Optimal imaging surveillance schedules after liver-directed therapy for hepatocellular carcinoma

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Abstract

Purpose: To optimize surveillance schedules for detecting 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. We applied these methods to 1766 consecutive chemoembolization (TACE), radioembolization (RE), and radiofrequency ablation (RFA) procedures performed on 910 patients between 2006 and 2011. The CT or MRI obtained just prior to repeat therapy was set as the time of recurrence. "Recurrence" included residual and locally recurrent tumor, as well as new liver tumors. Time-to-recurrence distribution was estimated using Kaplan-Meier. 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, compared to the second. Therefore, screening should be much more frequent in the first year. For 8 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 to published schedules, and is cost effective.

Conclusion: 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.

Keywords: surveillance, hepatocellular carcinoma, transarterial chemoembolization, radioembolization, radiofrequency ablation

Introduction

The goal of follow-up imaging after liver-directed therapy for hepatocellular carcinoma (HCC), including transarterial chemoembolization, radioembolization, and radiofrequency 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 post-treatment surveillance schedules have been developed for other malignancies, including testicular cancer (3), but not for HCC. Proposed surveillance schedules after liver-directed therapy include: at 1 month and every 3 months thereafter (4, 5), or with the interval stretched to every 6 months after 1 year post treatment (1). It is unknown whether these schedules are optimal. In this paper, 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 two years.

Materials and methods

Time-to-recurrence distribution

The institutional review board approved this retrospective HIPAA-compliant study; informed patient consent was waived. We examined 1766 consecutive chemoembolization (TACE), radioembolization (RE), and radiofrequency ablation (RFA) procedures performed on 910 patients between 2006 and 2011 at a single institution. The CT or MRI obtained just prior to 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 MRI, although the exact time is not known.) "Recurrence" included residual incompletely treated tumor, locally recurrent tumor, or new tumor within the liver requiring treatment. Progression that did not trigger repeat therapy was excluded (for example, intervening transplant, liver failure, or death). The time-to-recurrence distribution (for the first 24 months after treatment) was calculated from the Kaplan-Meier survival function. Comparison of time-to-recurrence distributions for subpopulations was performed using single-factor ANOVA.

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 (Figure 1). Specifically:

$$\text{Average diagnostic delay} = \sum_i \int_{t_{i-1}}^{t_i} p(x)(t_i - x)dx$$

where t_i is the time of surveillance point i, t_0=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, and 60% of recurrences occur 3 months after treatment, and the next surveillance time point is 4 months after treatment, then 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 either 1 or 2 months post-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 up to 3 months (6). At our institution, the initial follow-up scan is routinely performed at 2-3 months post 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 find 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 Microsoft Excel 2013, and optimization was performed using Excel's "Solver" function.

Cost effectiveness

Cost effectiveness of each surveillance schedule was calculated using the following parameters. In a study comparing 6-month and 12-month screening for HCC in cirrhotic patients, detection of HCC 4.6 months earlier resulted in 10.3 months of survival benefit (after correcting for lead time bias) (2). We assumed a quality-of-life weight of 0.8 for patients with cirrhosis (10). We used Medicare prices from 2014 (national payment amount, including both the technical and professional components): $242.52 for a contrast-enhanced CT of the abdomen, and $524.80 for a contrast enhanced MRI of the abdomen (11).

