Hepatic Resection vs Minimally Invasive Radiofrequency Ablation for the Treatment of Colorectal Liver Metastases

A Markov Analysis

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Hypothesis: Current literature evaluating radiofrequency ablation (RFA) for treatment of colorectal liver metastases describes high-risk surgical candidates or patients with unresectable disease. This creates bias when comparing RFA and hepatic resection. A Markov analysis would define theoretical outcomes necessary for RFA to demonstrate equivalence to resection.

Design: A multistate Markov decision analytic model was constructed. Second-order Monte Carlo analysis was used to simulate a randomized controlled trial. Sensitivity analyses were performed to determine the projected outcomes necessary for RFA to achieve equivalence with resection.

Setting: Tertiary care teaching hospital.

Patients: A systematic review of published literature was performed, identifying studies involving patients with colorectal liver metastases treated with RFA or resection. Data were also included from a prospective database of patients undergoing laparoscopic RFA at our institution.

Interventions: Percutaneous or laparoscopic RFA and hepatic resection.

Main Outcome Measures: Quality-adjusted life expectancy and quality of life–adjusted survival.

Results: The base-case analysis (60-year-old man) demonstrated a mean ± SD quality-adjusted life expectancy of 5.67 ± 0.71 years and a 5-year survival of 38.2% following resection. Based on current literature, the mean ± SD quality-adjusted life expectancy for RFA was 3.61 ± 0.49 years, with a 5-year survival of 27.2%. Sensitivity analyses demonstrated that RFA becomes the preferred strategy if the median disease-free survival reaches 1.42 years. When limited to patients from our institution with resectable lesions, the quality-adjusted life expectancy for RFA improved to a mean ± SD of 5.72 ± 0.50 years.

Conclusions: Classical Markov analysis demonstrates that based on current literature, resection is superior to RFA in the treatment of colorectal liver metastases. When input is limited to laparoscopic RFA in patients with resectable lesions, projected 5-year survival is superior to that of hepatic resection.


Hepatic resection has been the standard treatment for patients with colorectal liver metastases confined to the liver for the past several decades. Five-year survival rates of 25% to 58% after resection have been reported, approaching 65% to 71% for patients with solitary colorectal liver metastases (CRLM).1,8 Unfortunately, only 10% to 25% of all patients with isolated CRLM are surgical candidates owing to the extent and location of the metastases or to associated comorbid conditions.9

Since its introduction in the mid 1990s, radiofrequency ablation (RFA) has emerged as a promising approach for the treatment of patients with unresectable CRLM. In fact, recent reports have shown 5-year survival rates of 44% to 55%, with median survivals of 6 to 30 months.8,10,11 This is in contrast to chemotherapy alone, where 5-year survival is 0% to 8% and the median survival is 5 to 22 months.5,12-15

Given the results of RFA in patients with unresectable CRLM, the question arises as to whether RFA poses an alternative to resection as a primary therapy in selected patients.10,21 Proponents of RFA have called for a randomized controlled trial to investigate the effectiveness of RFA compared with resection.22,23 Such an initiative is likely to be faced with several challenges: accrual of a sufficient number of patients would require a multi-institutional trial, but there is currently no uni-
formity in RFA treatment protocols, technologies, and procedural approaches between institutions.

We propose that Markov modeling would be useful in defining the theoretical outcomes required for RFA to demonstrate equivalence to resection in terms of quality-adjusted life expectancies. To determine the target result needed to demonstrate equivalence between RFA and resection, a decision analysis model was used. Markov analysis is a well-established technique for performing a simulated randomized controlled trial. It is a validated method for assessment of variability and uncertainties in pooled data obtained from a wide range of sources. Markov analysis also allows for estimation of the effect of various nononcologic outcomes such as quality of life, procedure-related morbidity and mortality, and the potential for repeated interventions. While this can be a powerful tool for modeling a randomized controlled trial, the model is limited by the selection bias in the available literature toward decreased survival in patients with unresectable disease. We address this bias by analyzing subgroups comprising patients with technically resectable lesions who were treated with RFA.

