has resulted in rapid changes in the landscape of systemic melanoma treatment. It is possible, therefore, that future therapeutic developments will result in increasingly effective systemic treatment options for patients with recurrent disease and that a subset of these patients will derive a survival benefit from early detection of disease recurrence. In the meantime, as rapid advances are being made in the areas of targeted therapies, vaccine trials, and innovative treatments combining traditional interleukin or cytotoxic chemotherapy agents with novel drugs, the identification of patients with locoregional melanoma recurrence who are appropriate candidates for enrollment into clinical trials must be considered when choosing individualized patient surveillance strategies.

In addition to the risk of locoregional or distant melanoma recurrence, we must not overlook the risk of patients with treated melanoma developing a second primary melanoma or other primary malignancy. Recent conditional survival analyses have demonstrated that the ongoing risk of dying of a treated melanoma decreases as survival time increases^{48,61}; however, the risk of developing a second primary malignancy increases over time. This risk is substantial; in a retrospective review using the Surveillance, Epidemiology, and End Results database, Spanogle and colleagues found that among 16,591 patients with previously treated melanoma, the risk of developing a second primary malignancy was 32% higher than in the general population without a melanoma diagnosis.⁶² The risk was highest among patients under the age of 40 years, highlighting the need for ongoing dermatologic surveillance aimed at detecting second melanomas and for routine medical care and guideline-recommended cancer screening, including mammography and colonoscopy.

SUMMARY

Cumulative findings support the current National Comprehensive Cancer Network guidelines for surveillance in early-stage melanoma (stages IA–IIA), which recommend lifelong dermatologic surveillance with regular comprehensive skin exams, adding imaging studies only if there is clinical suspicion of recurrence.¹ Regular clinical examination offers the highest diagnostic yield in detecting melanoma recurrences, with additional diagnostic benefit seen when imaging is used for patients in whom clinical evaluation or symptomatic presentation suggests the presence of distant disease.

However, for patients with locally or regionally advanced melanoma (stages IIB–IIIC), there is a paucity of data to support the use of rigorous, routine surveillance imaging studies

following appropriate staging and surgical treatment of their disease. Contemporary guidelines recommend, on the basis of low-level evidence (category 2B), that clinicians consider the addition of CT and/or PET/CT every 3 to 12 months for these patients.¹ However, current data indicate that such a regimen would result in an exceedingly large number of studies performed to detect a limited number of surgically treatable recurrences and would have little impact on patient survival. Although there likely is a subset of patients with high risk melanoma in whom routine oncologic imaging surveillance has the potential to offer survival benefit, a more judicious approach to the use of imaging studies may be equally effective with little detrimental impact on survival. Such considerations are of increasing interest in the modern era of rising health care costs and impending limitations on resource utilization.

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Key Points

- Current surveillance practices for melanoma are based on low-level evidence with unknown clinical impact
- Surveillance for melanoma recurrence is most frequently based on preferences of patient and provider
- Serial routine surveillance imaging has demonstrated limited evidence for detecting recurrent melanoma at a time in which it is treatable

Figure 1.

Melanoma-specific 5-year Conditional Survival estimates stratified by disease stage.

From Xing Y, Chang GJ, Hu CY, et al: Conditional survival estimates improve over time for patients with advanced melanoma: results from a population-based analysis. *Cancer* 2010 May 1;116(9):2234–41, with permission.

Figure 2.

Markov model representing the stage-specific natural history of surgically treated melanoma. Time horizon: lifetime. λ_{12} indicates monthly transition rate from no evidence of disease (NED) to regional recurrence; λ_{13} , monthly transition rate from NED to distant recurrence; λ_{14} , monthly transition rate from NED to death from other causes; $\lambda_1 = \lambda_{12} + \lambda_{13} + \lambda_{14}$ = monthly transition rate of NED.

From Rueth NM, Xing Y, Chiang YJ, et al: Is Surveillance Imaging Effective for Detecting Surgically Treatable Recurrences in Patients With Melanoma? A Comparative Analysis of Stage-Specific Surveillance Strategies. *Ann Surg*, 2014 Jun;259(6):1215–22, with permission.

