Performing Gadoxetic Acid–Enhanced MRI After CT for Guiding Curative Treatment of Early-Stage Hepatocellular Carcinoma: A Cost-Effectiveness Analysis

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OBJECTIVE. We determined the cost-effectiveness of two different diagnostic imaging strategies in guiding curative treatment of early-stage hepatocellular carcinoma (HCC).

MATERIALS AND METHODS. We developed a decision analytic model using as its starting point a cohort of patients aged 55 years with early-stage HCC detected at dynamic multiphasic CT and with Child-Pugh class A cirrhosis. The model compared two strategies on the initial workup: conventional CT strategy using dynamic multiphasic CT only and gadoxetic acid–enhanced MRI strategy using additional gadoxetic acid–enhanced MRI after initial CT. A Markov cohort model simulated a cohort of patients after curative or adjuvant treatment, with follow-up over the remaining life expectancy. We analyzed mean life-years gain, quality-adjusted life-years (QALYs), costs per person, and incremental cost-effectiveness ratio (ICER). To evaluate results, we performed one-way, two-way, and probabilistic sensitivity analyses.

RESULTS. The life expectancies and QALY were 7.22 years and 5.08 for the conventional CT strategy and 7.79 years and 5.52 for the gadoxetic acid–enhanced MRI strategy, respectively. The expected costs were $99,770 for conventional CT and $105,025 for gadoxetic acid–enhanced MRI in the United States. The ICER with gadoxetic acid–enhanced MRI was $11,957, as opposed to that with conventional CT, which was lower than the cost-effectiveness threshold of $50,000/QALY. One-way, two-way, and probabilistic sensitivity analyses showed unchanged results over an acceptable range.

CONCLUSION. Gadoxetic acid–enhanced MRI after CT is cost-effective for detecting additional HCC in patients with early-stage HCC who can undergo curative treatment (besides liver transplantation). The cost-effectiveness of gadoxetic acid–enhanced MRI may be considered in the management of patients with early-stage HCC during staging.

Keywords: cost-effectiveness analysis, gadoxetic acid–enhanced MRI, hepatocellular carcinoma, incremental cost-effectiveness ratios, quality-adjusted life-years

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second most common cause of cancer mortality in the world [1]. The implementation of surveillance for the early detection of HCC in high-risk populations and improvements in management modalities have increased the likelihood of curative treatment [2, 3]. However, the prognosis remains poor, even after curative treatment, mainly because of the high rate of early intrahepatic recurrence of HCC [4, 5]. Intrahepatic recurrence may represent metastasis of the primary tumor that was undetected before curative treatment. Therefore, accurate identification of the number, size, and location of HCCs is required for the final therapeutic decision. Dy-