**METHODS**

**MARKOV MODEL**

A multistate Markov state-transition decision analytic model with a 1-year cycle length, shown schematically in Figure 1, was constructed using widely accepted principles. The model simulates patients with CRLM randomized to hepatic resection or RFA and assumes that patients entering either treatment arm remain in a finite number of health states. These health states, referred to as Markov states, are a description of the patient’s health at a specific time. Examples of the health states used in this model include disease-free state, recurrent reoperable disease state, recurrent progressive disease state, and death, referred to as the final absorbing state of the model. Each Markov state was assigned an incremental utility using quality-of-life data. The output was then analyzed to estimate the quality-adjusted life expectancy based on the length of time patients spent in each Markov state. We defined a 60-year-old man with synchronous or metachronous liver metastases arising from a colorectal primary tumor as our base case. To balance underestimations and overestimations, transitions from one state to another were assumed to occur, on average, halfway through each cycle (half-cycle correction).

The patients surviving without any recurrences for at least 5 years were assumed to be disease free, and their time to death was modeled using age-specific mortality rates.

**DATA SOURCES**

Data on the probabilities of entering each health state and quality of life for the various health states included in our model were obtained through a systematic literature search. The MEDLINE, EMBASE, and Cochrane Collaboration electronic databases were searched using appropriate key words including “colorectal cancer,” “liver metastases,” “hepatic resection,” “radiofrequency ablation,” “percutaneous,” “laparoscopic,” “CT [computed tomography] guided,” and “quality of

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**Figure 1.** Simplified schematic representation of the model flow. $p_{1a}$ and $p_{1b}$ indicate probability of perioperative mortality; $p_{2a}$ and $p_{2b}$, probability of operative complications; $p_{3a}$ and $p_{3b}$, probability of recurrence; $p_{4a}$ and $p_{4b}$, probability of undergoing repeated operation for recurrence; $p_{5a}$ and $p_{5b}$, probability of undergoing repeated hepatic resection; $p_{6a}$ and $p_{6b}$, probability of dying of progressive disease; and $p_{7a}$ and $p_{7b}$, probability of dying of age-specific natural causes. Label A indicates that patients were limited to 5 cycles in this pathway because most reports indicate that the probability of re-recurrence plateaus after 5 years; label B, patients developing recurrences following initial surgery were considered for repeated surgery only once, and all subsequent recurrences were transitioned to the progressive disease state. HR indicates hepatic resection; RFA, radiofrequency ablation; and #, number of patients.
life.” The literature search was limited to articles published after January 1990. The inclusion criteria were broad and included all retrospective and prospective studies and large case series. After the initial search, more than 40 articles presenting survival data on hepatic resection, percutaneous RFA, or laparoscopic RFA were included. Studies that either included open RFA or reported data on outcomes from noncolorectal primary tumors were excluded if the data were not reported separately. In the case of articles presenting overlapping data on the same patient population, only the most recent publication with the largest study population was selected. Letters, reviews without original data, and animal studies were also excluded. After exclusion, the remaining 30 articles were used to obtain data on probabilities used in the model and quality of life.

Additional data for the RFA arm were obtained from a prospective database of more than 900 patients considered for liver surgery at our institution since January 1, 1996. All patients who underwent laparoscopic RFA for CRLM, except those with a concomitant hepatic resection, were included (n=99). All procedures were performed by the senior author (P.D.H.) under general anesthesia. Preoperative, operative, and early postoperative data were collected prospectively. Preoperative imaging of the patients was reviewed by a hepatobiliary-trained surgical oncologist (Kevin Billingsley, MD) who was blinded to all other clinical information. Based on imaging, the patients were classified as having resectable (n=64) or unresectable (n=35) disease. Long-term outcomes and survival data were collected either prospectively during follow-up visits or retrospectively by telephone interviews, medical record reviews, and the Social Security Death Index.

ESTIMATION OF PROBABILITIES

The probabilities used in our model are shown in Figure 1. The data used for the base-case analysis are summarized in Table 1. The probabilities used in our model are shown in Figure 1. The data used for the base-case analysis are summarized in Table 1.

Survival Data

Oncologic outcomes are generally reported in terms of overall survival (time from intervention until death) and disease-free survival (DFS; time from intervention until relapse or death). Because mortality following any intervention for cancer depends on incidence, time to recurrence, and outcomes of retreatment for relapse, our model flow was based on these probabilities. The median DFS was obtained through a systematic literature search. In the case of overlapping studies, data were extracted only from the most recent publications that included the largest study population.

