Feasibility of Conducting a Randomized Control Trial for Liver Cancer Screening: Is a Randomized Controlled Trial for Liver Cancer Screening Feasible or Still Needed?

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Screening for hepatocellular carcinoma (HCC) is commonly practiced and recommended in published guidelines, but evidence for its efficacy has been controversial. We tested the feasibility of conducting a randomized controlled trial (RCT) of HCC surveillance in patients with cirrhosis and followed up those offered screening to detect clinical outcomes. Participation was offered to patients with cirrhosis attending liver clinics at three university hospitals. Following discussion, patients received a decision aid (DA) that outlined the risks and benefits of surveillance. The proposed screening program comprised ultrasonography 6-monthly and serum alpha-fetoprotein every 3 months. We envisaged five groups of patients: those who agreed to randomization, those choosing nonrandomized screening, those wanting continuation of usual care, those who were undecided, and those refusing participation. Among 205 patients, 204 (99.5%) declined randomization. Of these, 181 (88%) elected for a nonrandomized screening program, 10% chose usual care (which typically included *ad hoc* screening), and two were undecided. Among 176 patients fluent in English communication skills, 160 (91%) preferred nonrandomized screening compared with 22/29 (76%) patients needing an interpreter ($P < 0.026$). Of 173 patients in nonrandomized screening followed up for a mean 13.5 ± 6.04 months, three developed HCC, two died from nonliver-related causes, and one underwent liver transplantation for liver failure. Eighteen of 21 patients in "usual care" received *ad hoc* screening. A simultaneous survey on the quality of the DA showed that the majority of participants believed that the information provided was unbiased. *Conclusion:* Although an RCT is theoretically ideal for determining the efficacy, efficiency, and cost-effectiveness of HCC screening, informed patients prefer surveillance. A randomized study of HCC screening is not feasible when informed consent is imparted. (HEPATOLOGY 2011; 54:1998-2004)

On a global scale, hepatocellular carcinoma (HCC) is the third commonest cause of cancer death.[1] In the United States the greatest increase in cancer death rate over the last decade has been from HCC, the incidence of which has risen faster than all cancers except for cancers of the lung.[2] Early detection, made possible through the use of imaging or serum markers, is desirable because of its dismal prognosis. At the same time, HCC fulfils several criteria that make it suitable for a surveillance program, most notably the fact that small lesions identified early may benefit from potentially curative

Abbreviations:: ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DA, decision aid; HCC, hepatocellular carcinoma; RCT, randomized controlled trial.

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therapy.[3] Other criteria include the relatively high disease burden in selected populations and the availability of reasonably accurate diagnostic tests. For these reasons, surveillance has been advocated in order to identify those with small tumors.[4] Several reports suggest an improved survival rate from liver cancer among patients who participate in a screening program.[5-9]

However, in the absence of a randomized controlled trial (RCT), these results are open to various types of bias, notably lead-time bias in determining quality years of life gained and cost-efficacy. Although RCTs offer the best design for comparing the effectiveness of an intervention,[10] to our knowledge only two RCTs have been conducted on screening for HCC.[11,12] Both studies were conducted in China, which has a high prevalence of chronic hepatitis B virus (HBV) infection and HCC. In both reports those with chronic HBV infection with[11] or without[12] evidence of chronic hepatitis were randomly assigned to either surveillance or to a control group. In neither study were patients offered the option of choosing nonrandomized screening and no information on individual informed consent or contemporary local clinical practice was available.

An important consideration in RCT design is that of patient willingness to participate. From the researcher's point of view, RCTs provide the best evidence for the efficacy of an intervention. However, the critical issue is whether this is also important to patients. Many reports indicate that patients are often unwilling to participate in RCTs when they are aware of the fact that *chance* determines their treatment allocation. McQuellon et al.[13] noted that 90% of breast cancer patients considering a hypothetical trial scenario would not allow the toss of a coin to determine their treatment arm.

Patient preference and the relative lack of intensity of screening programs already in routine clinical practice are two obstacles to having a control group in an RCT related to surveillance. Although RCTs seem justified when there is uncertainty about the effectiveness of two drugs for a particular condition,[14] it is difficult to convince patients to accept participation in a control group in the context of a cancer surveillance program.