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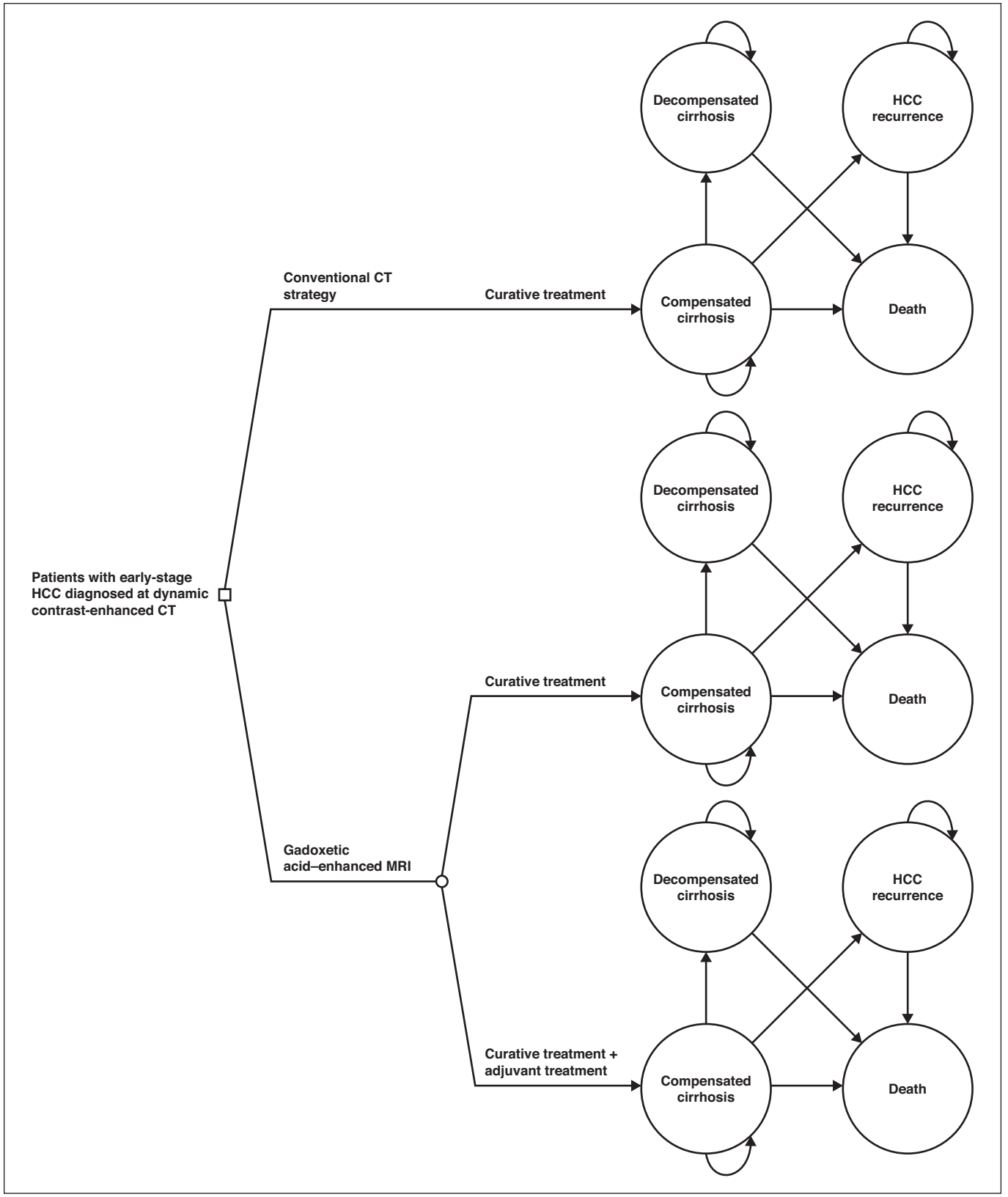

Fig. 1—Decision analytic model for diagnostic imaging strategies in decision making for curative treatment of early-stage hepatocellular carcinoma (HCC). Lines with arrows indicate transition from one health state to another state per cycle.

namic multiphasic CT is a widely used and standardized method for evaluation of HCC. However, the sensitivity of dynamic multiphasic CT is only approximately 60% for nodules 2 cm or smaller [6, 7].

Gadoxetic acid (Eovist or Primovist; Bayer Schering) is a dual-function contrast agent that combines the properties of an extracellular contrast agent for dynamic imaging with those of a hepatocellular-specific contrast agent. Recently, several published studies have reported that gadoxetic acid–enhanced MRI has a higher sensitivity compared with dynamic multiphasic CT and MRI enhanced with nonspecific contrast agents for the detection of HCC [8–12]. Regarding therapeutic efficacy, it has been shown in a large multicenter trial that gadoxetic acid–enhanced MRI changed the surgical strategy for 19 of 131 patients (14.5%) [8], and an observation study showed that treatment decisions were changed from the decision on the basis of CT alone for 11 of 33 patients (33.3%) [11]. Kim et al. [12] recently reported that, among 323 patients who underwent dynamic CT analysis of single-nodule HCC, additional evaluation by gadoxetic acid–enhanced MRI led to the detection of additional HCC nodules in 53 (16.4%) patients, reduction of the risk of disease recurrence, and decreased overall mortality.

Despite the additional cost of the novel contrast agent, no attempt has yet been made to analyze the cost-effectiveness of gadoxetic acid–enhanced MRI. In addition, there are limited data on the influence of gadoxetic acid–enhanced MRI on therapeutic decision making for curative treatment in early-stage HCC; most reports consist of retrospective observational studies. Therefore, clinicians still use gadoxetic acid–enhanced MRI without a clear understanding of the ultimate cost and benefit. Cost-effectiveness information comparing dynamic multiphasic CT versus the addition of gadoxetic acid–enhanced MRI in decision making for curative treatment of HCC would greatly affect and contribute to evidence-based standardized management of patients with early-stage HCC. Thus, the purpose of this study was to determine the cost-effectiveness of two different diagnostic imaging strategies in decision making for curative treatment of early-stage HCC.

