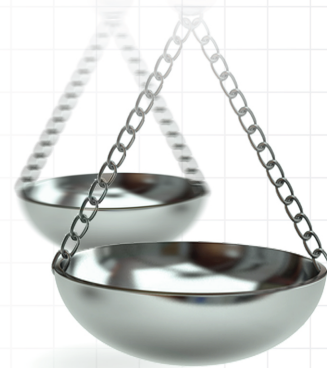




Cost-effectiveness analysis of treatments involving radioembolization in intermediate-stage hepatocellular carcinoma

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Carla Rognoni^{*1}, Oriana Ciani^{1,2}, Silvia Sommariva^{1,3} & Rosanna Tarricone^{1,4}

¹Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Via Roentgen 1, 20136, Milan, Italy

²Evidence Synthesis & Modelling for Health Improvement (ESMI), University of Exeter Medical School, South Cloisters, St Luke's Campus, Exeter, EX1 2LU, UK

³Department of Community and Family Health, College of Public Health, University of South Florida, 3010 USF Banyan Circle Tampa, FL 33612, USA

⁴Department of Policy Analysis and Public Management, Bocconi University, Via Roentgen 1, 20136, Milan, Italy

* Author for correspondence: Tel.: +39 02 5836 2729; Fax: +39 02 5836 2598; carla.rognoni@unibocconi.it

Aim: We evaluated two treatment sequences, transarterial radioembolization followed by transarterial chemoembolization and possibly sorafenib (=TTS) versus transarterial radioembolization followed by sorafenib alone (=TS), to identify the most cost-effective pathway to treat intermediate-stage hepatocellular carcinoma from the Italian healthcare system perspective. **Materials & methods:** A Markov model was developed to project costs and health outcomes for TTS and TS over a lifetime horizon. Data available at three hospitals in Italy were collected. Healthcare resource utilization was derived from standard clinical protocols. Costs were obtained from official regional tariffs. **Results & Conclusion:** Taking into consideration 16 patients for TTS and 22 patients for TS pathways, the TTS sequence provided a dominant strategy in comparison to TS. Further evidence is desirable to confirm these results.

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Keywords: cost-effectiveness • hepatocellular carcinoma • intermediate stage • real-world evidence • sorafenib • TACE • TARE

Hepatocellular carcinoma (HCC) is the most common primitive liver tumor and is found in most cases in patients with chronic liver disease (70–90% of cases of HCC) [1], presenting in a multifocal form to diagnosis in 75% of cases [2].

HCC is diagnosed in the majority of cases in intermediate-advanced stage (stage B and C according to the Barcelona Clinic Liver Cancer staging system), when radical therapy is no longer practicable [3]. Few curative or palliative therapies are available for this condition, characterized by different safety and efficacy profiles. These include transarterial chemoembolization (TACE), transarterial radioembolization (TARE) and systemic chemotherapy (i.e., sorafenib).

In intermediate-stage HCC patients, the main treatment approach is typically TACE [4]. It is a local method of administering chemotherapy directly to the liver tumor through a catheter. Chemoembolic particles are used to occlude hepatic arterial supply to the tumor with resultant necrosis. There is wide variability in the type of embolization particles, chemotherapy and timing [5]. This procedure is contraindicated in patients with portal vein thrombosis/occlusion (PVT) since they may have a greater risk of hepatic decompensation after embolic therapy as a result of diminished portal venous blood flow, which compensates to maintain oxygenation of the liver when the arterial circulation is interrupted.

More recently, the catheter-based approach of TARE has been considered in this group of patients [4]. TARE, also called selective internal radiation therapy, consists of a selective administration of microspheres to the liver through a percutaneous access. The microspheres are loaded with a radioactive material, usually Yttrium90. Glass

(TheraSphere®) or resin (Sir-Spheres®) microspheres are available. They differ in size, activity for individual bead, and number of microspheres injected, but available data suggest the equivalence of the two devices [6].

Preliminary data on the use of TARE have demonstrated a good tolerability profile and promising results of this technique in terms of disease control [3]. Differing from TACE, TARE is a microembolic procedure causing minimal occlusion of hepatic arteries and, therefore, it can be used securely in patients with PVT. TARE is a relatively new and valuable option for the management of nonresectable HCC [7–11] but, although it is cited in actual clinical guidelines [12–15], it is not explicitly recommended.

As regard systemic chemotherapy, patients treated with sorafenib are typically those in advanced stage of disease, which is defined as symptomatic HCC, usually with vascular invasion and/or extrahepatic spread. Patients with intermediate-stage HCC may be candidates for sorafenib when local approaches (e.g., TACE) are not able to control the disease.

The literature presents a few cost–effectiveness studies comparing single treatment options for HCC, for example, TARE versus TACE [16,17] or TACE versus sorafenib [18], but only few clinical and cost data are currently available for the comparison of different treatment sequences or combinations. For example, regarding radioembolization and sorafenib, one recent study provided a prospective analysis of patients treated with the combination of TARE and sorafenib as a bridge to transplant [19], showing that the addition of sorafenib did not increase response to TARE for HCC. Concerning TACE and sorafenib, it has been reported that HCC patients who respond to TACE do not benefit from sorafenib treatment [20]. However, a randomized trial that included patients with chronic hepatitis C virus infection showed that conventional TACE followed by sorafenib resulted in a significantly longer time to progression [21].