To date, there is no study to systematically document whether an RCT for liver cancer screening is practical in an at-risk population in a developed country in the modern era of readily available hepatic imaging and serological testing, and whether patients with advanced liver disease are willing to participate in such a trial. In the present study we attempted to determine if conducting an RCT for liver cancer surveillance was feasible and to determine the willingness of patients with cirrhosis to participate in such a study, as well as the outcomes if they did not.

Patients and Methods

The study was undertaken in the liver clinics of three university-affiliated teaching hospitals (Westmead, Royal Prince Alfred, and Concord Hospitals), all in Sydney, Australia. The study and all documents were approved by the respective Human Research Ethics Committees of the hospitals and that of the University of Sydney. Patients with cirrhosis and Childs-Pugh A or B status attending the liver clinics between March 2004 and August 2005 were invited to participate in an RCT that compared screening with a nonscreening approach for the detection of primary liver cancer.

The surveillance protocol comprised estimations of alpha-fetoprotein every 3 months and hepatic ultrasonography every 6 months. To ensure the tests were performed based on scheduled time, patients were reminded by investigators if their tests were past due. Patients with Childs-Pugh C cirrhosis were excluded, as it was considered that a high rate of non-HCC related endpoints including death and liver transplantation may result in an inadequate number of incident cases. Cirrhosis was confirmed by liver biopsy. In the absence of histology, cirrhosis was defined by the presence of at least one of the following clinical stigmata: ascites, esophageal varices or splenomegaly, and laboratory findings of a low serum albumin, a prolonged prothrombin time, or thrombocytopenia at enrolment.

Random allocation to either the screening or the nonscreening group was offered to all participants. Patients not consenting to random allocation were asked to choose the group they wished to join (or to decline participation). To enable participants to make an informed choice, a written decision aid (DA) (online Supporting Material) was developed and provided in addition to the participant information and consent form. Patients were given the opportunity to discuss issues around their participation with the investigators, their local general practitioner, family members, and significant others. The information and

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Table 1. Demographic Characteristics of Participants in the Feasibility Study

Variable		N (%)
Gender	Male	155 (75)
	Female	50 (25)
Ethnicity	Caucasian	128 (62.5)
	Asian	46 (22.5)
	Middle Eastern	29 (14)
	Others	2 (1)
Severity of liver disease	Child Pugh A	188 (92)
	Child Pugh B	17 (8)
English proficiency	Native	98 (48)
	Fluent	78 (38)
	Need interpreter	29 (14)
Dependency for attending clinic visits	Dependent	19 (9)
	Independent	186 (91)
Education (n = 110)	No formal schooling / primary school	27 (24.5)
	High school / university	83 (75.5)
Age range (mean)	21-78 (54.5)	
Total	205	

consent form included a summary of the study and details about the screening protocol.

The DA provided detailed simple information to ensure patients fully understood the implications of undergoing surveillance for HCC. Topics addressed included risk factors for liver cancer and its natural history, the results of previous studies of HCC screening, and the probable advantages and disadvantages of surveillance. The DA emphasized that outcomes of HCC surveillance programs varied in different parts of the world and that there were no data demonstrating a long-term survival benefit for patients subjected to screening. More practical considerations such as the inconvenience of undergoing regular surveillance and clinic visits were discussed. The DA was provided to patients and their families in the presence of an interpreter for those not fluent in English. After 2 weeks, patients were reinterviewed and consented if appropriate.

We envisaged five groups of patients following this process: those agreeing to randomization to screening or to nonscreening (group 1), those choosing nonrandomized screening (group 2), those wanting continuation of usual care (which may or may not have included an element of screening) (group 3), those who were undecided (group 4), and those who refused participation (group 5). A follow-up questionnaire was developed that addressed patients' attitudes and their involvement in the decision-making process. This was provided to all consenting participants.

To determine what was likely to be "usual care" for individuals refusing study entry, we asked 35 gastroenterologists and gastroenterology trainees attending meetings of the Sydney Liver Group to complete a questionnaire about their attitudes to screening, and routine practice in relation to patients with known cirrhosis.

