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## Patients' preferences and trade-offs for the treatment of early stage hepatocellular carcinoma

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### ABSTRACT

**Background:** Radio frequency ablation (RFA) and hepatic resection (HR) provide similar survival for early stage hepatocellular carcinoma (ES-HCC). Although RFA has a higher recurrence rate, HR is associated with an increased risk of complications and death. When multiple treatments are available, patients should be enabled to direct their preferred therapy. Yet there is lack of knowledge on patients' preferences for the treatment of ES-HCC. The objective of this study was to assess treatment preferences between HR and RFA for ES-HCC.

**Methods:** A cohort of 75 cirrhotic adults was educated about the natural history of HCC, treatment options, and the risks and the benefits of HR and RFA. Probability trade-off interviews were used to elicit participants' preferences between the two treatments and strength of their decisions.

**Results:** RFA was preferred by 70% of participants ( $P = 0.001$ ) who identified the risk of perioperative morbidity and mortality of HR as the main reasons for their decision. Participants changed their minds if HR could provide better 5 ( $\geq 15\%$ ) and 3-y disease-free survival ( $\geq 10\%$ ) when compared with RFA. Their preference also changed when RFA had a median  $\geq 8\%$  risk for complications,  $\geq 5\%$  for mortality,  $\geq 8\%$  for nonradical therapy, and  $\geq 5\%$  for tumor seeding.

**Conclusions:** Informed cirrhotic patients prefer RFA for the treatment of ES-HCC. Participants who preferred RFA were more concerned about the risks of perioperative morbidity and mortality of HR than long-term cancer outcomes. Patients' values and attitudes toward risks and benefits for the treatment of ES-HCC should be explicitly elicited and included in multidisciplinary treatment decisions.

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## 1. Introduction

Cirrhosis is a well-recognized predisposing factor for hepatocellular carcinoma (HCC) [1,2] and radiological surveillance of

cirrhotic patients has shown to improve the detection rate of early stage HCCs (ES-HCCs) and reduce mortality [3]. In countries where surveillance is commonly practiced,  $>50\%$  of HCCs are diagnosed when  $<5$  cm [4] and for which ablation

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can provide overall survival similar to hepatic resection (HR) [5]. In recent years, the American Association for the Study of Liver Disease updated the guidelines for the management of HCC [6] and included radio frequency ablation (RFA) among the potentially curative therapies for ES-HCC. Yet, there is still some reticence to regard ablative techniques as equivalent to HR mainly because of the increased risk of local recurrence [5]. Ideally, when treatments have similar outcomes, patients should be enabled to choose the therapy that they feel fit best with them [7,8]. Allowing patients to choose is one of the keys of patient-centered care and is known to improve patients' satisfaction [9,10]. As an example, a radical change in the treatment approach for breast cancer [11]. Although tumor recurrence is higher for locoregional therapy, long-term survival of breast cancer patients is equivalent [12,13]. Some similarities exist with the modern management of ES-HCC because long-term survival depends more on the degree of liver dysfunction, vascular invasion, and tumor biology rather than therapeutic modality used to treat the disease [14–16]. Despite the known benefits of patient-centered medicine [17], there is very little knowledge about the factors that influence patients' preferences for the different treatment options for ES-HCC [18].

Because of these limitations, we designed a prospective study that used probability trade-off (PTO) techniques to elicit participants' preference between HR and ablation as they are the most common intervention performed for HCC worldwide [19]. Secondary objectives of this study were to assess patients' thresholds for 5-y survival benefit, 3-y disease-free survival, perioperative morbidity and mortality, and the risk of non-radical therapy when choosing between RFA and HR.

## 2. Methods

### 2.1. Study population

The study population was recruited at two Canadian University Medical Centers during the period between November 2004 and July 2009 (the University of Alberta Hospital, Edmonton, Alberta, and the Queen Elizabeth II Medical Centre, Dalhousie University, Halifax, Nova Scotia). All participants had cirrhosis and were screened or surveyed for HCC.

### 2.2. Inclusion criteria

Eligible participants were aged  $\geq 18$  y, fit to undergo surgery and with Child-Pugh class A or B cirrhosis. Cirrhosis was diagnosed by liver biopsy, radiological characteristics of the liver (e.g., caudate lobe hypertrophy, irregular hepatic contour, reduced liver volume, and so forth), or clinical presentation consistent with portal hypertension (e.g., ascites, hypersplenism, upper gastroesophageal varices, and so forth).

### 2.3. Exclusion criteria

The following criteria were used for exclusion: inability to comply with the study protocol for medical or socioeconomic reasons, presence of cognitive disabilities or comorbidities that could contraindicate surgical therapy and Child-Pugh

class C liver dysfunction. To avoid cognitive bias, patients who underwent previous treatments for primary or secondary hepatic tumors were also excluded.

### 2.4. Recruitment

During the outpatient clinic hours of three different services, (hepatology, solid organ transplantation, and hepatobiliary surgery), eligible individuals were approached by the primary investigators, or by a study coordinator. Potential participants were fully informed on the objectives of this study. To prevent unnecessary anxiety or fear, participants were reassured that they were not affected by HCC and that their participation would not modify their future care. The option of withdrawing from the study was also explained to each participant before their interviews.

### 2.5. Preinterview education

Education on the risks and the benefits of RFA and HR for the treatment of early stage HCC was performed by using data from scientific articles published during the last 10 y [20]. Educational material provided to all participants was written for an audience with an educational level of grade 8. Participants were informed on the definition of curative therapy, palliative treatment, disease free survival, overall survival, morbidity, mortality, recurrent disease, and the risk of tumor seeding or nonradical resection. The information covered the technical aspects, duration of therapy and expected hospital stay (Appendix 1), side effects and the probability of tumor recurrence, and the likelihood of success and failure for the two competing treatments (Table 1). Additional visual aids were used to explain probabilities more clearly as described in the recommendations by the International Patient Decision Aid Standards [21] (Fig. 1).

### 2.6. PTO interviews

PTO technique was chosen to elicit patients' inclination toward the risk and benefits of RFA and HR [22]. PTO is a well-established method used for clinical decision-making research [23,24]. Participants were asked to place themselves in the position of a hypothetical individual affected by early HCC treatable by either RFA or HR. Then they were asked to choose which treatment they preferred based on the information received during their educational session. The next step was to determine the variables that influenced their decision and their thresholds. To do that, the probabilities of favorable or unfavorable outcomes were modified in a systematic way to make the least preferred treatment more attractive or *vice versa* (i.e., more efficacious or less toxic). Participants were asked to choose which treatment they preferred after probabilities of events were changed. At some point, the subjects switched their initial preference (i.e., chose the more toxic regimen for a greater treatment efficacy). The probability when that occurred (i.e., the "switch point") was measured and reflected the strength of their preference (Fig. 2).

To minimize selection bias, participants were enrolled in a consecutive fashion. Cognitive dissonance bias (undesired psychological condition that makes individuals change their

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