Another ongoing study, the SORAMIC trial [22], is investigating the benefits of different therapeutic approaches in HCC: local ablation therapy of liver lesions by radiofrequency ablation followed by sorafenib or placebo (local ablation group), or TARE in combination with sorafenib or sorafenib alone (palliative treatment group).

To our knowledge, only the recent study by Zhao *et al.* [23] has estimated the relative cost–effectiveness of TACE against TACE plus sorafenib for unresectable HCC using a decision analytic model. The authors concluded that TACE is a more cost-effective strategy than TACE plus sorafenib for the treatment of unresectable HCC.

The aim of the present study is to compare two treatment sequences involving TARE, that is TARE followed by TACE and possibly sorafenib, and TARE followed by sorafenib alone, in order to identify the most cost-effective pathway from the Italian Healthcare Service perspective.

Methods

The present study follows the primary cost–effectiveness analysis presented in [24] comparing TARE using Yttrium90-embedded glass or resin microspheres with sorafenib for the treatment of intermediate-advanced HCC patients. The analysis was performed starting from the collection of prospective real-world data (from 2005 to 2015) from three oncology centers in Italy, for a total of 389 patients treated primarily with TARE and 241 treated with sorafenib. In order to compare patients with similar clinical characteristics and prognostic factors in both groups, a one-to-one nearest neighbor propensity score matching procedure [25] was performed on the following parameters: Child–Pugh score, presence/absence of PVT, number of nodules (one vs more than one). The Child–Pugh score assesses the prognosis of chronic liver disease. Patients are classified according to different expected survivals from A to C (2-year survival: A 85%, B 57%, C 35%) based on five clinical measures of liver disease (total bilirubin, serum albumin, prothrombin time, ascites, hepatic encephalopathy).

Target population

The present analysis (secondary analysis) was performed focusing on 109 intermediate-stage patients who underwent TARE to evaluate following (second-line) treatments (see flow-chart in Supplementary Figure 1). In particular, we considered TARE followed by TACE and possibly sorafenib (=TTS) and TARE followed by sorafenib alone (=TS), to identify the most cost-effective pathway from the Italian Healthcare Service perspective.

The model

Two Markov models (Figure 1) were developed to project costs and health outcomes (life expectancies and quality-adjusted life years – QALYs) associated to TTS and TS.

Intermediate-stage HCC patients (mean age 68 years) start the Markov process in the ‘stable disease’ health state. Then, month after month, they may move to ‘progression’ health state, where they may remain or may die for

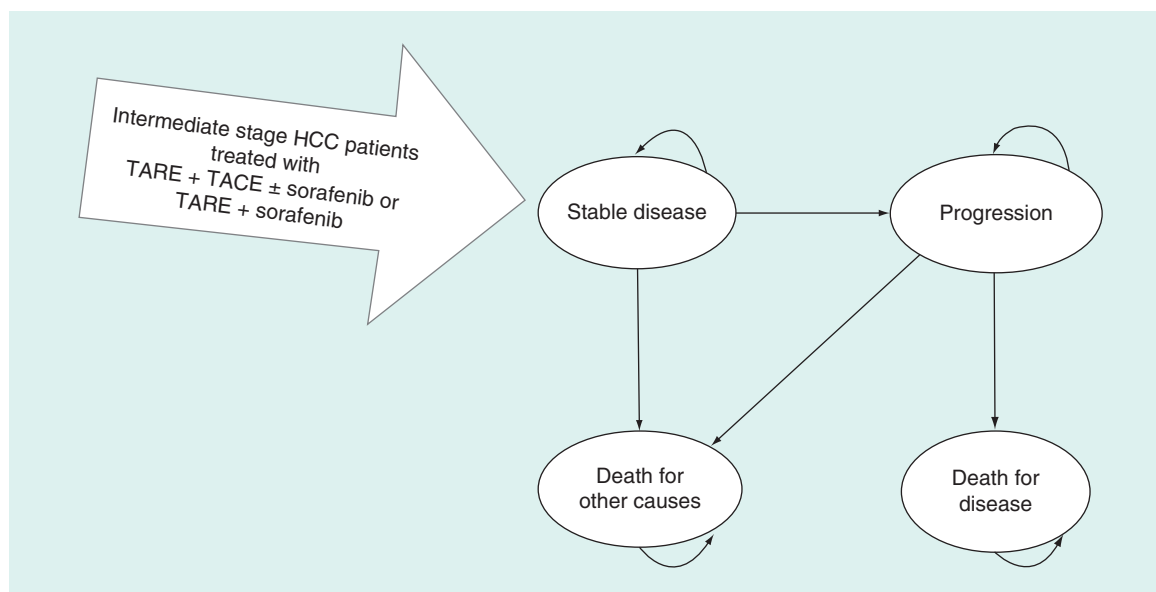


Figure 1. Markov model. A hypothetical cohort of intermediate-stage HCC patients enters the Markov process in the stable state – that is, with stable HCC.

HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

the disease (the model assumes that death for disease affects only progressive patients). The model takes also into account the possibility to die for causes other than HCC ('death for other causes'). As this regard, mortality rates were adjusted for age and gender according to Italian mortality tables [26].

Transition probabilities between health states for TTS and TS have been estimated from the two cohorts of patients. In particular, patient-level data were used to fit overall survival (OS) and progression-free survival (PFS) curves. Different curve functions (i.e., Weibull, Gompertz and exponential) have been fitted for PFS curves emerging from TTS and TS cohorts. The best curve fitting was determined by standard evaluation criteria (i.e., lower Bayesian Information Criterion). Transition probabilities from disease progression to death were considered time-dependent and were calibrated to approximate the Kaplan–Meier postprogression survival curves as measured by the area under the curve calculated on the patient-level data.

A 1-month Markov cycle length and a lifetime horizon were chosen for baseline analysis. The model was developed with TreeAge Software (TreeAge Software, Inc., MA, USA).

Healthcare resource consumption & costs

The model considered only direct healthcare resource consumption, which was derived from standard management protocols for TARE, TACE and sorafenib.

The treatment path with TARE considers a first oncology visit, a procedure simulation (diagnosis-related group [DRG] 203), laboratory exams and the treatment itself (DRG 409). After 1 month, a follow-up oncology visit and laboratory exams are repeated, including an abdomen CT scan. In the follow-up, every 3 months the oncology visit, laboratory exams and the abdomen CT scan are performed. The same schedule for visits/exams is considered for TACE, which is related to DRG 203.

Sorafenib (package of 112 cp 200 mg each, hospital cost €3536.17) is given monthly after TARE or TACE for a mean time duration of 7.5 months (as reported in primary analysis [24]), after a first oncology visit. The recommended dose of 800 mg per day has been considered for a cost of €3787 per month. An abdomen CT scan is performed 2 months after sorafenib initiation while laboratory exams follow the schedule considered for TARE.

As for the primary analysis [24], the model considers only liver decompensation as the most economically and clinically relevant adverse event, leading to hospitalization (DRG 464, see Table 1).

For the primary analysis, comparing TARE and sorafenib, data on costs were obtained from DRGs' reimbursement rates and official tariffs from Lombardy Region in Italy. This region has the highest reimbursement rate for TARE among the Italian Regions and the choice has been considered conservative to reflect the broader Italian

Table 1. Healthcare resources and costs used in the model.

Exam/procedure/DRG	Code	Cost (€)	Ref.
CT scan (abdomen) [†]	88.01.5	137.23	Regional Healthcare Service price list
First visit	89.7B.6	22.50	Regional Healthcare Service price list
Control visit [†]	89.01.F	17.90	Regional Healthcare Service price list
Blood count [†]	90.62.2	4.05	Regional Healthcare Service price list
Creatinine [†]	90.16.3	1.70	Regional Healthcare Service price list
Sodium [†]	90.40.4	1.70	Regional Healthcare Service price list
Potassium [†]	90.37.4	1.70	Regional Healthcare Service price list
Calcium [†]	90.11.4	1.70	Regional Healthcare Service price list
Prothrombin time [†]	90.75.4	2.60	Regional Healthcare Service price list
Albumin [†]	90.05.1	2.90	Regional Healthcare Service price list
Bilirubin [†]	90.10.4	1.55	Regional Healthcare Service price list
Alpha-fetoprotein [†]	90.05.5	11.05	Regional Healthcare Service price list
Alanine amino transferase [†]	90.04.5	1.70	Regional Healthcare Service price list
Gamma-glutamyl transpeptidase [†]	90.25.5	1.70	Regional Healthcare Service price list
Alkaline phosphatase [†]	90.23.5	1.70	Regional Healthcare Service price list
TARE simulation	203	4052	Regional DRG reimbursement
TARE	409	9510	Regional DRG reimbursement
TACE	203	4052	Regional DRG reimbursement
Hospitalization for liver decompensation	464	1688	Regional DRG reimbursement

[†]Every 3 months.
 DRG: Diagnosis-related group; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization.

Healthcare System perspective. The same perspective has been adopted for the present secondary analysis on the treatment pathways involving TARE to allow cost comparisons.

Table 1 summarizes the different healthcare resources and costs used in the model.

Quality of life estimates

As described in [24] for the primary analysis, health-related quality of life measures were not available in the patient-level dataset, hence a literature search was conducted. Utility weights of 0.51 and 0.35 were used for ‘stable disease’ and ‘progression’ health states, respectively.

Baseline analyses

Incremental cost–effectiveness and cost–utility ratios (ICER, ICUR) were calculated dividing the difference of costs by the difference of health outcomes for the two strategies. LYs, QALYs and costs (€, 2016) have been discounted at 3.5% annually [27].

One-way, two-way deterministic sensitivity analyses and a probabilistic sensitivity analysis were performed on the main model parameters.

Results

Target population

The final database used for primary analysis resulted in 308 patients (154 TARE and 154 sorafenib) with matched clinical characteristics. Supplementary Table 1 shows the characteristics of unmatched and matched treatment groups.