Materials and Methods

Overview of Model

We developed a decision analytic model using TreeAge Pro (version 2016, TreeAge Software) to evaluate expected costs and outcomes associated with diagnostic imaging strategies in decision making for curative treatment of early-stage HCC. We simulated a cohort of patients aged 55 years with early-stage HCC, which enabled curative treatment, including surgical resection and radiofrequency ablation (RFA). The degree of liver function impairment in all patients was assumed to be Child-Pugh class A cirrhosis.

At the starting point, the model included patients with early-stage HCC that was diagnosed at dynamic multiphasic CT (Fig. 1). Early-stage HCC was defined as a single HCC nodule or up to three nodules smaller than 3 cm (Barcelona Clinic Liver Cancer stage A) [13]. We defined dynamic multiphasic CT as a four-phase contrast-enhanced liver CT, including the unenhanced phase, hepatic arterial phase, portal venous phase, and equilibrium phase. The model compared two main diagnostic imaging strategies: a conventional CT strategy using dynamic multiphasic CT only, and a gadoxetic acid–enhanced MRI strategy using additional gadoxetic acid–enhanced MRI on the initial workup. A Markov model was developed to simulate a cohort of patients aged 55 years with early-stage HCC and Child-Pugh class A cirrhosis who were undergoing curative or adjuvant treatment and who were followed up over their remaining life expectancy.

In the conventional CT strategy, all patients directly underwent curative treatment (surgical resection or RFA), because all patients were assumed to have early-stage HCC. In the gadoxetic acid–enhanced MRI strategy, if the gadoxetic acid–enhanced MRI showed negative results (i.e., failed to detect additional HCC nodules), all patients would undergo curative treatment, just like the patients in the conventional CT strategy. If the gadoxetic acid–enhanced MRI showed positive results (i.e., detected additional HCC nodules, which could influence the treatment strategy), curative treatment would be performed for primary HCC nodules, with adjuvant treatment including additional surgical resection, RFA, or transarterial chemoembolization for additional HCC nodules. After the first treatment, we applied the Markov model composed of four health states: compensated cirrhosis, decompensated cirrhosis, HCC recurrence, and death. In the model, a 1-year cycle time was selected. During each cycle, a patient occupied one health state and moved to another state according to transition probabilities. Each health state had associated costs and utilities, and these were accumulated over the lifetime of the simulated cohort.

Transition Probability

Published literature reports were systematically reviewed to obtain the transition probabilities, costs, and utilities. A full list of parameters used in this model is presented in Tables 1–3. We assumed that all patients who underwent curative or adjuvant treatments were in the state of compensated cirrhosis. The patients in the state of compensated cirrhosis were subjected to the risks of decompensation, HCC recurrence, and age-specific mortality. We assumed that the annual probability of decompensation in compensated cirrhosis after curative treatment was 0.07 on the basis of several studies [14–18]. The results of various studies provided the range for the sensitivity analysis. The annual probability of decompensation in compensated cirrhosis after curative and adjuvant treatments of 0.0926 was based on the findings of Garwood et al. [19] We estimated the annual probabilities of HCC recurrence in the conventional CT strategy or the gadoxetic acid–enhanced MRI strategy on the basis of the study by Kim et al. [12], who reported that the estimated 4-year recurrence-free survival rates were 56.2% in the CT plus MRI group and 42.0% in the CT group [12]. The annual mortality risk of compensated cirrhosis was based on age-specific mortality published in the 2011 U.S. life table [20]. The decompensated cirrhosis 5-year cumulative survival of 0.35 was the median derived from relevant studies [14–16, 21, 22]. The annual mortality risk of HCC recurrence of 0.301 was based on the findings of Lim et al. [23]. A probability of having additional HCCs of 0.164 with gadoxetic acid–enhanced MRI was the median value derived from three studies [8, 11, 12].