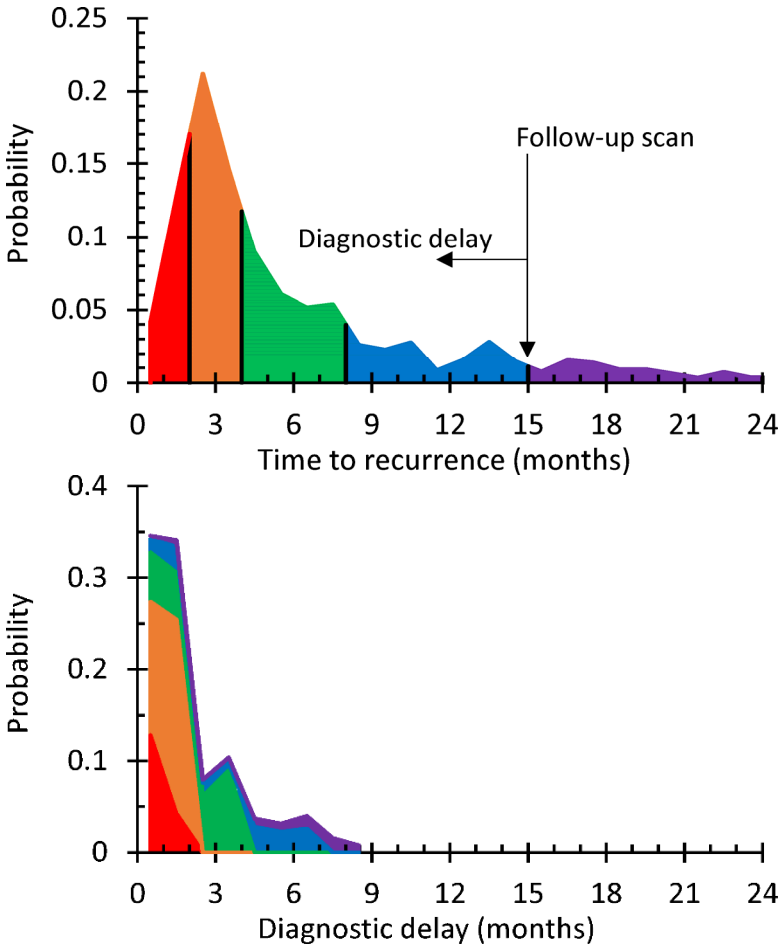

Figure 1. Example of average diagnostic delay calculation. **A**. Distribution of time to recurrence on imaging (Figure 3). In this example, the surveillance schedule is 2, 4, 8, 15, and 24 months. The colors indicate the surveillance time point when recurrence is detected. For example, recurrences detected 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 in order to find the schedule that minimizes the average delay.

Results

The Kaplan-Meier curve and time-to-recurrence distribution are shown in Figure 2 and Figure 3. Time to recurrence that triggered repeat therapy was 5.3 ± 4.5 months after TACE, 8.8 ± 6.6 months after RE, and 6.4 ± 5.8 months after RFA (mean ± SD). No recurrence within 24 months was seen after 24% of TACE, 43% of RE, and 41% of RFA procedures (Table 1). These statistics cannot be used to compare the effectiveness of each treatment modality, for several reasons. First, each treatment modality was used on a different patient population with different tumor characteristics and prior treatments. Second, "recurrence" in this paper included both locally recurrent or residual tumor, as well as distant metachronous tumor within the liver requiring treatment. Finally, progression that did not result in repeat treatment was excluded (for example, intervening transplant, liver failure, or death). However, this time to recurrence distribution is appropriate for determining an optimal surveillance schedule, given that we are primarily interested in detecting recurrences that require additional treatment.

There was no statistically significant difference in the average time to recurrence as a function of treatment modality (TACE, RE, or RFA), number of prior treatments, or age (Table 1). Therefore, we pooled all of the data into a single time-to-recurrence distribution for the purposes of calculating an optimal surveillance schedule.

If we allow 5 imaging follow-up time points in the first 2 years, the optimal surveillance schedule is 2, 4, 8, 15, and 24 months, resulting in an average diagnostic delay of 2.0 months. If we allow 8 time points, the optimal schedule is 2, 4, 6, 8, 11, 14, 18, and 24 months, resulting in an average delay of 1.2 months. A range of other optimal surveillance schedules were calculated (Table 2), which show the tradeoff between cost and average diagnostic delay (Figure 4). All of the schedules listed in Table 2 are cost effective, using a cutoff of US $50,000 per quality adjusted life year gained. MRI has greater sensitivity for detecting HCC compared to CT, which presumably translates into earlier detection and a lower cost per QALY than is shown in Table 2, although we do not have the data to quantitate this effect.