Sixty-one and forty-nine percent of patients belonged to intermediate-stage HCC for TARE and sorafenib cohorts, respectively.

Thirty-eight patients out of 109 with intermediate-stage disease treated with TARE-reported subsequent treatments: 16 patients underwent TTS (47% with sorafenib administration) and 22 patients underwent TS.

The mean number of TARE treatments per patient resulted 1.27 and 1.05 for TTS and TS, respectively.

For TS, the model considers that 14% of patients develop liver decompensation (from data) and are hospitalized (assumption). As regard TTS, no patients reported liver decompensation.

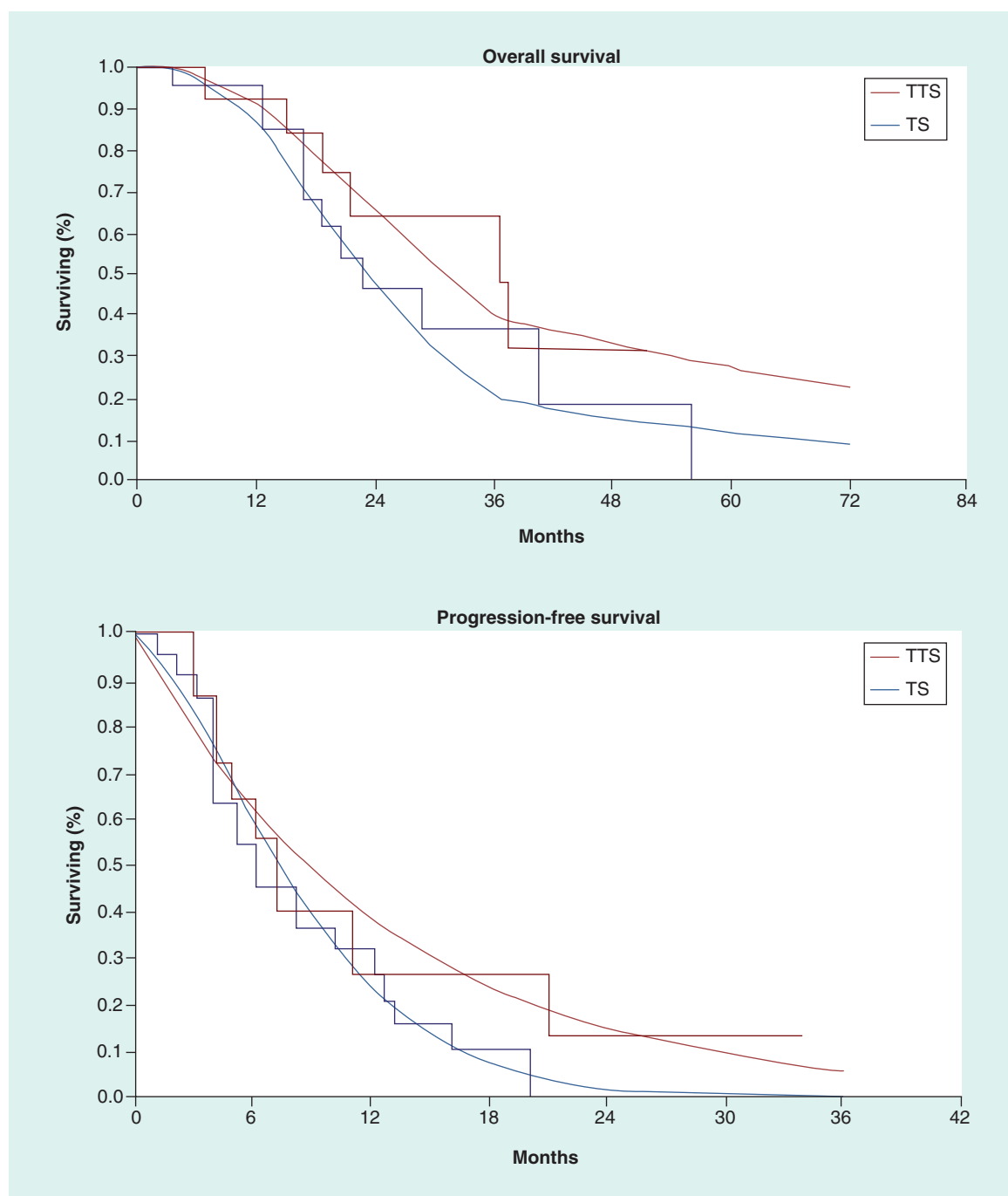


Figure 2. Curves for overall survival and progression-free survival for transarterial radioembolization followed by transarterial chemoembolization and possibly sorafenib and transarterial radioembolization followed by sorafenib alone. Continuous lines represent the model results while segmented lines represent patient-level data. TS: Transarterial radioembolization followed by sorafenib alone; TTS: Transarterial radioembolization followed by transarterial chemoembolization and possibly sorafenib.

Curve fitting

The actual historical OS and PFS curves and the fitted OS and PFS curves for the different treatment sequences, TTS and TS, are shown in Figure 2. As regard PFS, the best fit was an exponential function for TTS and a Weibull function for TS.