Costs

Costs were estimated using a health care perspective (Table 2). Analysis was performed for a U.S. cost setting. Costs were converted to U.S. dollars for the year 2015. In our model, there are three major sets of cost-estimation factors: gadoxetic acid–enhanced MRI, onetime cost of treatment, and annual follow-up cost. Cost estimations of gadoxetic acid–enhanced MRI and RFA were based on 2015 Medicare reimbursement in the United States. For cost estimation of partial hepatectomy, we used the macrocosting method, because there are reliable data from the study by Lim et al. [23]. We estimated total costs of curative treatment on the basis of the results of the study by Kim et al. [12], in which, among 456 patients who underwent curative treatment, 377 (82.7%) underwent partial hepatectomy and 79 (17.3%) underwent RFA. We estimated total cost of curative treatment using the following formula: total cost of curative treatment = (cost of partial hepatectomy × 0.827) + (cost of RFA × 0.173). We estimated total costs of adjuvant treatment using a conservative approach. We estimated annual follow-up costs on the basis of the studies by Lim et al. [23] and Northup et al. [24]. Both costs and utilities were discounted by 3% yearly [25].

TABLE 1: Base-Case Value and Sensitivity Range for Transition Probabilities

Parameter	Mean Value	Literature Range Tested	Distribution Used in Probabilistic Sensitivity Analysis[a]	Data Sources
Annual probability of decompensation in compensated cirrhosis after curative treatment	0.07	0.039–0.125		D'Amico et al. [14], Fattovich et al. [15, 16], Fleming et al. [17], Hu and Tong [18]
Annual probability of decompensation in compensated cirrhosis after curative and adjuvant treatments	0.0926		Beta (41–402)	Garwood et al. [19]
Annual probability of HCC recurrence in conventional CT strategy[b]	0.135	0.0675–0.2025		Kim et al. [12]
Annual probability of HCC recurrence in gadoxetic acid–enhanced MRI strategy[b]	0.104	0.052–0.156		Kim et al. [12]
Annual mortality risk of compensated cirrhosis	Age specific			Arias [20]
Decompensated cirrhosis-related 5-y cumulative survival	0.35	0.14–50.8		D'Amico et al. [14], Fattovich et al. [15, 16], de Jongh et al. [21], Planas et al. [22]
Derived annual mortality risk of decompensated cirrhosis[c]	0.122			
Annual mortality risk of HCC recurrence	0.301			Lim et al. [23]
Probability of having additional HCCs by gadoxetic acid–enhanced MRI	0.164	0.145–0.333	Beta (53–270)	Kim et al. [12], Hammerstingl et al. [8], Yoo et al. [11]

Note—HCC = hepatocellular carcinoma.

[a]Values in parentheses are 95% CIs (i.e., continuous probability distribution parameterized by two positive shape parameters).

[b]We estimated annual probabilities of HCC recurrence with conventional CT strategy or gadoxetic acid–enhanced MRI strategy according to Kim et al. [12], using the following formula: estimated annual recurrence rate = (1 – 4-year recurrence-free survival rate) / 4. Annual recurrence rates were converted to probability using the following formula: probability = $1 - e^{(-\text{rate} \times \text{time})}$.

[c]We estimated annual mortality risk of decompensated cirrhosis from decompensated cirrhosis-related 5-year cumulative survival using the following formula: The derived annual mortality rate of decompensated cirrhosis = (1 – decompensated cirrhosis-related 5-year cumulative survival) / 5. Annual mortality rate was converted to probability using the following formula: probability = $1 - e^{(-\text{rate} \times \text{time})}$.

Incremental Cost-Effectiveness Ratios

We used the following study endpoints: mean life-years gain, quality-adjusted life-years (QALY), costs per person, and incremental cost-effectiveness ratios (ICERs). ICER is the difference in costs divided by the corresponding difference in QALYs. We adopted the commonly cited cost-effectiveness threshold of $50,000/QALY [26].

Sensitivity Analysis

To evaluate the robustness of the results of the model, we explored wide distributions around uncertain parameters using one-way and two-way sensitivity analyses. As a one-way sensitivity analysis, we performed a tornado analysis to determine the influential variables and those ranges in which the most cost-effective strategy would change. For two-way sensitivity analysis, two variables were changed simultaneously, and the effect on the results was analyzed. Specifically, we performed two-way analysis for a pair of influential values, which could alter the conclusion. We also performed a probabilistic sensitivity analysis to introduce variability simultaneously in two parameters—that is, the annual probability of decompensation in compensated cirrhosis after curative and adjuvant treatments and the probability of having additional HCCs revealed by gadoxetic acid–enhanced MRI.

