Long-term Follow-up for Melanoma Patients

Is There Any Evidence of a Benefit?

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KEYWORDS

• Evidence-based surveillance • Cost-effectiveness • Melanoma • Survivorship • Guidelines • Diagnostic imaging

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.

INTRODUCTION

Contemporary surveillance guidelines for cancer survivors are low-level, category 2A to 2B recommendations (ie, "based upon lower-level evidence, there is *uniform* consensus [category 2A] or *consensus* [category 2B] that the intervention is appropriate")[1] and therefore heavily depend on expert opinion. Even the handful of tumor types for which surveillance recommendations have been rigorously studied lack category 1 (ie, "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

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Surg Oncol Clin N Am 24 (2015) 359–377
http://dx.doi.org/10.1016/j.soc.2014.12.012 **surgonc.theclinics.com**
1055-3207/15/$ – see front matter

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 regarding 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. Because of 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 to detect disease recurrence while it is still treatable?

Half of all patients treated for melanoma have a recurrence.[17,18] Of these recurrences, approximately 50% are in the regional lymph nodes, 20% are local recurrences, and 30% arise at distant sites.[19–21] Although most recurrences develop in the first 2 to 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[22] reported that the overall rate of recurrence 10 years after the diagnosis of the primary was 2.4%. 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 colleagues[27] 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 (**Fig. 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.