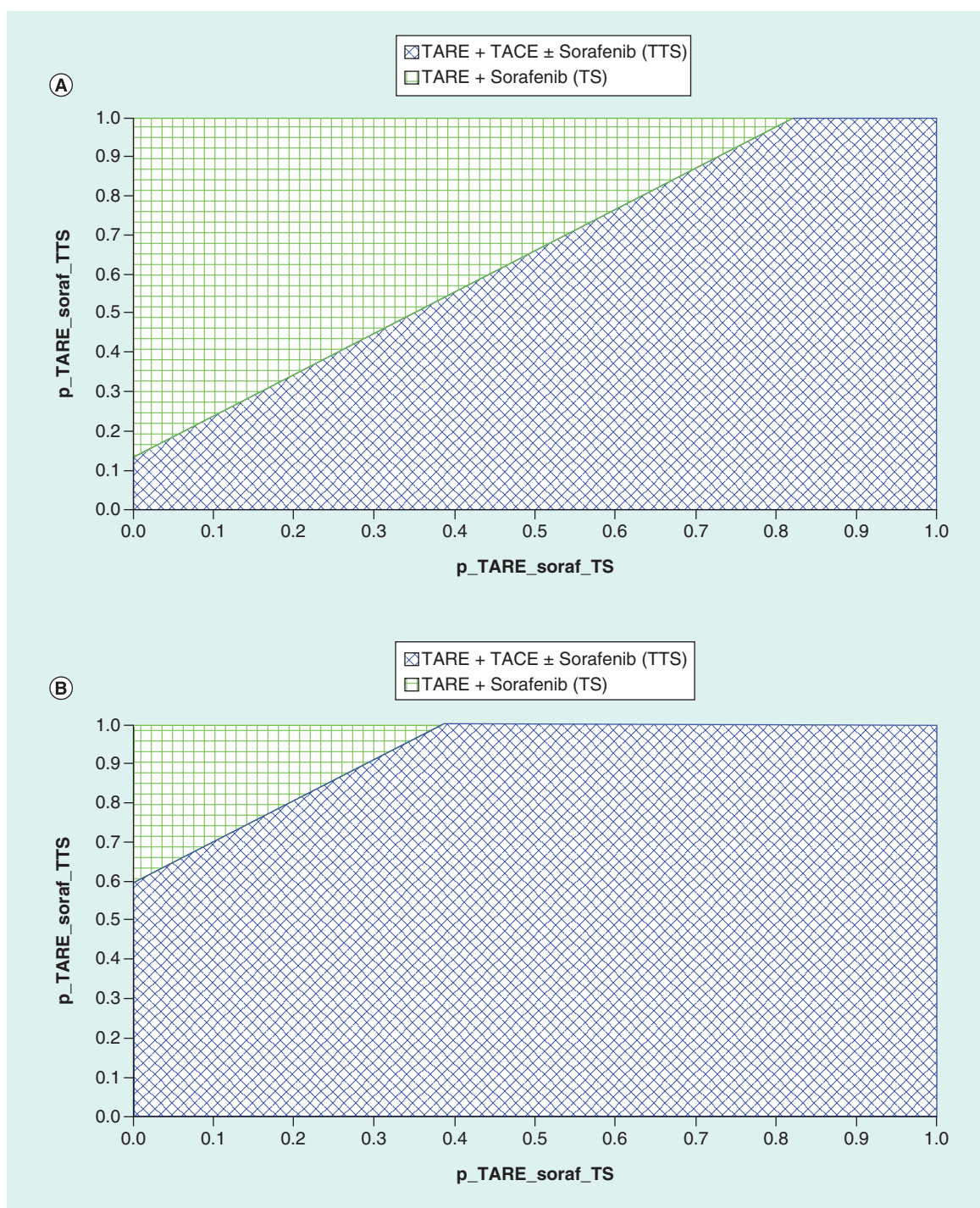


Figure 3. Two-way sensitivity analyses. Two-way sensitivity analysis on the proportion of patients undergoing sorafenib after TARE for TS ($p_TARE_soraf_TS$) and for TTS ($p_TARE_soraf_TTS$) for the scenarios considering a willingness to pay of €25,000/QALY (A) and €50,000/QALY (B). TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TS: TARE followed by sorafenib alone; TTS: TARE followed by TACE and possibly sorafenib.

Table 2. Model results.

Strategy	Cost (€)	Δ Cost (€)	LYG	Δ LYG	QALYs	Δ QALYs	ICER (€/LYG)
TTS	36,509		3.494	1.133	1.385	0.448	Dominant
TS	42,812	6303	2.361		0.937		

ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALY: Quality-adjusted life year; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TS: TARE followed by sorafenib alone; TTS: TARE followed by TACE and possibly sorafenib.

Analyses

The model estimated an average lifetime cost per patient of €36,509 and €42,812 for TTS and TS, respectively. Health outcomes resulted 3.494 years (1.385 QALYs) for TTS and 2.361 years (0.937 QALYs) for TS (Table 2).

The analyses showed that TTS sequence can be considered a dominant strategy in comparison to TS for the treatment of intermediate-stage HCC patients.