TABLE 2: Base Case Value and Sensitivity Range for Costs for Patients With Hepatocellular Carcinoma (HCC)

Variable, Costs	Mean Cost/Patient (2015 U.S. Dollars)	Range Tested (50–150% of Base-Case Value)	Data Sources
Gadoxetic acid–enhanced MRI			
MRI scanning	508		Medicare
Gadoxetic acid	140		Medicare
Sum	648	326–977	
Onetime cost of treatment			
Cost of partial hepatectomy	27,412		Lim et al. [23]
Cost of radiofrequency ablation	1598		Medicare
Total cost of curative treatment[a]	22,946	10,512–31,535	Kim et al. [12]
Total cost of adjuvant treatment[b]	22,946	10,512–31,535	Kim et al. [12]
Annual follow-up cost			
Compensated cirrhosis	800	366–1098	Lim et al. [23], Northup et al. [24]
Decompensated cirrhosis	19,918	9114–27,342	Lim et al. [23]
HCC recurrence	22,533	10,620–31,860	Lim et al. [23]

[a]We estimated total costs of curative treatment according to Kim et al. [12]. Among the 456 patients who underwent curative treatment, 377 (82.7%) underwent partial hepatectomy and 79 (17.3%) underwent radiofrequency ablation. Total cost of curative treatment = (cost of partial hepatectomy × 0.827) + cost of (radiofrequency ablation × 0.173).

[b]We estimated total costs of adjuvant treatment conservatively on the basis of total cost of curative treatment.

TABLE 3: Base Case Value and Sensitivity Range for Utilities

Parameter	Base-Case Value	Literature Range Tested[a]
Compensated cirrhosis	0.76	0.65–0.90
Decompensated cirrhosis	0.66	0.37–0.86
HCC recurrence	0.63	0.26–0.86

[a]Data for testing are from Lim et al. [23].

Results

Base Case Results

The results of our base case analysis are as follows. The mean number of life-years gained was 7.22 with the conventional CT strategy and 7.79 with the gadoxetic acid–enhanced MRI strategy. The QALY was 5.08 with the conventional CT strategy and 5.52 with the gadoxetic acid–enhanced MRI strategy. The total expected costs were $99,770 for the conventional CT strategy and $105,025 for the gadoxetic acid–enhanced MRI strategy in the United States (in 2015 dollars). In the cost-effectiveness analysis, the incremental cost was $5265 with the gadoxetic acid–enhanced MRI strategy, and the incremental effectiveness was 0.44. The ICER of the gadoxetic acid–enhanced MRI strategy was $11,957, compared with the conventional CT strategy, which was lower than the cost-effectiveness threshold of $50,000/QALY.

Sensitivity Analysis

On the basis of a one-way sensitivity analysis, among many variables, the annual probability of HCC recurrence with gadoxetic acid–enhanced MRI strategy was the most sensitive parameter. The next most sensitive parameters were utilities in compensated cirrhosis, decompensated cirrhosis, and HCC recurrence state. The gadoxetic acid–enhanced MRI strategy was cost-effective, with an annual probability of HCC recurrence less than 0.126. In one-way sensitivity analysis according to the probability of having additional HCCs revealed by gadoxetic acid–enhanced MRI, our conclusion remained unchanged in the range from 0.145 to 0.333. No other parameters were sufficiently sensitive to bring ICER below the cost-effectiveness threshold.

Two-way sensitivity analysis of the annual probability of HCC recurrence with gadoxetic acid–enhanced MRI strategy versus conventional CT strategy revealed that the preferred strategy varied between gadoxetic acid–enhanced MRI and conventional CT, according to the annual probability of HCC recurrence (Fig. 2).

The result of the probabilistic sensitivity analysis is displayed as an acceptability curve (i.e., the probability of each strategy being cost-effective at different thresholds according to the willingness-to-pay) (Fig. 3). With a willingness-to-pay threshold greater than $11,957, the gadoxetic acid–enhanced MRI strategy was cost-effective compared with the conventional CT strategy.

