Evidence-Based Follow-Up Schedules After Primary Cancer Treatment

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It seems logical to assume that more-intensive patient follow-up after initial treatment of a primary malignancy will result in earlier diagnosis of recurrence, allowing earlier treatment of that recurrence and improving survival outcome. However, there is scant evidence that this assumption is true, and claimed survival benefits may be due to lead time bias, with earlier diagnosis of recurrent malignancy creating the false impression that survival time is extended. On the other hand, some studies have indicated that less-intensive follow-up schedules may be just as effective, are generally well accepted by patients, and do not have an adverse effect on survival outcomes, while providing substantial savings in healthcare costs.^{1–3}

High-quality evidence from systematic reviews of randomized controlled follow-up trials is available for several cancer types, in particular non-metastatic colorectal cancer and breast cancer. A recent Cochrane review of randomized trials that has compared more-intensive and less-intensive follow-up schedules in colorectal cancer (19 trials, 13,216 participants) found no significant difference in overall survival (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.80–1.04); cancer-specific survival (HR 0.93, 95% CI 0.81–1.07); or relapse-free survival (HR 1.05, 95% CI 0.92–1.21). In seven trials that examined psychosocial outcomes, there were no differences in quality of life, anxiety, or depression. In addition, colonoscopies

performed as part of intensive follow-up for colorectal cancer resulted in an increased rate of complications (odds ratio 7.30, 95% CI 0.75–70.69).⁴

Similarly, a Cochrane review of early-stage breast cancer follow-up (five trials, 4023 participants) comparing more-intensive with less-intensive regimens found no significant difference in overall survival (HR 0.98, 95% CI 0.84–1.15) or disease-free survival (HR 0.84, 95% CI 0.71–1.00).⁵ One trial included in this review reported no significant difference in quality-of-life domains (including body image, emotional wellbeing, social functioning, symptoms, or satisfaction with care) at 1 or 5 years.⁶ A further Cochrane review of follow-up in multiple cancer types, i.e. colorectal, breast, non-small cell lung, testicular, and Hodgkin lymphoma (12 studies, 11,276 participants), concluded that less-intensive follow-up probably increased time to detection of recurrence (HR 0.85, 95% CI 0.79–0.92), but made no difference to overall survival (HR 1.05, 95% CI 0.96–1.14).⁷

In the current issue of *Annals of Surgical Oncology*, Moncrieff and colleagues⁸ report the second of only two randomized controlled trials of follow-up frequency among patients with early-stage melanoma (American Joint Committee on Cancer [AJCC] stage IB–IIC).^{1,8,9} The interim 3-year findings corroborate results from the previously published Dutch MEL-FO trial (which used essentially the same protocol), with no significant differences in patient-relevant quality-of-life outcomes at 1 and 3 years with reduced-frequency follow-up. Nor were there any differences in secondary endpoints after a follow-up period of 3 years, with similar proportions of patients developing recurrence (a new primary melanoma, or locoregional or distant recurrence), and no difference in melanoma-specific survival.

In both the UK trial reported by Moncrieff and colleagues and the Dutch MEL-FO trial, over 75% of recurrences were detected by patients during the intervals between follow-up visits.^{1,8} After treatment of primary breast cancer, a systematic review of 13 studies reported that 41% of recurrences were identified through self-examination.¹⁰ These results in melanoma and breast cancer have largely been achieved in the absence of specific patient education, which would be likely to increase the already substantial self-detection rates.¹¹ To provide better patient education for melanoma patients, several initiatives are underway to support their own cancer surveillance using specifically designed applications (apps) and dermoscopes that attach to smartphones.^{12,13} If shown to be effective and cost effective, these initiatives may further reassure both patients and clinicians that frequency of follow-up can safely be reduced.

The findings from follow-up trials are important for quantifying the impact of reduced frequency follow-up schedules on real-world healthcare use. In the Dutch MELFO report, it was estimated that costs were 39% lower over 3 years (€1005 per patient vs. €1655; $p = 0.001$) for the less-intensive follow-up group, as a result of fewer primary care and specialist clinic visits, diagnostic tests, and surgical procedures.¹ Similarly, a reduction in healthcare costs (of between 32% and 67%) has been reported for less-intensive follow-up strategies in other cancer types.⁷ These substantial cost reductions are attractive to governments responsible for health care budgets, because savings quickly accumulate once the per-patient cost reduction is multiplied by the steadily increasing number of primary cancer survivors.

Melanoma trials in which follow-up components are randomized are rare, doubtless due to the challenges in conducting them. For detection of new primaries, there has been one randomized study of a skin surveillance app in people at high risk of melanoma,¹⁴ and one trial of family physician-led versus specialist-led follow-up among patients with AJCC stage 0–II melanomas.¹⁵ The only other trial of reduced frequency of follow-up of which we are aware (MEL-SELF) is currently in progress (<https://clinicaltrials.gov/ct2/show/NCT03581188>). High-level evidence from randomized trials such as these are required to accurately inform national and international melanoma clinical management guidelines.^{16–18}

We commend the investigators of the two MEL-FO trials for undertaking these difficult but important studies, the results of which are likely to change practice in favour of a reduced frequency of follow-up for patients with AJCC stage IB–IIC melanoma. The interim results of both MEL-FO trials support previously existing evidence that less-intensive follow-up after surgical treatment of primary malignancies can achieve patient-relevant outcomes that

are not significantly different from those achieved by more frequent follow-up. We look forward to pooled results from the two studies after more time has elapsed, because these combined trial results are likely to have sufficient power to determine whether, after longer follow-up, there are differences in the important secondary endpoints of recurrence and survival.

A good follow-up schedule for any cancer type has the ability to provide many things, including specialized assessment to detect recurrence early and allow therapy to be initiated promptly, the provision of reassurance to patients, and education about self-surveillance for ongoing monitoring.^{19,20} Detection of new primary tumors is another, separate objective of follow-up. However, follow-up consumes time for health professionals and utilizes scarce healthcare resources. Randomized trials such as the MEL-FO studies will better determine the optimal frequency of follow-up for cancer patients, providing an acceptable trade-off between time to detection of recurrence, patient reassurance, and healthcare costs.

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