Figure 3.

Stage-Specific Relative Increase in Life Expectancy for Imaging Surveillance Compared to Clinical Examination Alone (By Stage and Frequency).

From Rueth NM, Xing Y, Chiang YJ, et al: Is Surveillance Imaging Effective for Detecting Surgically Treatable Recurrences in Patients With Melanoma? A Comparative Analysis of Stage-Specific Surveillance Strategies. *Ann Surg*, 2014 Jun;259(6):1215–22, with permission.

Table 1

Surveillance strategies for melanoma patients

Location and imaging method	Median sensitivity (%) (95% credible interval)	Median specificity (%) (95% credible interval)	Median diagnostic odds ratio (95% credible interval)
Regional lymph nodes			
Ultrasonography	96 (85–99)	99 (95–100)	1675 (226–15,920)
CT	61 (15–93)	97 (70–100)	46 (2–1354)
PET	87 (67–96)	98 (93–100)	391 (68–2737)
PET/CT	65 (20–93)	99 (92–100)	196 (11–4675)
Distant sites			
CT	63 (46–77)	78 (58–90)	6 (2–18)
PET	82 (72–88)	83 (70–91)	22 (9–51)
PET/CT	86 (76–93)	91 (79–97)	67 (20–230)

Adapted from Xing Y, Bronstein Y, Ross MI, et al: Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. *J Natl Cancer Inst* 103:129–42, 2011 and Xing Y, Cromwell KD, Cormier JN. Review of Diagnostic Imaging Modalities for the Surveillance of Melanoma Patients. *Dermatology Research and Practice* 2012; 2012, with permission.

Table 2

Unadjusted 5-year disease-free survival, disease-specific survival, and increase in life expectancy with surveillance imaging

Stage/Modality	6-month exam interval			12-month exam interval		
	5-year NED (%)	5-year DSS (%)	Average increase in life expectancy (months)	5-year NED (%)	5-year DSS (%)	Average increase in life expectancy (months)
Stage I						
CT	87.7	91.8	0.3	87.7	91.5	0.2
PET/CT	87.7	91.9	0.4	87.7	91.5	0.2
Stage II						
CT	70.5	77.0	0.9	70.5	76.2	0.5
PET/CT	70.5	77.4	1.1	70.5	76.3	0.5
Stage IIIA						
CT	72.0	76.1	0.8	72.0	75.7	0.4
PET/CT	72.0	76.3	0.9	72.0	75.8	0.4
Stage IIIB						
CT	48.3	52.9	1.4	48.3	52.4	0.7
PET/CT	48.3	53.4	1.7	48.3	52.5	0.7
Stage IIIC						
CT	32.1	37.0	1.8	32.1	36.4	0.8
PET/CT	32.1	37.6	2.0	32.1	36.5	0.8

NED indicates no evidence of disease; DSS, disease-specific survival

Adapted from Rueth NM, Xing Y, Chiang YJ, et al: Is Surveillance Imaging Effective for Detecting Surgically Treatable Recurrences in Patients with Melanoma? A Comparative Analysis of Stage-Specific Surveillance Strategies. *Ann Surg*. 2014 Jun;259(6):1215–22, with permission.