Discussion

In this cost-effectiveness analysis, we determined that additional gadoxetic acid–enhanced MRI improved decision making for curative treatment of early-stage HCC. In the base-case analysis of our model, the mean life-years gain and QALY using the gadoxetic acid–enhanced MRI strategy tended to be higher than those using the conventional CT strategy. The ICER of the gadoxetic acid–enhanced MRI strategy was $11,957 compared with the conventional CT strategy, which was lower than the cost-effectiveness threshold of $50,000/QALY. Therefore, the gadoxetic acid–enhanced MRI strategy is cost-effective for detecting additional HCC lesions in patients with early-stage HCC.

The most successful therapies for HCC designed for curative treatment are surgical resection, RFA, and transplantation. The detection of all HCC nodules during staging is a key to avoiding recurrence after curative treatment [27]. However, the prognosis of patients with early-stage HCC is poor even after curative treatment, mainly because of the high rate of early intrahepatic recurrence [4, 5]. Therefore, early detection of intrahepatic recurrence is crucial for patients with early-stage HCC who are candidates for curative treatment. Our study showed that evaluation of early-stage HCC with additional gadoxetic acid–enhanced MRI is associated with an improvement in the mean life-years gain, QALY, and ICER, compared with the conventional CT strategy. The detection of additional HCCs by gadoxetic acid–enhanced MRI and adjuvant treatment may have resulted in life-years gained and QALY improvement. Because surgical resection is a potentially high-risk surgery, it should be performed only when complete removal of all HCCs is possible [28, 29]. The improved outcome of patients who had additional HCCs detected by gadoxetic acid–enhanced MRI may have originated from the avoidance of futile surgery [12].

Many previous studies have reported that gadoxetic acid–enhanced MRI shows higher sensitivity in detecting HCC than does dynamic multiphasic CT [8–12]. A recent systematic review and meta-analysis found that MRI showed higher per-lesion sensitivity than did dynamic multiphasic CT (80% vs

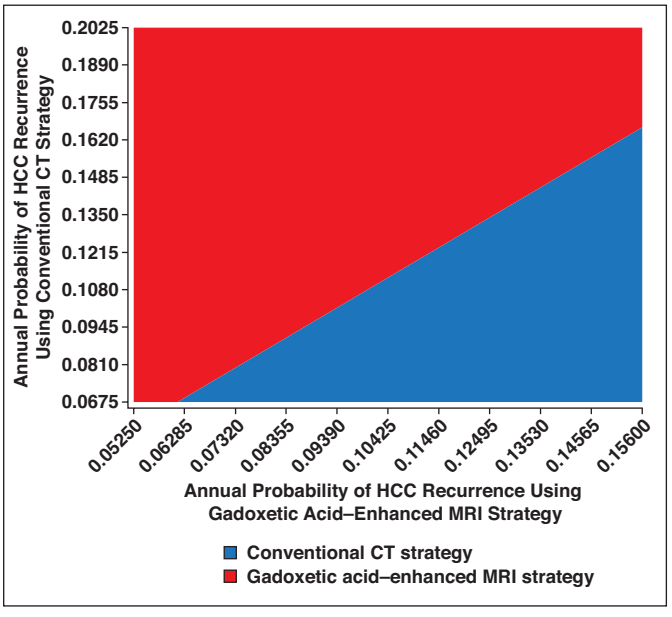

Fig. 2—Two-way sensitivity analysis for annual probabilities of hepatocellular carcinoma (HCC) recurrence using conventional CT strategy versus gadoxetic acid–enhanced MRI strategy.