One-way sensitivity analyses were performed for ICUR (discounted scenario) on the main model parameters. For patient proportions, the variation range 0–100% was applied, while for the other parameters a variation of $\pm 30\%$ of the baseline value was considered. The results are presented in Table 3. Time horizon and the proportion of patients undergoing sorafenib after TARE for both treatment sequences were the parameters mainly influencing the ICUR. For TS, a proportion of patients undergoing sorafenib after TARE lower than 75% led TTS to report greater costs and greater QALYs and the evaluation of the ICUR, with the limit value of €43,193 in case sorafenib is not administered at all. As regard TTS, a proportion of patients undergoing sorafenib after TARE higher than 73% exclude the dominance of this treatment sequence, leading to the ICUR evaluation, with ICUR limit of €14,660 in case all patients receive sorafenib. As regard time horizon, an analysis performed on an interval shorter than 7 months let TS to be the dominant strategy. For time horizons between 8 and 13 months, the ICUR of TTS versus TS is over €50,000/QALY, while for a time horizon longer than 14 months the ICUR becomes lower than €50,000/QALY and even TTS becomes the dominant strategy in comparison with TS.

A two-way sensitivity analysis was performed varying simultaneously the proportion of patients undergoing sorafenib after TARE for TS (p_TARE_soraf_TS) and for TTS (p_TARE_soraf_TTS). Figure 3 shows the cost-effectiveness areas for the different value combinations in the scenarios considering a willingness to pay of €25,000/QALY (A) and €50,000/QALY (B).

A probabilistic sensitivity analysis was performed on the ICUR considering the discounted scenario and the model parameters presented in Supplementary Table 2.

Figure 4 reports the scatterplot representing 10,000 Monte Carlo simulations for the ICUR. Considering a threshold value of €50,000/QALY (dotted line), the administration of TTS showed to be a cost-effective choice in about 83% of simulations.

Discussion & conclusion

Unresectable liver malignancies present a major problem in the treatment of solid tumors. TARE is a relatively new procedure for treating various types of malignant liver tumors, and a valuable option for the management of nonresectable HCC. If, from the one hand, the literature presents few cost-effectiveness studies comparing single treatment options for HCC, on the other hand, there is paucity of studies presenting efficacy and especially cost data considering different treatment sequences. The aim of the present study was to conduct a cost-effectiveness analysis comparing two treatment sequences involving TARE, TARE followed by TACE and possibly sorafenib (=TTS) and TARE followed by sorafenib alone (=TS), to identify the most cost-effective pathway from the Italian Healthcare Service perspective.

Considering a lifetime perspective, TTS pathway provided the dominant strategy in comparison with TS. The results proved to be robust according to deterministic and probabilistic sensitivity analyses. Although there is no official cost-effectiveness threshold for Italy, the thresholds reported in the literature ranges between €25,000 and €40,000 [28], €36,500 [29] and €60,000 [30]. Only the proportion of patients undergoing sorafenib after TARE for TS and a time horizon shorter than 14 months could lead to an ICUR above €25,000/QALY or to TS dominance. Taking into account that the median survival of TS cohort is about 24 months (see Figure 2), it is advisable to consider a longer time horizon to completely capture clinical and economic effects of both considered treatment sequences.

Table 3. One-way sensitivity analyses.

Parameter	ICUR (€/QALY) TTS vs TS
Baseline	TTS dominant
Hospitalization cost for liver decompensation (range $\pm 30\%$)	
€1182	TTS dominant
€1351	TTS dominant
€1519	TTS dominant
€1688	TTS dominant
€1857	TTS dominant
€2025	TTS dominant
€2194	TTS dominant
Hospitalization cost for TACE (range $\pm 30\%$)	
€2836	TTS dominant
€3241	TTS dominant
€3647	TTS dominant
€4052	TTS dominant
€4457	TTS dominant
€4863	TTS dominant
€5268	TTS dominant
Hospitalization cost for TARE (range $\pm 30\%$)	
€6657	TTS dominant
€7608	TTS dominant
€8559	TTS dominant
€9510	TTS dominant
€10,461	TTS dominant
€11,412	TTS dominant
€12,363	TTS dominant
Sorafenib monthly cost (range $\pm 30\%$)	
€2651	TTS dominant
€3030	TTS dominant
€3408	TTS dominant
€3787	TTS dominant
€4166	TTS dominant
€4544	TTS dominant
€4923	TTS dominant
Mean number of TARE procedures per patient (TS; range $\pm 30\%$)	
0.73	TTS dominant
0.84	TTS dominant
0.94	TTS dominant
1.05	TTS dominant
1.15	TTS dominant
1.26	TTS dominant
1.36	TTS dominant
Mean number of TARE procedures per patient (TS; range $\pm 30\%$)	
0.89	TTS dominant
1.02	TTS dominant
1.14	TTS dominant
1.27	TTS dominant
1.40	TTS dominant
1.52	TTS dominant
1.65	TTS dominant
ICUR: Incremental cost-utility ratio; QALY: Quality-adjusted life year; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TS: TARE followed by sorafenib alone; TTS: TARE followed by TACE and possibly sorafenib.	

Table 3. One-way sensitivity analyses (cont.).