Results

Characteristics of Patients. In all, 212 patients with cirrhosis (Child-Pugh A and B) were approached to participate. Of these, 7 (3%) declined, whereas 205 (97%) accepted. Reasons given by patients for nonparticipation included time constraints (n = 3), lack of interest (n = 2), and already being screened (n = 2). The demographic characteristics of the remaining 205 consenting participants are shown in Table 1. The majority (75%) were men with a mean age of 54.5 years (21-78 years), largely reflecting the known gender differences in chronic HBV and HCV infections. Most were Caucasian (62.5%), followed by participants of Asian (22.5%) and Middle Eastern (14%) ethnicity. A total of 176 (86%) spoke English fluently, whereas 29 (14%) required the assistance of an interpreter. The most common cause of liver disease was chronic hepatitis C (CHC) (n = 101, 49%) followed by chronic hepatitis B (CHB) (n = 56, 27.5%), and alcoholic cirrhosis (n = 18, 8.5%) (Table 2).

Patient Election to the Study Arms. When offered participation into the RCT of HCC screening versus nonscreening (Gp 1), 204 of the 205 (99.5%) patients declined entry. Of these, 181/204 (88.3%) elected for nonrandomized screening (Gp 2), 21 (10.2%) chose nonrandomized "usual care" (Gp 3) and two (1%) were undecided (Gp 4).

We next determined whether demographic variables influenced patient selection of study arm (Gp1-5). By univariate analysis, effective English communication skills influenced choice: 160/176 (91%) of those who were fluent in English preferred nonrandomized screening compared with 22/29 (76%) of patients who

Table 2. Underlying Cause of Liver Disease

Cause of Liver Disease	N	%
CHC	101	49
CHB	56	27.5
ALD	18	8.5
CHC+ALD	11	5.5
CHC+CHB	9	4.5
Autoimmune hepatitis	4	2
NASH	3	1.5
Others	3	1.5
Total	205	100

CHC, chronic hepatitis C; CHB, chronic hepatitis B; ALD: alcoholic liver disease; NASH, nonalcoholic steatohepatitis.

Table 3. Variables That Influenced Patient Choice (n=205)

Variables\Group		Elected for Screening (Gp 1 and 2) N (%)	Elected Usual Care (Gp 3) N (%)	*P Value
Gender	Male	140 (90)	15 (10)	0.218
	Female	42 (84)	8 (16)	
Age	≤50	67 (87)	10 (13)	0.534
	>50	115 (90)	13 (10)	
Dependency	Independent	167 (90)	19 (10)	0.098
	Dependent	15 (79)	4 (21)	
Ethnicity	Caucasian	115 (90)	13 (10)	0.534
	Others	67 (87)	10 (13)	
English proficiency	Native or fluent	160 (91)	16 (9)	0.026
	Need interpreter	22 (76)	7 (24)	

*Chi-square test.

needed an interpreter ($P < 0.03$). Likewise, patients who could attend the liver clinic independently were more likely to choose nonrandomized screening than those who relied on others to come to the hospital (90% versus 79%, respectively), but this difference did not attain statistical significance. Other variables such as gender, age, and ethnicity did not influence the decision to select screening (Gp 2) versus usual care (Gp 3) (Table 3). We performed multiple logistic regression analysis that included all variables with an initial $P < 0.25$. English proficiency was the only independent predictor of patient choice (odds ratio [OR] 0.387; 95% confidence interval [CI] 0.150-0.952, $P = 0.04$).

Outcomes for Screened Patients. The mean follow-up for patients was 13.5 ± 6.04 months when data were censored for the analysis in this report. During this period, 173 (95%) patients who chose nonrandomized screening (Gp 2) continued to receive active follow-up according to the protocol. Of these, three (1.5%) had developed HCC, two (1%) died from nonliver-related causes, and one (0.5%) underwent liver transplantation for liver failure. Nine (5%) patients withdrew and were subsequently lost to follow-up. The majority of patients in usual care (Gp 3) (18 of 21) continued to receive *ad hoc* screening as part of their clinical care.

Patient Involvement in Decision Making and Quality of the Decision Aid. Patient involvement in the decision to participate in screening was assessed by their responses to a questionnaire. Of 205 patients provided with the questionnaire, 110 responses were received; 56 (51%) patients determined their surveillance arm allocation on their own, or after discussion with their doctor, whereas 16 (14%) made the decision jointly with their doctor. In only one (1%) case did the doctor solely make the final decision on behalf of the patient. About one-third (32%) of respondents did not discuss the program with their doctor. Two participants (2%) did not respond to this question.