At our institution, the initial follow-up scan is generally performed at 2-3 months post treatment (7). As a result, recurrences before 2-3 months are likely underestimated in the calculated time-to-recurrence distribution, which will affect the accuracy of the estimated diagnostic delay for surveillance time points before 2-3 months. Thus, the data in this paper are insufficient to determine whether the initial follow-up should be performed at 1 or 2 months.

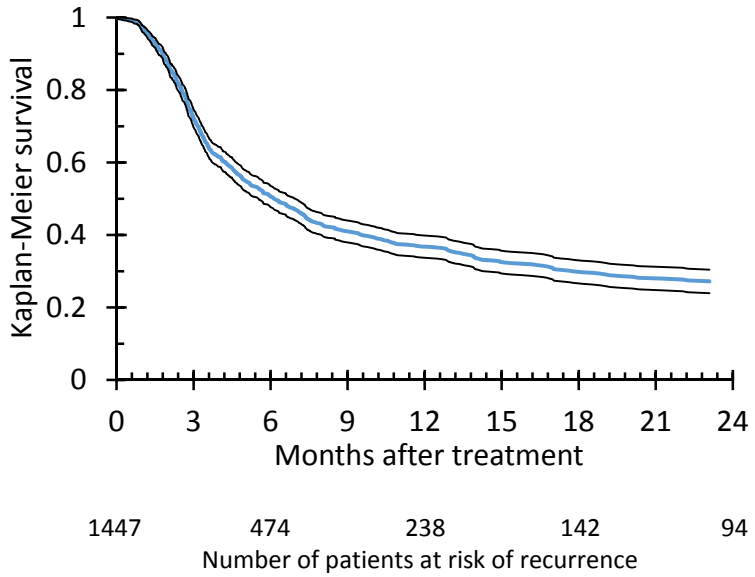

Figure 2. Kaplan-Meier curve (with 95% confidence interval) showing the fraction of patients without recurrence as a function of time after liver-directed therapy. "Recurrence" is defined as recurrence on imaging that required repeat treatment.

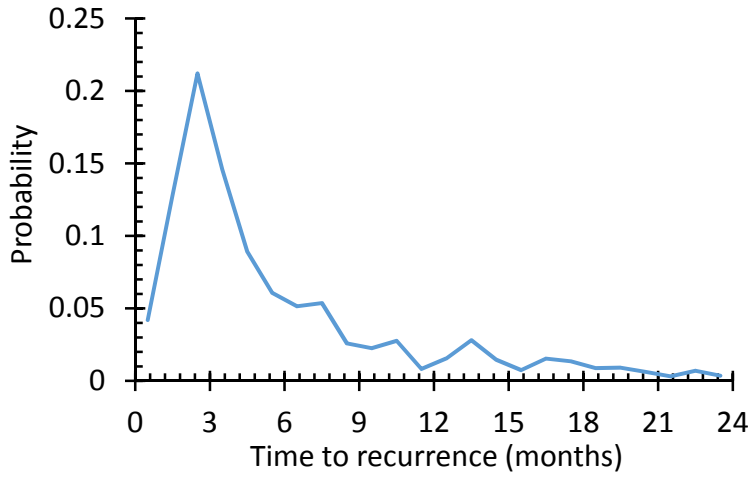

Figure 3. Distribution of time to recurrence on imaging, calculated from the Kaplan-Meier curve in Figure 2.

			Time to recurrence (months)		No recurrence at 24 months
		#	Average	St. dev.	
All		1766	5.7	4.9	27%
Treatment type	**TACE**	1347	5.3	4.5	24%
	RE	271	8.8	6.6	43%
	RFA	148	6.4	5.8	41%
# prior treatments	**0**	910	6.2	5.2	31%
	1	419	5.4	5.0	26%
	2	211	4.1	2.7	28%
	> 2	226	5.1	3.8	20%
Age	**< 60**	683	4.9	4.4	31%
	≥ 60	1083	6.1	5.1	25%

Table 1. Time to recurrence requiring repeat treatment, after liver-directed therapy.