Parameter	ICUR (€/QALY) TTS vs TS
Proportion of patients with liver decompensation (TS; range 0–100%)	
0.00	TTS dominant
0.17	TTS dominant
0.33	TTS dominant
0.50	TTS dominant
0.67	TTS dominant
0.83	TTS dominant
1.00	TTS dominant
Proportion of patients with liver decompensation (TTS; range 0–100%)	
0.00	TTS dominant
0.17	TTS dominant
0.33	TTS dominant
0.50	TTS dominant
0.67	TTS dominant
0.83	TTS dominant
1.00	TTS dominant
Proportion of patients undergoing sorafenib after TARE (TS; range 0–100%)	
0.00	€43,193/QALY
0.17	€33,646/QALY
0.33	€24,100/QALY
0.50	€14,554/QALY
0.67	€5007/QALY
0.83	TTS dominant
1.00	TTS dominant
Proportion of patients undergoing sorafenib after TARE (TTS; range 0–100%)	
0.00	TTS dominant
0.17	TTS dominant
0.33	TTS dominant
0.50	TTS dominant
0.67	TTS dominant
0.83	€5621/QALY
1.00	€14,660/QALY
Time horizon (months)	
1	TS dominant
2	TS dominant
3	TS dominant
4	TS dominant
5	TS dominant
6	TS dominant
7	TS dominant
8	€9,970,105/QALY
9	€1,430,233/QALY
10	€608,969/QALY
11	€317,972/QALY
12	€176,447/QALY
13	€96,286/QALY
14	€46,367/QALY
15	€14,439/QALY
ICUR: Incremental cost–utility ratio; QALY: Quality-adjusted life year; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TS: TARE followed by sorafenib alone; TTS: TARE followed by TACE and possibly sorafenib.	

Table 3. One-way sensitivity analyses (cont.).	
Parameter	ICUR (€/QALY) TTS vs TS
16	TTS dominant
17	TTS dominant
18	TTS dominant
19	TTS dominant
20	TTS dominant
21	TTS dominant
22	TTS dominant
23	TTS dominant
24	TTS dominant

ICUR: Incremental cost–utility ratio; QALY: Quality-adjusted life year; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; TS: TARE followed by sorafenib alone; TTS: TARE followed by TACE and possibly sorafenib.

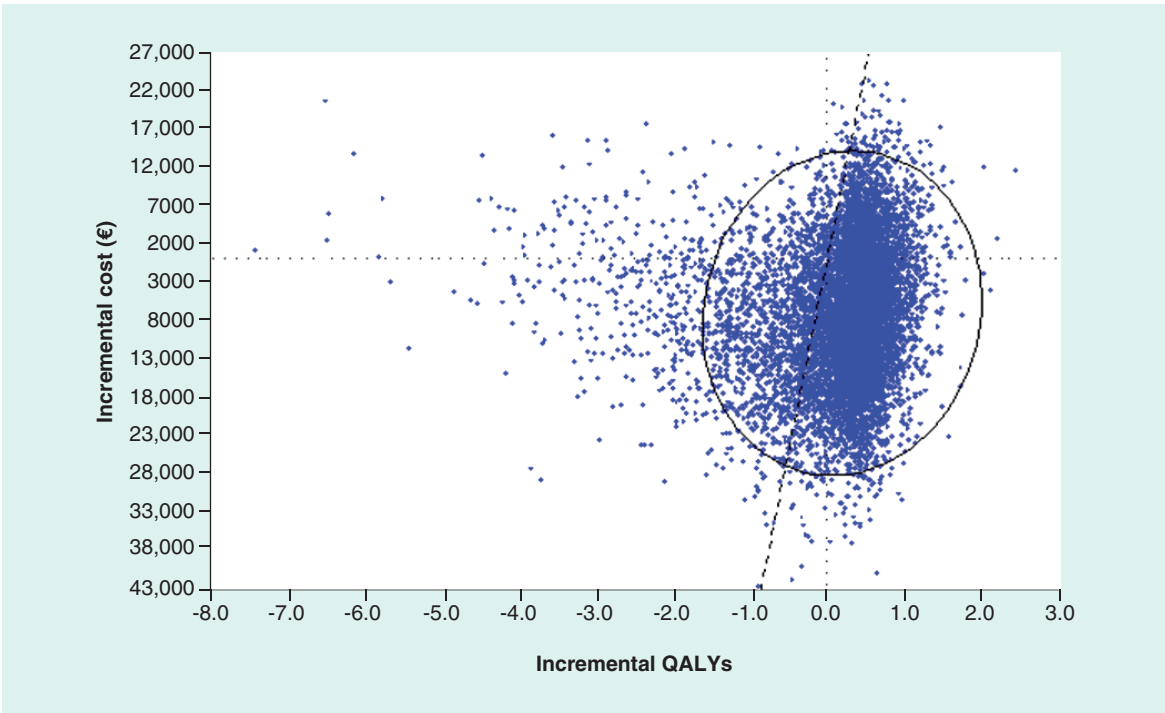


Figure 4. Incremental costs versus incremental quality-adjusted life years for transarterial radioembolization followed by transarterial chemoembolization and possibly sorafenib versus transarterial radioembolization followed by sorafenib alone.
QALY: Quality-adjusted life year.