A univariate analysis of factors associated with a patients' decision to consider the liver cancer screening program is presented in Table 4. Only the level of education (high school or more versus less education) influenced patient attitudes toward screening. Thus, those with greater education were more likely to make the decision alone (47 [57.3%]) than those who had no education or who had only completed primary school education (10 [38.5%]; $P = 0.034$).

As part of the study design patients were questioned about the quality of the DA and whether the aid was biased in favor of or against participation in a RCT of screening. Fifty-nine (53.5%) patients believed that all information in the DA was clear, whereas 41 (37.5%) thought most of the information was clear. The majority of patients (62 [56.5%]) believed that the information provided was unbiased; 16 (14.5%) considered the DA to be very biased in favor of screening, whereas 27 (24%) considered it was slightly biased in favor of screening. One patient considered that the DA did not favor screening. The majority of respondents (79%) considered that the amount of information

Table 4. Factors Influencing the Decision-Making Process to Join the Surveillance Program Among 108 Responders to the Questionnaire

		Myself or myself After Discussion with my Doctor N (%)	My Doctor After Considering My Ideas or My Doctor Alone N (%)	Me and My Doctor Shared Equally N (%)	Not Discussed with Doctor N (%)	*P Value
Gender	Male	44 (50)	0 (0)	13 (15)	31 (35)	0.142
	Female	13 (65)	1 (5)	2 (10)	4 (20)	
Age	≤ 50	13 (395)	0 (0)	4 (12)	16 (48.5)	0.103
	>50	44 (58.7)	1 (1.3)	11 (14.7)	19 (25.3)	
Ethnicity	Caucasian	38 (50.7)	0 (0)	11 (14.7)	26 (34.7)	0.476
	Others	19 (57.6)	1 (3)	4 (12.1)	9 (27.3)	
Education	No education or primary	10 (38.5)	1 (3.8)	7 (26.9)	8 (30.8)	0.034
	High school-University	47 (57.3)	0 (0)	8 (9.8)	27 (32.9)	

*Fisher's Exact test.

Table 5. Demographic Characteristics of Doctors Who Participated in the Survey

Variables		N (%)
Work location	Hospital only	20 (57)
	Consulting room only	2 (6)
	Hospital and consulting room	13 (37)
Experience	<5 years	13 (37)
	5-10 years	7 (20)
	>10 years	15 (43)
Cirrhosis patients per week	≤5 patients	16 (45.5)
	>5 patients	19 (54.5)

in the DA was adequate, although 19 (17.5%) would have liked more information. When asked whether the DA would be helpful for other patients in the same scenario, 72 respondents (65.5%) agreed that it would be very helpful, 33 (30%) considered it somewhat helpful, and four (3.5) patients stated that the DA would be of little help.

Physician Attitudes Toward Screening for Liver Cancer. Finally, we undertook a survey among gastroenterologists and gastroenterology trainees attending meetings of the Sydney Liver Group to ascertain their views about screening for HCC in cirrhotic patients; 35 of 40 attendees completed the questionnaire. Most respondents (20 [57%]) cared for patients in hospital, 19 (54.5%) saw more than five cirrhotic patients each week, and 15 (43%) had more than 10 years experience. The characteristics of the respondents are summarized in Table 5.

Thirteen respondents (37%) believed that screening of cirrhotic patients did not increase patient survival, whereas four (11.5%) were unsure. Twenty-three (65.5%) believed there was no evidence that screening was cost-effective. Despite these concerns, the majority of respondents (26 [74%]) routinely screened all cirrhotic patients. Only seven (20%) discussed the options available with their patients before undertaking screening. Thirty (86%) participants screened all cirrhotic patients, two (5.5%) screened patients with cirrhosis caused by CHC, CHB, or alcohol, whereas one (3%) screened HBV- and HCV-infected cirrhotic patients only. One respondent (3%) screened all patients with abnormal liver tests.

Discussion

To our knowledge, the present report is the first attempt to systematically test the feasibility of conducting an RCT of surveillance for liver cancer in a clinic-based population of cirrhotic patients at high risk for developing primary liver tumors. Entry into this study was informed by a DA developed specifically for this purpose that outlined the risks and benefits of screening. This approach was deemed ethically necessary, as screening has been recommended in published guidelines, whereas clinical surveys[15-18] suggest that screening is frequently undertaken, despite borderline and controversial evidence of its benefits.

