

Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma

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Background & Aims: Both hepatic resection and radiofrequency ablation (RFA) are considered curative treatments for hepatocellular carcinoma (HCC), but their economic impact still remains not determined. Aim of the present study was to analyze the cost-effectiveness (CE) of these two strategies in early stage HCC (Milan criteria).

Methods: As first step, a meta-analysis of the pertinent literature of the last decade was performed. Seventeen studies fulfilled the inclusion criteria: 3996 patients underwent resection and 4424 underwent RFA for early HCC. Data obtained from the meta-analysis were used to construct a Markov model. Costs were assessed from the health care provider perspective. A Monte Carlo probabilistic sensitivity analysis was used to estimate outcomes with distribution samples of 1000 patients for each treatment arm.

Results: In a 10-year perspective, for very early HCC (single nodule <2 cm) in Child–Pugh class A patients, RFA provided similar life-expectancy and quality-adjusted life-expectancy at a lower cost than resection and was the most cost-effective therapeutic strategy. For single HCCs of 3–5 cm, resection provided better life-expectancy and was more cost-effective than RFA, at a willingness-to-pay above € 4200 per quality-adjusted life-year. In the presence of two or three nodules ≤3 cm, life-expectancy and quality-adjusted life-expectancy were very similar between the two treatments, but cost-effectiveness was again in favour of RFA.

Conclusions: For very early HCC and in the presence of two or three nodules ≤3 cm, RFA is more cost-effective than resection; for single larger early stage HCCs, surgical resection remains the best strategy to adopt as a result of better survival rates at an acceptable increase in cost.

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Introduction

Diagnosis of hepatocellular carcinoma (HCC) at an early stage (single nodule ≤5 cm or 2–3 nodules ≤3 cm), enables the application of potentially curative treatments [1]. Liver transplantation, can be offered rarely; hence, most patients are currently considered for hepatic resection (HR) or ablation as first-line therapies. New randomised controlled trials (RCT), large enough to arrive at a conclusion as to the equivalence or superiority of either of the two modalities, in terms of survival, are eagerly awaited [2–4]. However, such large trials with a real randomisation seem difficult to be carried out, due to the difficulty in selecting patients equally eligible for both techniques [5]. In the absence of grade A recommendations, current international guidelines suggest surgical resection for early single HCC (≤5 cm) and cirrhosis without signs of portal hypertension, whereas they propose ablation for early multifocal HCC (two or three nodules ≤3 cm) and for single small HCCs not having a perfectly preserved liver function [6,7]. Recent expert opinion raised a point in favour of ablation rather than surgery in very early HCC (single <2 cm), since an extremely high rate of patients can apparently achieve a complete sustained response when undergoing radiofrequency ablation (RFA) [8,9]. On the other hand, other experts favour the use of resection in early HCC even in the presence of portal hypertension [10]. These uncertainties point out how the recommended first choice treatment strategy for early stage HCC is still a matter of debate without any forecast of a definitive solution [5].

Keywords: Hepatocellular carcinoma; Cirrhosis; Hepatic resection; Radiofrequency ablation; Meta-analysis; Cost-effectiveness.

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Abbreviations: HCC, hepatocellular carcinoma; HR, hepatic resection; RFA, radiofrequency ablation; CE, cost-effectiveness; QALY, quality-adjusted life-year; NHS, National Healthcare System; WTP, willingness-to-pay; RR, relative risk.



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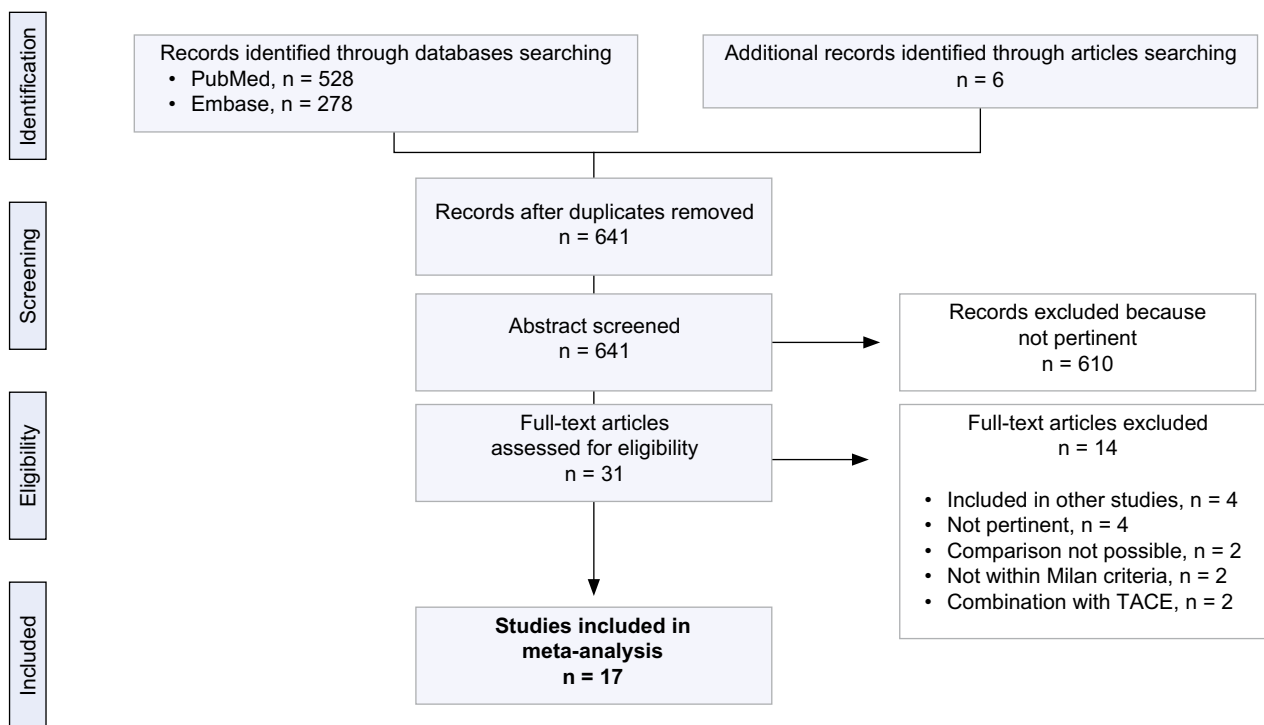