The study is affected by some limitations. First of all, the clinical effectiveness was derived on patient-level data coming from selected major oncology centers, therefore the generalizability of the real-world patient data collected to the broader Italian HCC population could not be tested. Even if we applied a propensity score matching approach on the whole sample of patients treated primarily with TARE or sorafenib in order to obtain comparability of groups under main observable characteristics, the same approach could not be applied to the subgroups treated with TTS or TS mainly due to the small sample size.

Second, the model results on a lifetime horizon are greatly influenced by the survival curves fittings derived from patient-level data. Continuous observation and collection of survival data in this population through registries or randomized controlled trials will be helpful to confirm the assumptions made.

Third, healthcare resource use was retrieved from the clinical data only for treatments related to HCC (i.e., number of TARE treatments, sorafenib treatment duration) while for the follow-up period the clinical plan for visits and

examinations was considered. This approach could have led to underestimation or overestimation of the actual healthcare resource consumption.

Fourth, TTS strategy did not consider the administration of sorafenib to all patients but only to 47% of them. This choice could have biased the analysis toward a lower mean cost per patient for this treatment pathway. Anyway, the scenario analysis performed considering 100% of patients undergoing sorafenib after TARE led to an ICUR for TTS versus TS of €14,660/QALY, which is still under most accepted thresholds of cost-effectiveness for Italy. An analysis focused only to patients undergoing TARE, TACE and sorafenib was not possible due to the limited data sample. Moreover, the limited number of patients available to perform the present study suggests that the generalizability of the results should be carried out with caution. The cost-effectiveness of TARE versus sorafenib for the treatment of intermediate-advanced HCC has been previously stated [24]. Our study, performed on a subset of patients with intermediate-stage HCC, revealed that TARE followed by TACE plus possibly sorafenib may be a dominant strategy compared with TARE followed by sorafenib alone. Randomized studies are ongoing, specifically considering sorafenib in the advanced setting, to better define the relative role of TARE in relation to systemic chemotherapy. The evaluation of different treatment pathways or sequences of therapeutic options is of utmost relevance, particularly in oncology, and an area of research that should be explored further. While waiting for RCTs to be completed, this study provides decision makers with real-world evidence that can help identifying the best patterns of care in terms of both clinical outcomes and economic costs. Under certain conditions, and especially for medical devices [31,32], real-world studies can provide relevant evidence to decision makers, even in absence of randomized controlled trials, therefore becoming not only a complementary source of evidence but also a low-cost, rapid and valuable substitute for technologies whose diffusion process has already started in regular practice [33]. Nevertheless, more evidence is needed to provide additional information to confirm these conclusions and to support the expansion of TARE with new developments in interventional oncology.

Future perspective

The collection of real-world data on different treatment pathways involving radioembolization will be of utmost importance in the future in order to allow comparative evaluations on different groups of primary liver cancer patients. Even though studies generally include patients across the spectrum of Barcelona Clinic Liver Cancer staging system, strict inclusion criteria should be defined to facilitate the comparison of patients with the same characteristics and enhance the robustness of results for selected populations.

Moreover, accurate information on healthcare resource use and patients' quality of life in this context will be of great importance to perform further cost-effectiveness analyses, which are not many in this field. Although radioembolization can be considered an expensive procedure, with upfront significant costs, such analyses could provide a long-term view on costs and outcomes, highlighting the overall economic sustainability of this innovative medical device procedure.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://www.futuremedicine.com/doi/suppl/10.2217/cer-2017-0050>

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Summary points

- Hepatocellular carcinoma (HCC), the most common primitive liver tumor, is diagnosed in the majority of cases in intermediate-advanced stage, when radical therapies are no longer feasible.
- Although in intermediate-stage HCC, the main treatment approach is typically transarterial chemoembolization (TACE), more recently transarterial radioembolization (TARE) has been introduced in this population.
- The literature presents a few cost-effectiveness studies comparing single treatment options for HCC, but only few clinical and cost data are currently available for the comparison of different treatment sequences or combinations.
- In this study, we compared two treatment sequences involving TARE for intermediate-stage HCC in order to identify the most cost-effective pathway from the Italian Healthcare Service perspective:
 - TARE followed by TACE and possibly sorafenib (TTS);
 - TARE followed by sorafenib alone (TS).
- Prospective real-world data (from 2005 to 2015) were collected from three oncology centers in Italy.
- Thirty-eight patients out of 109 with intermediate-stage HCC treated with TARE reported subsequent treatments: 16 patients underwent TTS (47% with sorafenib administration) and 22 patients underwent TS.
- Two Markov models were developed to project costs and health outcomes associated to TTS and TS.
- Considering a lifetime perspective, the analyses showed that TTS sequence can be considered a dominant strategy (cost: €36,509, quality-adjusted life years: 1.385) in comparison to TS (cost: €42,812, quality-adjusted life years: 0.937) for the treatment of intermediate-stage HCC patients.
- The present study supports the use of TARE followed by TACE and possibly sorafenib in intermediate-stage HCC but more evidence is needed to confirm these conclusions and to support the expansion of TARE with new developments in interventional oncology.

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