This study demonstrates that (1) RCTs in cirrhotic patients in developed nations is not possible and should not be further considered, and (2) given the responsibility to decide whether to accept randomization or not, the approach and concerns of patients differed radically from that of researchers. Despite the fact that there is no convincing data on the cost-effectiveness of HCC screening, almost all participants rejected randomization and preferred surveillance. One reason for declining randomization is fear of the arbitrary nature of the process. Consistent with this notion, the results of an earlier study demonstrated that 63% of patients refused entry based purely on an aversion to randomization. In this regard, emphasis given to chance in the explanation of the concept of randomization is known to increase patient unease,[19] whereas a literature review to assess factors that influence an individual's willingness or not to participate in a clinical trial noted that the patient's degree of uncertainty, random allocation to treatment, and the use of a placebo were the three factors that caused the greatest concern and led patients to decline study entry.[20]

A further reason for the overwhelming lack of interest in randomization by our study participants might be the adequacy of information about the study process. We supplemented the standard participant information sheet and consent form with a decision aid in order to ensure that patients were well informed about the purposes of the study and the methods by which they were to be allocated to a study group, if they chose randomization. This assertion is supported by the results of published reports that suggest that individuals are unaware of being "randomized," despite a participant information sheet.[16-18,21] Thus, if more information is provided, patients may be less likely to agree to randomization.[12-14] For example, in a study among patients with various types of cancer, the overall attitudes to participation in medical research was positive, with 69% of respondents agreeing to take part in a protocol comparing two treatments. However, this figure dropped to 34% when the treatment arm was chosen by random allocation.[22] Similar results have been reported by others.[23-25]

Reluctance of patients to participate in RCTs may also stem from their desire to have a more active role in medical decision-making. In the present study, 56

of 112 (50%) respondents made the final decision to join the screening program alone. Indeed, a third did not discuss the program with their family physician. Several publications have emphasized this aspect, noting that patients usually refuse participation in RCTs because of a preference by either the treating physician or themselves to make the decision about treatment choices.[26,27]

We observed that the majority of patients chose nonrandomized surveillance in the belief that screening helps doctors to detect cancer earlier. This points to a general misconception about, and unrealistic expectations of, the benefits of screening in the general population that has been confirmed in other reports. For example, in a study of 4,140 women surveyed on the benefits of breast cancer surveillance, 68% believed that screening prevented or reduced the risk of breast cancer, whereas 62% believed that screening halved breast cancer mortality.[28] In a further publication, of women over 40 and men over 50 with no known history of cancer, 87% believed that routine cancer surveillance is always a good idea, whereas 74% considered that finding cancers earlier saved lives.[29]

It should be noted that some participants who chose the control arm (usual care), were already in an *ad hoc* screening program. When we examined doctors' attitudes towards HCC screening, our results suggested that although the benefits of surveillance for patients are not clear to doctors, it is currently routine practice among the majority of gastroenterologists in Sydney. The overwhelming majority believed that all cirrhotic patients, irrespective of their underlying liver disease, would benefit from screening, a result that is consistent with a report among members of the American Association for the Study of Liver Diseases (AASLD) that revealed that 84% routinely screen patients with cirrhosis for primary liver cancer.[15] Based on our findings, it is clearly impractical to use random allocation to assign cirrhotic participants to HCC surveillance and impossible to have a control cohort in this high-risk population, despite the lack of strong efficacy data.

Although most of the information required for decision-making on an individual basis was provided for participants, it is possible that they were not aware of all the potential harms of a surveillance program, including the risks involved in work-up of potentially benign incidental lesions, including that of biopsy and radiation exposure, not to mention mental anxiety and community costs of a surveillance program.

An RCT is the ideal method to assess the efficacy of a cancer surveillance program. In practice, we found that when patients with cirrhosis are asked to make an informed choice about participation in a randomized clinical trial, the vast majority declined randomization and preferred to undergo surveillance rather than to accept possible allocation to nonscreening. Further, because screening for liver cancer in cirrhotic patients is routine practice for the majority of clinicians, even if patients show no interest in such a program, they are highly likely to be "screened," thus making it impossible to allocate to a genuine control group. Hence, RCTs of screening for HCC is not ethically feasible in current clinical practice. However, while this is the case, carefully conducted prospective studies to compare individual HCC screening strategies and modalities are needed to improve early diagnosis and hopefully to improve the outcomes of liver cancer.

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