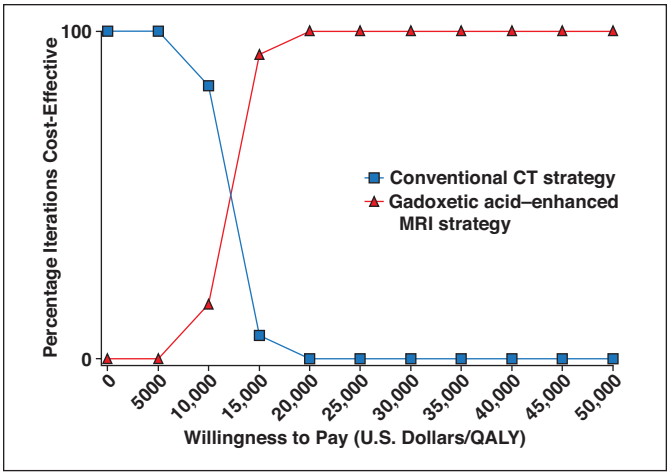

Fig. 3—Cost-effectiveness acceptability curve comparing conventional CT strategy and gadoxetic acid–enhanced MRI strategy. According to willingness-to-pay threshold (i.e., U.S. dollars per quality-adjusted life-years [QALY]), graph shows proportion of our simulated trials in probabilistic sensitivity analysis that would fall within budget.

68%) and that gadoxetic acid–enhanced MRI showed significantly higher per-lesion sensitivity than that shown by MRI performed with other contrast agents (87% vs 74%) [30]. In addition, another recent meta-analysis showed that sensitivity was significantly higher for studies performed with hepatobiliary phase imaging than for those without such imaging (87% vs 65%) for small HCCs measuring up to 2 cm and that gadoxetic acid–enhanced MRI showed a significant independent association with higher sensitivity [31]. For HCCs smaller than 1 cm, the authors reported a significant improvement in detecting lesions with gadoxetic acid–enhanced MRI, compared with dynamic multiphasic CT [32].

Although radiologic evidence is accumulating, most evidence consists of retrospective observational studies. In addition, despite the additional cost of the novel contrast agent, no attempt has yet been made to analyze the cost-effectiveness of gadoxetic acid–enhanced MRI for the diagnosis of early-stage HCC. Although clinical practice guidelines in Asian countries, including the Asian-Pacific Association for the Study of the Liver [33], Korean Liver Cancer Study Group and the National Cancer Center (NCC) Korea practice guidelines [34, 35], and Japan Society of Hepatology guidelines [36], included gadoxetic acid–enhanced MRI, gadoxetic acid–enhanced MRI has not yet been included in American and European guidelines, such as those proposed in 2014 by the American College of Gastroenterology [37], the Association for the Study of Liver Diseases [28], and European Association for the Study of the Liver–European Organization for Research and Treatment of Cancer [29]. To our knowledge, our decision analytic model is the first to use a distinct health state to account for the effect of gadoxetic acid–enhanced MRI used in detecting additional lesions in patients with early-stage HCC. We hope that evidence favoring the use of gadoxetic acid–enhanced MRI including the results of our model will be considered in future clinical guidelines.

Although we attempted to simulate actual clinical practice as much as possible, there are several limitations to our model. First, a key limitation of this study was the paucity of published data on clinical outcomes that are specific for patients with early-stage HCC diagnosed at gadoxetic acid–enhanced MRI. Although several studies have been conducted for this group, the overwhelming majority were retrospective. However, as more specific data become available, with more precise estimations of parameters by country, our model will progressively improve and strengthen. Second, our model is limited by several assumptions. For example, we considered curative treatment as only comprising surgical resection and RFA. Owing to the complexity of the model and the fact that liver transplantation is rarely performed for early-stage HCC (1.3%) [12], we excluded liver transplantation as a curative treatment. In addition, we assumed that all patients who underwent curative and adjuvant treatments were in a state of compensated cirrhosis. Because all patients were assumed to have early-stage HCC, we assumed that patients were cured even after adjuvant treatment. Therefore, our study results should be cautiously interpreted for the patients with early-stage HCC who can undergo curative treatment, except for liver transplantation. Third, our model is limited by several parameter estimates. In our analysis, parameter estimates were extracted from multiple data sources. The input data we collected do not have the same evidence quality as data obtained during a clinical trial. To minimize any uncertainty, we performed one-way and two-way sensitivity analyses and a probabilistic sensitivity analysis over a wide range of estimates.

In conclusion, a gadoxetic acid–enhanced MRI strategy is cost-effective for the detection of additional HCC lesions in patients with early-stage HCC who can undergo curative treatment (except for liver transplantation), compared with the conventional CT strategy. Thus, in the current era of limited economic resources, gadoxetic acid–enhanced MRI may be considered in the management of patients with early-stage HCC during staging.

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