Fig. 1. Flow diagram showing the selection of articles reporting comparative data between hepatic resection and radiofrequency ablation for early hepatocellular carcinoma. One recent RCT from Feng did not satisfy the inclusion criteria as it included also patients beyond the Milan criteria [2]. Since it was not possible to derive data and results for only early HCC, the study was excluded from the analysis.

Together with uncertainties regarding the effectiveness of these two competing strategies, there is a significant difference in costs. Nowadays, the clinical utility of any therapeutic strategy should consider not only the magnitude of the survival benefit but also its related cost, i.e., its cost-effectiveness (CE). However, a formal analysis of cost-effectiveness capable of assisting physicians, scientific societies and, ultimately, healthcare managers in the decision-making processes has not yet been elucidated for these two competing treatments. The aim of the present study was therefore to construct a model to estimate CE of resection vs. ablation for early HCC (Milan criteria) in Child–Pugh class A patients and in different tumour size categories, based on a systematic review of the literature and a detailed meta-analysis of the results.

Materials and methods

At first, a meta-analysis of the pertinent literature extracted between January 1, 2000 and April 1, 2012 was performed following the PRISMA and MOOSE guidelines (Fig. 1) [11,12]. Details about literature search strategy can be found in the [Supplementary Materials and methods](#). Then, results obtained from meta-analysis were utilized to construct a Markov simulation model using TreeAge-Pro-2008 (TreeAge Software Inc., Williamstown, MA, USA), which followed a hypothetical cohort of adult cirrhotic patients, suffering from early HCC, who underwent HR or RFA, covering over 10 years as they moved through different health states until death.

Meta-analysis of literature

The meta-analysis was carried out with patient and disease-free survival (DFS) as the main outcome measures, using R-project (version 2.13.0; The R Foundation for Statistical Computing) and applying statistical approaches suggested by Hoza

and DerSimonian and Laird [13,14]. Two-tailed *p*-values <0.050 were considered statistically significant. Statistical heterogeneity was explored by inconsistency (*I*²) statistics [15]. Patients were stratified, as suggested by the MOOSE guidelines, according to detailed tumour size, following accepted clinical thresholds. [6,12] Other details about meta-analysis approach are reported in the [Supplementary Materials and methods](#).

Utility and costs

Base-case estimates for all costs assumed and utilities extracted from the literature are detailed in [Table 1](#); ranges were assumed to be within 20% of the base-case value [16,17]. Costs were assessed from the perspective of the health care providers and were extracted from the current payments within the Italian National Health System (NHS), converted to 2012 Euros (€), and compared with the Medicare database and previous cost-effectiveness reports [18–20]. All costs and utilities were discounted at a real annual rate of 3%, to adjust for the relative value of the Euro at present [21]. Information on the uncertainty in cost-effectiveness was reported as a cost-effectiveness acceptability curve (CEAC) [22]. The cost-effectiveness analysis was conducted in accordance with the EVEREST guidelines [21]. Further details regarding utilities and costs assumed in the present model are reported in the [Supplementary Materials and methods](#).

Model calibration and Monte Carlo simulation

A schematic representation of the present Markov model can be found in [Supplementary Fig. 1](#). Of note that the model was adjusted for distributions of the Child–Pugh classes and different patient ages of the two treatment arms as detailed in the [Supplementary Materials and methods](#) [23,24]. The correct calibration of the Markov model was checked for all patients within the Milan criteria for both patient and disease-free survival (Fig. 2), confirming that the predicted survivals of the model were within the 95% confidence intervals derived from the meta-analysis. Such verification was repeated for each subgroup analysis showing a good calibration of the model for each tumour stage considered. In the probabilistic sensitivity analysis (second-order Monte Carlo simulation), 1000 patients belonging to Child–Pugh class A with identical tumour characteristics and who underwent hepatic resection or radiofrequency ablation were considered for

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