Optimal Imaging Surveillance Schedules after Liver-Directed Therapy for Hepatocellular Carcinoma

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ABSTRACT

Purpose: To optimize surveillance schedules for the detection of recurrent hepatocellular carcinoma (HCC) after liver-directed therapy.

Materials and Methods: New methods have emerged that allow quantitative analysis and optimization of surveillance schedules for diseases with substantial rates of recurrence such as HCC. These methods were applied to 1,766 consecutive chemoembolization, radioembolization, and radiofrequency ablation procedures performed on 910 patients between 2006 and 2011. Computed tomography or magnetic resonance imaging performed just before repeat therapy was set as the time of "recurrence," which included residual and locally recurrent tumor as well as new liver tumors. Time-to-recurrence distribution was estimated by Kaplan–Meier method. Average diagnostic delay (time between recurrence and detection) was calculated for each proposed surveillance schedule using the time-to-recurrence distribution. An optimized surveillance schedule could then be derived to minimize the average diagnostic delay.

Results: Recurrence is 6.5 times more likely in the first year after treatment than in the second. Therefore, screening should be much more frequent in the first year. For eight time points in the first 2 years of follow-up, the optimal schedule is 2, 4, 6, 8, 11, 14, 18, and 24 months. This schedule reduces diagnostic delay compared with published schedules and is cost-effective.

Conclusions: The calculated optimal surveillance schedules include shorter-interval follow-up when there is a higher probability of recurrence and longer-interval follow-up when there is a lower probability. Cost can be optimized for a specified acceptable diagnostic delay or diagnostic delay can be optimized within a specified acceptable cost.

ABBREVIATIONS

HCC = hepatocellular carcinoma, RF = radiofrequency

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The goal of follow-up imaging after liver-directed therapy for hepatocellular carcinoma (HCC), including transarterial chemoembolization, radioembolization, and radiofrequency (RF) ablation, is to detect residual or recurrent disease that requires additional treatment. Earlier detection results in better outcomes (1,2). Shorter interval follow-up results in earlier detection, but at a higher financial cost, potentially more radiation and contrast medium exposure, and more false positives in evolving necrotic lesions.

Optimal posttreatment surveillance schedules have been developed for other malignancies, including testicular cancer (3), but not for HCC. Proposed surveillance schedules after liver-directed therapy include surveillance at 1 month and every 3 months thereafter (4,5), or with the interval stretched to every 6 months after 1 year after treatment (1). It is unknown whether these schedules are optimal. In the present study, we examined the timing of recurrence for HCC and used this information to

develop optimal surveillance schedules. These schedules were optimized based on the time-to-recurrence distribution. They minimize the average delay between recurrence and detection for a given number of surveillance scans (and associated expenses) in the first 2 years after treatment.

MATERIALS AND METHODS

Time-to-Recurrence Distribution

The institutional review board approved this retrospective Health Insurance Portability and Accountability Act–compliant study; informed patient consent was waived. We examined 1,766 consecutive chemoembolization, radioembolization, and RF ablation procedures performed in 910 patients between 2006 and 2011 at a single institution. Computed tomography (CT) or magnetic resonance (MR) imaging performed just before repeat liver-directed therapy was used as an estimate for the time of "recurrence" as detected by imaging. (The actual time of recurrence is before that CT or MR imaging study, although the exact time is not known.) Recurrence included residual incompletely treated tumor, locally recurrent tumor, or new tumor within the liver that required treatment. Progression that did not trigger repeat therapy was excluded (eg, intervening transplantation, liver failure, or death). The time-to-recurrence distribution (for the first 24 mo after treatment) was calculated from the Kaplan–Meier survival function. Comparison of time-to-recurrence distributions for subpopulations was performed by single-factor analysis of variance.

Diagnostic Delay

We define diagnostic delay as the time between recurrence and detection. For a given surveillance schedule, the average diagnostic delay was calculated based on the time-to-recurrence distribution (Fig 1). Specifically, average diagnostic delay was calculated as follows:

$$\sum_i \int_{t_{i-1}}^{t_i} p(x)(t_i - x)dx$$

where t_i is the time of surveillance point i, t_0 is 0, and $p(x)$ is the probability density function of time to recurrence. As a simple example use of this formula, if 40% of recurrences occur 2 months after treatment, 60% of recurrences occur 3 months after treatment, and the next surveillance time point is 4 months after treatment, the average diagnostic delay is 40% × (4 – 2) + 60% × (4–3) = 1.4 months.

Optimal Surveillance Schedule

The first follow-up scan was fixed at 1 or 2 months after treatment to evaluate response to treatment. Many institutions perform the first follow-up imaging at 1 month after liver-directed therapy (1), but evaluation of imaging response after radioembolization may take as long as 3 months (6). At our institution, the initial follow-up scan is routinely performed at 2–3 months after treatment, with results that are comparable or superior to other published survival data (7). Follow-up scans were required to be at least 2 months apart to allow adequate time for differences between scans to become detectable.

Within these constraints, we established the surveillance schedule with the minimum average diagnostic delay (3,8). We calculated the average diagnostic delay for thousands of possible schedules that were proposed by an evolutionary algorithm (9), which "evolved" schedules over multiple generations by making random changes to the best schedules from the previous generation. Calculations were performed in Excel 2013 (Microsoft, Redmond, Washington), and optimization was performed by using the Solver function in Excel.

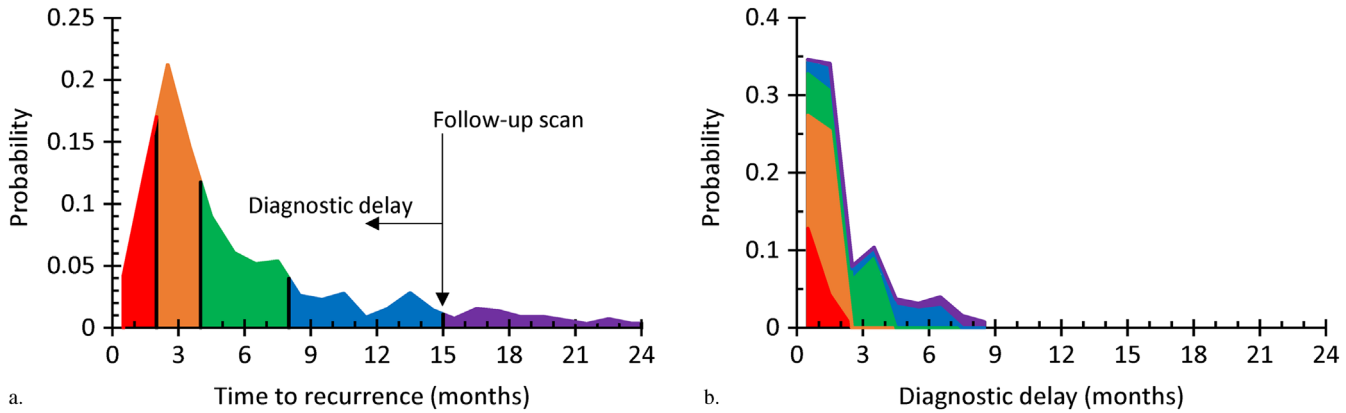

Figure 1. Example of average diagnostic delay calculation. **(a)** Distribution of time to recurrence on imaging (Fig 3). In this example, the surveillance schedule is 2, 4, 8, 15, and 24 months. The colors indicate the surveillance time point when recurrence is detected. For example, recurrences detected at the 2-month follow-up are shown in red. **(b)** Diagnostic delay distribution for that surveillance schedule. The average diagnostic delay is calculated for thousands of proposed schedules to find the schedule that minimizes the average delay.