Table 3

Stage-specific surveillance guidelines by country during years 1 to 5

Stage/Mean of Detection	Australia/New Zealand ⁶⁴⁻⁶⁶	Canada ⁶⁷	Germany ⁶⁸⁻⁷¹	United Kingdom ⁷²⁻⁷⁴	United States ^{1,36,75-77}	The Netherlands ⁷⁸⁻⁸¹	Switzerland ^{82,83}
<i>Number of visits per year</i>							
Stage I							
Years 1-2	1-2	2-4	3-4	2-6	1-3	3-4	2
Year 3	1-2	2-4	3-4	2-3	1-3	3-4	2
Years 4-5	1-2	2-4	2	1-2	1-3	4-5	1-2
Stage II							
Years 1-2	1-4	4	2-4	4	2-4	3	2-4
Year 3	1-4	4	2-4	2	1-4	3	2-4
Years 4-5	1-4	2	2-4	2	1-4	2	2-3
Stage III							
Years 1-2	2-4	4	2-4	4	2-4	4	4
Year 3	2-4	4	2-4	2	1-4	4	4
Years 4-5	2-4	2	2-4	2	1-4	4	2
Self-examination	Yes	Yes	Yes	Yes	Yes	Yes	Yes
<i>Recommended evaluations</i>							
<i>Routine diagnostic imaging</i>							
Stage I	Sonography of regional nodal basin	No	Sonography of regional nodal basin	Photography, abdominal sonography, chest radiography	Chest x-ray	No	Chest x-ray, sonography of regional nodal basin
Stage II	Sonography of regional nodal basin	Chest radiography, bone and liver-spleen scan	Chest x-ray, CT/MRI, and PET	Photography, abdominal sonography, chest radiography	Chest x-ray, CT of chest, abdomen and pelvis	No	Sonography of regional nodal basin, PET or CT
Stage III	Sonography of regional nodal basin	Chest x-ray, bone and liver-spleen scan	Chest radiography, CT/MRI, PET	Clinical photography, abdominal sonography, chest radiography	PET/CT	No	Sonography of regional nodal basin, PET or CT
Symptom-initiated					Chest radiography, PET, CT, MRI, PET/CT		Abdominal sonography, CT, MRI, PET-CT (for non-stage III)

Stage/Mean of Detection	Australia/New Zealand ⁶⁴⁻⁶⁶	Canada ⁶⁷	Germany ⁶⁸⁻⁷¹	United Kingdom ⁷²⁻⁷⁴	United State ⁷⁵⁻⁷⁷	The Netherlands ⁷⁸⁻⁸¹	Switzerland ^{82,83}
Laboratory assessment	No	CBC, liver function test	S100 serum protein (stage 2)	CBC, liver function, creatinine, lactate dehydrogenase	No	No	S-100 serum protein (stage II)

MRI indicates magnetic resonance imaging.

Adapted from 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* 22:376-85, 2012, with permission.

Table 4

Stage-specific surveillance guidelines by physician specialty during years 1–5

Stage/Mean of Detection	General practitioner ^{84–90}	Dermatologist ^{69,91,92}	Medical oncologist ^{71,91}	Surgical oncologist ^{38,80}
<i>Number of visits per year</i>				
Stage I	4	2	2	NA
Stage II				
Years 1–2	4	4	4	4
Year 3	4	4	4	4
Years 4–5	4	4	4	2
Stage III	4	4	4	4 (years 1–3) 2 (years 4–5)
<i>Recommended evaluations</i>				
Self-examination	Yes	Yes	Yes	Yes
Routine diagnostic imaging	No	CT for stage III	Sonography of regional lymph nodes	CT of chest, abdomen, and pelvis
Laboratory assessment	No	LDH, AP, protein S-100 β	LDH, AP	CBC, LDH (>stage II)

NA indicates not available; LDH: lactate dehydrogenase; AP: alkaline phosphatase

Adapted from 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* 22:376–85, 2012, with permission.

Table 5

Stage-specific recommendations for number of surveillance visits per year after year 5

Country/Specialty	Stage		
	I	II	III
<i>By country</i>			
Australia/New Zealand ^{64–66}	1	1	1
Canada ⁶⁷	1	1	1
Germany ^{68–71,93}	1–2	1–2	2
United Kingdom ^{72–74}	As needed	As needed	As needed
United States ^{1,75}	1	1	1
Switzerland ⁸²	1	1	1
The Netherlands ^{78–81}	1	1	1
<i>By physician specialty</i>			
Dermatologist ^{69,91,92}	1	1–2	2
General practitioner ^{84–90}	1	1	1
Medical oncologist ^{71,91}	1–2	1–2	2
Surgical oncologist ^{38,80}	1	1	1

Adapted from 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* 22:376–85, 2012, with permission.