DOI: 10.1002/cncr.34597

EDITORIAL

The mystery of posttreatment cancer surveillance

Genuinely paradigm-breaking discoveries sometimes happen when our most fundamental assumptions are proven wrong, and we muster up the courage and energy to understand why. One long-standing assumption that has been a truism of patient-centered oncology and survivorship is that cancer patients who complete treatment must be regularly monitored for signs of cancer recurrence. It takes little imagination or wisdom to think of logical reasons supporting this assumption, most of which have to do the plausible idea that cancer therapy is more likely to be effective against earlier (smaller) cancer recurrences than later (bulkier) cancer recurrences. It therefore seems slightly unnecessary that so much investigative effort has been directed at quantifying the impact of post-treatment surveillance on long-term oncological outcomes. Yet, the most striking conclusion to be drawn from this surprisingly large body of work is the absence of a striking conclusion; the salutary effects of surveillance have been so difficult to measure, that if it has a positive impact on survival, that impact must be very small indeed.[1–4]

How could we have been so wrong about this? One potential explanation is that maybe we are making fundamentally incorrect assumptions about the nature of metastatic cancer. It is useful to remember that the survival benefits of screening and early detection for some primary cancers are well-established.[5–7] For localized, nonmetastatic cancers, there appears to be some lead-time bias favoring survival for people with cancers detected at small and earlier stages. Perhaps this inverse correlation between cancer burden and treatment efficacy only exists in nonmetastatic disease. Maybe the prognostic impact of factors like tumor size and number diminish into triviality once cancer has metastasized. In many respects, we already know this to be true; traditional staging systems are designed (and redesigned) to optimally stratify significant prognostic differences that clearly exist between patients with stage I, II, or III disease, but there is rarely much to be gained from substratifying outcomes within the statistically homogeneous category of stage IV disease.

Of course, three caveats must be applied to this thought exercise. The first is that questions like "does surveillance improve cancer survival?" can only be asked and answered in generalities that intentionally ignore subtle differences that exist between histologies, organs, and patients. The second is that contemporary cancer therapy is meant to become obsolete as soon as we can make it so, and the survival impact of surveillance may become more manifest once our systemic therapies become uniformly stronger against disseminated cancer.

The third caveat is that not all cancer recurrences are metastatic. Just as screening should be advocated for some patients at risk of primary cancers, it should also be applied to survivors at persistent risk of developing new primary cancers. A perfect example of this is hepatocellular carcinoma (HCC), where oncogenesis is often driven by underlying chronic liver disease, and patients who undergo successful treatment often remain at risk for both metastasis and new primary cancers. Indeed, although the histopathological distinction between multifocal recurrent HCC (a new primary cancer arising in a different location of the liver) and intrahepatic metastatic HCC (the same cancer metastasizing to a different location of the liver) can be challenging,[8] their prognostic difference is quite significant (with multifocal recurrent HCC being far more treatable than intrahepatic metastases).[9]

Taking all of these simultaneous variables into account in this issue of *Cancer*, Fu and coauthors approach the topic of optimal HCC surveillance with appropriate data-driven detachment.[10] Drawing from a sizable multicenter data set with mature follow-up, they use temporal patterns of recurrence to calculate risk-based probabilities of post-treatment HCC recurrence. Their conclusions are concordant with our emerging awareness of conditional probabilities of survival, as the likelihood of recurrence is not fixed but diminishes over time. Interestingly, the authors reach very similar conclusions to those suggested in an earlier analysis by Hatzaras and coauthors[11] in 2014, who used published surveillance data to recommend a schedule of post-surgical follow-up of patients with HCC and cirrhosis comprised of intensive monitoring in early years (when the likelihood of recurrence is highest), followed by gradually diminishing intensity of monitoring in later years (as the statistical likelihood of cure increases).

The opportunity to prospectively test the impact of these surveillance guidelines on long-term survival is outside the scope of this present study. However, this work merits external validation. In doing so, if we learn that these rational approaches to post-treatment HCC surveillance improve long-term cancer-specific survival, it may substantiate the probability that the general inefficacy of post-treatment cancer surveillance is driven by the shortcomings of available therapies against metastatic disease. On the other hand, if we learn that these approaches still do not measurably impact HCC survival, it may indicate that there is yet more to the mystery of cancer surveillance and recurrence that we still do not understand.

CONFLICTS OF INTEREST

Clifford S. Cho reports consulting fees from HistoSonics.

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See referenced original article on pages 569–79, this issue.

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