	Surveillance schedule (months)										Average diagnostic delay (months)	Cost per QALY (US$) CT	MRI
†	1	8	24								5.5		
†	2	8	24								4.7		
†	1	5	11	24							3.2		
†	2	5	11	24							2.9		
*	1	3	6	12	24						2.6		
†	1	4	8	15	24						2.2	$0	$0
†	2	4	8	15	24						2.0	$0	$0
†	1	3	6	10	15	24					1.9	$3104	$6716
†	2	4	7	11	17	24					1.6	$2417	$5230
*	1	3	6	9	12	18	24				1.6	$4675	$10116
†	1	3	5	8	11	17	24				1.4	$3952	$8552
†	2	4	6	8	11	17	24				1.4	$3779	$8177
*	3	6	9	12	15	18	21	24			1.5	$5994	$12971
†	1	3	5	8	11	14	18	24			1.2	$5043	$10913
†	2	4	6	8	11	14	18	24			1.2	$4854	$10504
*	1	4	7	10	13	16	19	22	25		1.6	$8764	$18964
†	1	3	5	7	9	11	14	18	24		1.1	$6212	$13441
†	2	4	6	8	10	12	15	19	24		1.1	$6270	$13567
†	1	3	5	7	9	11	14	17	20	24	1.0	$7349	$15902
†	2	4	6	8	10	12	14	17	20	24	1.1	$7451	$16124

Table 2. Optimal surveillance schedules (†), compared to standard surveillance schedules (*) (1, 4, 5). These schedules were calculated from the time-to-recurrence distribution in Figure 3. The table also shows cost per quality adjusted life year (QALY) for additional surveillance beyond the minimum recommended in the literature (1, 3, 6, 12, 24 months).

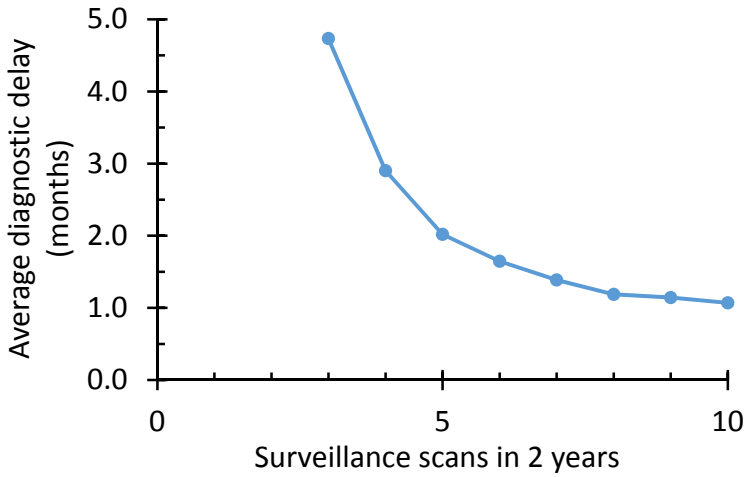

Figure 4. Trade-off between cost (number of scans in the first 24 months) and average diagnostic delay, for the optimal surveillance schedules listed in Table 2 (for 2 month initial follow-up).

Discussion

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. This is consistent with previous work showing that the optimal time between scans is approximately proportional to the reciprocal of the square root of the probability of recurrence (8). That approximation assumes that the rate of recurrence changes slowly over time. In this paper, we find the optimal schedule without relying on that approximation. Cost can be optimized for a specified acceptable diagnostic delay, or diagnostic delay can be optimized within a specified acceptable cost.

Our data show that recurrence is 6.5 times more likely in the first year after treatment, compared to the second year after treatment. This dramatic difference is not reflected in conventional surveillance schedules, which either maintain a constant 3 month follow-up interval in the second year, or double the follow-up interval to 6 months in the second year. The surveillance schedules presented in this paper specify more frequent surveillance in the first year after treatment, when recurrence is most likely to occur. These schedules minimize the delay between when the tumor recurs, and when the recurrence is detected on imaging. Furthermore, we show that screening more frequently than the minimum published recommendation is cost effective.

