The Importance of Studying Our Surveillance Strategies

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Patients with resected stage III melanoma are at high risk for recurrence. Clinical trials primarily including stage IIIB or higher patients have demonstrated a 2-year relapse-free survival rate of less than 50% without adjuvant therapy. With the advent of effective immunotherapy and targeted therapy for melanoma, there has been an increased interest in early detection of recurrent disease with hopes of improving survival through earlier treatment. However, there is still much that needs to be studied to determine whether more frequent surveillance imaging actually helps achieve that goal. Current National Comprehensive Cancer Network (NCCN) guidelines state that one should consider imaging every 3–12 months for 2 years, then every 6–12 months for another 3 years, for all stage IIB–IV patients in whom there has been no evidence of disease.^{1,2} The wide range of imaging frequency and the lack of distinction between different stages and substages leave a lot to be determined by individual physicians and create great variability in how we follow patients.

Decisions about surveillance strategies need to be thought of in terms of balancing risk and benefit, similar to how we think of treatment strategies. One potential risk of increased surveillance imaging is the increased anxiety around the time of surveillance imaging, often termed “scanxiety,” which can impact a patient’s quality-of-life measures. A second potential risk is cumulative radiation exposure over time. Although there has not been a clear causative effect of computed tomography (CT) scans and radiation-associated cancers, data regarding radiation doses suggest that the risk after multiple CT scans is not

negligible.³ Additionally, one needs to consider the cost of more frequent surveillance imaging. This includes not only the actual cost of the test itself but also the cost of false positive results that require additional workup and likely contribute further to the fear of cancer recurrence that patients experience. Identifying cost-effective strategies is particularly important when patients are being treated in lower-resource settings. Insurance companies and hospitals with fewer resources will need to choose which tests to advocate for covering, and patients with fewer resources will need to decide how much time and money they can or should sacrifice for additional visits and tests. On the other hand, patients are likely willing to undergo surveillance imaging if catching and treating recurrences earlier will improve their overall survival, as well as for the piece of mind provided by a test that shows no evidence of disease. The burden of proof is on us to determine what types of surveillance strategies have the potential to benefit patients by improving survival rates and/or quality of life.

One example of a prospective study for melanoma surveillance strategies is the MELFO Study, a multicenter, prospective, randomized clinical trial on the effects of a reduced stage-adjusted follow-up schedule for stage IB–IIC cutaneous melanoma patients. This study included four different questionnaires and scales to assess patient-reported outcome measures including anxiety, worry about cancer recurrence, and overall quality of life. The 3-year follow-up results of this study found that a reduced follow-up schedule did not impact recurrence-free or disease-free survival, but did lower stress response symptom scores on the Impact of Event Scale.⁴

It is natural to next ask whether these findings will be replicated in patients with a baseline higher risk of recurrence. In Dieng et al.’s study entitled “The impact of surveillance imaging frequency on detection of distant disease for patients with resected stage III melanoma,” the authors performed a retrospective study of a large prospective melanoma database (2000–2017) and grouped

resected, asymptomatic stage III melanoma patients into a 3–4-monthly, a 6-monthly, or a 12-monthly surveillance imaging schedule based on prescription by their treating physician.² The authors analyzed for differences in melanoma-specific survival (MSS), distant disease-free survival (DDFS), post distant recurrence MSS (dMSS), and overall survival (OS) based on the frequency of imaging surveillance. Although retrospective, this study benefits from having a large number of patients ($n = 473$) that followed a regular surveillance pattern with a median follow-up of 6.2 years. Their results demonstrate that more frequent surveillance imaging yielded a higher proportion of imaging-detected distant recurrences but was not associated with improved survival. Indeed, the median MSS, OS, and dMSS was *shorter* in those undergoing 3–4-monthly imaging versus 12-monthly imaging. Given the retrospective nature of this study and differences in baseline characteristics, this is likely a reflection of clinician judgment of recurrence risk based on primary tumor characteristics. However, although patients in the 3–4-monthly group were more likely to have recurrences found on routine surveillance imaging compared with the 12-monthly group, in every substage undergoing 3–4-monthly surveillance the majority of distant recurrences were still detected during workup of clinical findings instead of during routine surveillance imaging—80% of IIIa, 57% of IIb, and 54% of IIc (Table 2 of Dieng et al.²). These data highlight the importance of following up on clinical findings or patient-reported symptoms as a key method of detecting recurrence. Patients diagnosed after 2010 were more likely to follow a more intensive schedule, which likely reflects practice patterns around the world as we entered the era of effective systemic therapy. However, the lack of improvement in OS, MSS, or DDFS for the intensive schedule on multivariable analysis should give us all pause to think about whether we are actually providing any benefit with more frequent surveillance imaging.

This study is an important step in evaluating our surveillance strategies for stage III melanoma patients. However, this study only provides data on distant recurrence, not locoregional recurrences. In particular, additional studies on the utilization of lymph node basin ultrasounds will be informative because the cost-effectiveness model may be different for a less expensive, low-risk test. This study also did not have sufficient numbers of patients to separately analyze positron emission tomography (PET)/CT scans, which would have the potential to pick up more recurrences, but at a higher financial cost and high risk of false positives.⁵ Additionally, this study cannot

evaluate how adjuvant therapy may affect the potential benefit of different surveillance frequency, as only 11 of the 473 patients received adjuvant immunotherapy or targeted therapy. While imaging may be more frequent in clinical trial designs to assess for efficacy and toxicity, one could hypothesize that, if adjuvant therapy improves recurrence-free survival, it may further decrease the benefit of a more intensive surveillance schedule.

In conclusion, this study provides helpful information in understanding recurrence risk and impact of imaging frequency. This study demonstrates continued equipoise in studying surveillance strategies and appropriately calls on the need for prospective trials such as the TRIM study, a multicenter prospective randomized trial evaluating the potential benefit of imaging and blood tests compared with clinical examinations only for resected high-risk cutaneous melanoma (stage IIB–III) (<https://clinicaltrials.gov/ct2/show/study/NCT03116412>), to overcome the inherent biases present in retrospective studies. The data from this and future prospective studies will greatly inform our surveillance guidelines as well as our discussions with our patients.

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