Perioperative Morbidity and Mortality

The probabilities of complications included all of the clinically significant intraoperative or postoperative complications during the same hospital stay. Perioperative mortality was defined as all deaths within 30 days of surgery as well as any hospital and/or procedure-related mortality.

Recurrences and Reinterventions

All of the patients with extrahepatic disease and those with local disease not amenable to repeated surgical intervention were transitioned to the progressive disease state. Because the reported outcomes of repeated surgery (both resection and RFA) are similar to those of the respective primary approach, the same probabilities were used for estimating outcomes after repeated surgery. All patients with recurrences following a second surgical intervention were transitioned to the progressive disease state.

Utilities

The utilities were estimated by reviewing published quality-of-life data applicable to the model (Table 2). The incremental utility of each predefined health state in the model was calculated using the method described by Naglie et al. The average time spent in the hospital or intensive care unit after uncomplicated or complicated surgery and the mean duration to achieve baseline quality of life after discharge from the hospital were defined as short-term health states (health states that affect quality of life for a defined period).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weighted Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60 (57-74)</td>
</tr>
<tr>
<td>Tumor size, cm</td>
<td>3.40 (3.8-4.2)</td>
</tr>
<tr>
<td>Tumors, median, No.</td>
<td>1.75 (1-3)</td>
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<tr>
<td>Disease-free survival, median, y</td>
<td>1.52 (0.6-2.5)</td>
</tr>
<tr>
<td>Probability of peroperative mortality, %</td>
<td>2.3 (0-2.8)</td>
</tr>
<tr>
<td>Probability of operative complications, %</td>
<td>27.8 (23-34)</td>
</tr>
<tr>
<td>Proportion of liver-only recurrences, %</td>
<td>35.6 (11-41)</td>
</tr>
<tr>
<td>Probability of reoperation, %</td>
<td>49.2 (14-69)</td>
</tr>
<tr>
<td>Probability of hepatic resection on repeated operation, %</td>
<td>64.9 (50-100)</td>
</tr>
<tr>
<td>Survival in patients with progressive disease, median, y</td>
<td>1.00 (0.4-1.33)</td>
</tr>
<tr>
<td>Age-specific mortality rate in 60-year-old man as base case</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Abbreviations: CRLM, colorectal liver metastases; HR, hepatic resection; RFA, radiofrequency ablation.

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DATA ANALYSIS

Data were analyzed using commercially available decision analysis software (TreeAge Pro 2009; TreeAge Software, Williams-town, Massachusetts). Input variables for the base-case scenario used weighted means calculated from data available in the included articles and weighted based on the number of applicable patients (Table 1).

The multistate Markov model was constructed to simulate a randomized trial involving a hypothetical cohort of 10,000 patients in each treatment arm. To determine the optimal treatment strategy, a decision tree was analyzed by rolling back, a standard technique that starts at the terminal node of each sub-tree in the model and works backward to the root node. The analysis was set to terminate when 99.9% of the patients reached the final absorbing state, death. The input variables were fixed at their weighted mean values during the rollback analysis.

To assess the effect of the input parameter uncertainties and variability on the outcomes, second-order Monte Carlo probabilistic sensitivity analyses were performed. For this purpose, it was assumed that all continuous input variables had a normal distribution, and a β distribution function was assigned to all of the proportions.

One-way and 2-way sensitivity analyses were performed to assess the effects of varying the value of any single input variable (probability) over a wide range while the values of all other probabilities were fixed. A threshold value was obtained in cases where the 1-way sensitivity analysis demonstrated a change in preferred strategy.

Model simulations were also performed to compare the outcomes of the subgroup of patients in the RFA arm who had potentially resectable CRLM. The data for this analysis were obtained from the 2 published reports on RFA in resectable CRLM and from the subset of patients (n=64) in our patient population who had resectable CRLM as determined by a blinded hepatobiliary-trained surgical oncologist.

The overall survival of the patients undergoing resection or RFA was estimated using the Markov cohort analysis function.