These calculated surveillance schedules should not be the sole determinants of follow-up scheduling, and are designed to be used only when there is no other evidence for recurrence. Closer follow-up or immediate imaging may be indicated if there is suspicion for incomplete treatment, equivocal imaging findings, new clinical symptoms, rising alpha fetoprotein, or other abnormal laboratory test values.

There are several limitations to this study. First, the time-to-recurrence distribution is based on when recurrence was actually detected on imaging, rather than when recurrence theoretically could have been detected on imaging. Thus, our measured time-to-recurrence distribution was shifted slightly later

than the true distribution. As a result, it might be reasonable to shift the calculated optimal surveillance schedules slightly earlier, although the amount of shift is unknown.

Second, the calculated optimal surveillance schedules minimize the average diagnostic delay. The implicit assumption here is that the harm due to delayed diagnosis is proportional to the length of the delay. In reality, there might be a threshold below which small delays in diagnosis have minimal clinical significance, and above which long delays in diagnosis can result in treatable disease progressing to untreatable disease. If there are threshold effects, then the time between surveillance scans should be kept under the threshold. However, there are no published data that quantitatively address this issue.

Third, we only examined post-treatment recurrences that triggered repeat therapy. Thus, the surveillance schedules given in this paper are appropriate for detecting post-treatment recurrences that require repeat therapy, but might not be optimal for other scenarios. However, previous studies that examined all post-treatment recurrences found a similar time to recurrence (12, 13).

In conclusion, in the era of cost containment and radiation reduction, an optimal surveillance schedule after liver-directed therapy for hepatocellular carcinoma should be implemented. The actual schedule may be customized to balance cost and diagnostic delay.

References

1. Llovet JM, Ducreux M. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal of hepatology 2012; 56:908-43.
2. Santi V, Trevisani F, Gramenzi A, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. Journal of hepatology 2010; 53:291-7.
3. Kantrowitz M. System for minimizing the cost and maximizing the effectiveness of monitoring for recurrence of a condition. 2010. US Patent 7,778,847.
4. Lim HK, Choi D, Lee WJ, et al. Hepatocellular carcinoma treated with percutaneous radio-frequency ablation: evaluation with follow-up multiphase helical CT. Radiology 2001; 221:447-54.
5. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009; 9:1920-8.
6. Rhee TK, Naik NK, Deng J, et al. Tumor response after yttrium-90 radioembolization for hepatocellular carcinoma: comparison of diffusion-weighted functional MR imaging with anatomic MR imaging. Journal of vascular and interventional radiology : JVIR 2008; 19:1180-6.
7. Ha BY, Ahmed A, Sze DY, et al. Long-term survival of patients with unresectable hepatocellular carcinoma treated with transcatheter arterial chemoinfusion. Alimentary pharmacology & therapeutics 2007; 26:839-46.
8. Kirch RLA, Klein M. Surveillance Schedules for Medical Examinations. Manage Sci B-Appl 1974; 20:1403-9.
9. Press WH, Teukolsky SA, Vetterling WT, Flannery BP. Numerical Recipes: The Art of Scientific Computing. 3rd ed. New York: Cambridge University Press, 2007.

10. Andersson KL, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clinical gastroenterology and hepatology 2008; 6:1418-24.
11. Darwin P, Goldberg E, Uradomo L. Jackson Pratt drain fluid-to-serum bilirubin concentration ratio for the diagnosis of bile leaks. Gastrointestinal endoscopy 2010; 71:99-104.
12. Min JH, Lee MW, Rhim H, et al. Recurrent hepatocellular carcinoma after transcatheter arterial chemoembolization: planning sonography for radio frequency ablation. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2011; 30:617-24.
13. Dai X, Han MJ, Su HY, et al. Study of recurrence and metastatic patterns of hepatic cellular carcinoma after transcatheter arterial chemoembolization. Journal of China medical imaging 2004; 11.