RESULTS

Data were obtained from 30 articles. The data sources with the weighted means and ranges of probabilities and utilities used for the analysis are summarized in Table 1 and Table 2. Data obtained from patients undergoing laparoscopic RFA at our institution are summarized in Table 3.
BASE-CASE ANALYSIS

Quality-Adjusted Life Expectancies and Survival

Analysis of the base-case scenario yielded a superior quality-adjusted life expectancy for patients (mean age, 60 years) randomized to hepatic resection compared with those randomized to the RFA arm. Second-order Monte Carlo probabilistic sensitivity analysis demonstrated that this difference was significant, with a mean ± SD quality-adjusted life expectancy of 5.67 ± 0.71 years for hepatic resection compared with 3.61 ± 0.49 years for RFA (P < .001). The model produced a 5-year overall survival of 38.2% after hepatic resection vs 27.2% for RFA, and the 5-year DFS was 29.8% after resection vs 15.5% after RFA (Figure 2A).

Sensitivity Analyses

Results of 1-way sensitivity analysis demonstrated that the model was sensitive only to variations in the median DFS. Simulation of the model for different ages at the time of treatment narrowed the difference between the 2 strategies as the age increased; however, resection remained the preferred strategy at all ages. Threshold analysis with the median DFS for hepatic resection fixed at 1.52 years (the estimated weighted mean value) revealed that if the median DFS after RFA reaches 1.42 years, then RFA becomes the preferred strategy (Figure 3A). A 2-way sensitivity analysis demonstrated that for any value of median DFS within the defined range of 1 to 2 years, RFA always yields higher quality-adjusted life expectancy than hepatic resection. Figure 3B is a standard graph for displaying the results of the 2-way sensitivity analysis. Each point on the line represents a different value for quality-adjusted life expectancy, with the horizontal axis showing the DFS for resection required to achieve that value of quality-adjusted life expectancy and the vertical axis showing the DFS required for RFA to achieve the same quality-adjusted life expectancy.

MODEL ANALYSIS FOR PATIENTS WITH RESECTABLE CRLM

When outcomes of patients with resectable CRLM treated with percutaneous or laparoscopic ablation were analyzed as a subgroup,6,29,40 the mean ± SD quality-adjusted life expectancy for RFA increased to 4.70 ± 0.53 years (Table 1). A full Markov cohort analysis for this scenario demonstrated a marginal quality of life-adjusted survival advantage over hepatic resection in the first 4 years, however, hepatic resection still provided better long-term survival (Figure 3B).
When the probabilities for the RFA arm were obtained from the cohort of patients undergoing laparoscopic RFA for small (<5 cm) resectable CRLM at our institution (Table 3),40 RFA became the preferred strategy with a mean ± SD quality-adjusted life expectancy of 5.72 ± 0.50 years and an improvement in projected 5-year survival over the hepatic resection group (Figure 3B).

**COMMENT**

Hepatic resection is currently the standard of care for patients with resectable CRLM. Radiofrequency ablation is usually considered when treating patients with unresectable CRLM or patients with significant comorbidities. A wide range of outcomes have been reported for RFA, with most series presenting 5-year survivals between 17% and 30%.9,27,30-36 Recent reports of 5-year survivals greater than 44% after RFA of CRLM have renewed interest in expanding the application of RFA to selected resectable tumors.10-20,50,53 However, this view is not universally accepted.9,22,23,34

The current decision analysis for the base-case scenario demonstrated a significantly higher quality-adjusted life expectancy for patients with CRLM who were treated with hepatic resection. One-way sensitivity analyses of our model demonstrated that RFA becomes a better strategy if the median DFS after treatment is at least 1.42 years (Figure 3A), which is lower than the median DFS for hepatic resection (1.56 years) from the pooled data. This difference demonstrates the benefits of RFA, including improved quality of life, decreased perioperative morbidity and mortality, and increased likelihood of repeated surgical treatment in the event of hepatic recurrence. All of this gives RFA an advantage in quality-adjusted life expectancy despite a lower median DFS. This finding was further confirmed by observation of improved outcome for the RFA arm when 2-way sensitivity analyses were performed using equal median DFS for both treatment arms (Figure 3B). Whether a median DFS of 1.42 years is reasonable for a patient treated with RFA is unknown. Most published studies report a median DFS shorter than 1 year.10,27,31,34,35,37,55 However, most of these patients were deemed as having disease unsuitable for resection. It has been suggested that various factors such as biology of the primary disease, selection bias, associated comorbidities, preexisting extrahepatic disease, and undetected metastases in the remnant liver adversely affected the survival and recurrence rates in these patients.23 To date, only limited data in selected patients with small resectable tumors demonstrate a median DFS approaching 1.42 years.8,30 It has also been questioned whether DFS is an appropriate end point, especially in light of the significant percentage of patients undergoing RFA who seem to be candidates for salvage therapy, either repeated RFA or hepatic resection, after an initial recurrence.

Reports of outcomes equivalent to hepatic resection after RFA have led some investigators to believe that RFA can replace hepatic resection in a selected subset of patients with potentially resectable CRLM.10-20,22,23,33 We tested this hypothesis by performing model simulations using input probabilities from the currently available data on the subgroup of patients who underwent RFA for resectable CRLM (including our data in Table 3). Although a significant improvement in the quality-adjusted life expectancy was observed in this subgroup compared with the original RFA group (mean ± SD, 4.70 ± 0.53 vs 3.61 ± 0.49 years, respectively; P < .001), hepatic resection still remained the preferred strategy (mean ± SD quality-adjusted life expectancy, 5.67 ± 0.71 years). The estimated weighted mean DFS for this subgroup was 1.20 years. This did not reach the threshold value (1.42 years) necessary according to our analysis for RFA to demonstrate quality-adjusted life expectancy superior to that of hepatic resection. Interestingly, the analysis demonstrated higher survival rates in the first 4 years after RFA when compared with resection (Figure 3B). This effect was related to the low perioperative mortality and the significant probability of patients with local recurrence being eligible for repeated surgical interventions, especially hepatic resection. In our model, recurrences after a second surgical intervention were transitioned into the progressive disease state; therefore, the initial survival advantage of RFA was subsequently lost.

Finally, when input was limited to laparoscopic RFA of resectable CRLM performed at our institution, the quality-adjusted life expectancy after ablation was found to be superior to that after hepatic resection (mean ± SD, 5.72 ± 0.50 vs 5.67 ± 0.71 years, respectively). In addition, the overall survival was better at all time points (Figure 3B). Whether these results can be replicated at other institutions remains to be seen.

The 5-year survivals obtained by Markov cohort analysis for the base-case analysis (hepatic resection, 38.2%; RFA, 27.2%) were very close to the estimated weighted means obtained from the pooled data for resection (38.6%) and RFA (26.9%). These results demonstrate the conceptual accuracy of our model design. However, like any decision analytic model, our study was not without limitations. These models estimate outcomes by assigning patients randomly to either treatment arm. The outcomes depend on the estimated probabilities used in the model. It is important to note that the available data on RFA come from a wide range of sources, with most reporting the use of percutaneous RFA to treat unresectable CRLM. Any systematic difference between patients treated with RFA and those treated with resection will be reflected in the outcome of the model, and proponents of RFA note that patients treated with RFA are generally not surgical candidates because of the extent of their disease or medical comorbidities, leading to a biased comparison. This holds true for the group of patients from our institution. Eighty percent of these patients had significant medical comorbidities or were felt to be at high risk for recurrence based on their original presentation. Differences in follow-up techniques and time from diagnosis to treatment (lead-time bias) can all influence the expected outcomes. Finally, it could be argued that the transition of all patients with a second recurrence into the progressive disease state in our model could adversely affect the outcomes of either arm. We assume that only a small number of patients would be eligible for surgery after a second recurrence; therefore, the effect of further reoperations on outcomes is presumed to be insignificant.
Based on the existing published data, our decision analysis demonstrates that hepatic resection remains the preferred strategy for the treatment of CRLM. However, at present RFA is primarily used for the treatment of patients with unresectable CRLM or advanced disease, introducing significant bias into the comparison of outcomes of RFA vs hepatic resection. Markov modeling demonstrates that RFA can provide outcomes equivalent to those of hepatic resection if the median DFS following RFA can be improved. Limited data suggest that a median DFS equivalent to that of hepatic resection can be achieved with laparoscopic RFA; furthermore, when input data were limited to a select subgroup of patients from our institution, the quality-adjusted life expectancy was superior after RFA. These results will need to be reproduced at other institutions, and randomized controlled trials will be required before more widespread use of RFA becomes acceptable.

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REFERENCES
