

Patterns of treatment and costs of intermediate and advanced hepatocellular carcinoma management in four Italian centers

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Background: Hepatocellular carcinoma (HCC) is a severe health condition associated with high hospitalizations and mortality rates, which also imposes a relevant economic burden.

Purpose: The aim of the present survey is to investigate treatment strategies and related costs for HCC in the intermediate and advanced stages of the disease.

Patients and methods: The survey was conducted in four Italian centers through structured interviews with physicians. Information regarding the stage of disease, treatments performed, and related health care resource consumption was included in the questionnaire. Direct health care cost per patient associated with the most relevant treatments such as sorafenib, transarterial chemoembolization (TACE), and transarterial radioembolization (TARE) was evaluated.

Results: Between 2013 and 2014, 285 patients with HCC were treated in the four participating centers; of these, 80 were in intermediate stage HCC (Barcelona Clinic Liver Cancer Classification [BCLC] B), and 57 were in the advanced stage of the disease (BCLC C). In intermediate stage HCC, the most frequent first-line treatment was TACE (63%) followed by sorafenib (15%), radiofrequency ablation (14%), and TARE (1.3%). In the advanced stage of HCC, the most frequently used first-line therapy was sorafenib (56%), followed by best supportive care (21%), TACE (18%), and TARE (3.5%). The total costs of treatment per patient amounted to €12,214.54 with sorafenib, €13,418.49 with TACE, and €26,106.08 with TARE. Both in the intermediate and in the advanced stage of the disease, variability in treatment patterns among centers was observed.

Conclusion: The present analysis raises for the first time the awareness of the overall costs incurred by the Italian National Healthcare System for different treatments used in intermediate and advanced HCC. Further investigations would be important to better understand the effective health care resource usage.

Keywords: disease costs, drugs cost, transarterial embolization, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, which causes approximately 500,000 deaths every year,¹ and it is characterized by biological and clinical heterogeneity and different prognoses.^{2,3} It is also the second most common cause of death from cancer worldwide and the second most rapidly increasing type of cancer in the United States.⁴⁻⁶ The incidence of HCC increases progressively with advancing age in all populations, reaching its peak at the age of 70.⁷ Moreover, HCC contributes substantially to health care spending.

In Italy, liver cancer is one of the first five causes of death in males (7%);⁸ 12,500 new cases of liver tumors were expected in 2014, accounting for 3% of the overall

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incidence of all tumors, with a male:female ratio of 2:1. The incidence of HCC has decreased in both sexes, since the mid 90s.⁸ Approximately 21,000 patients with a previous diagnosis of HCC (1% of all patients with a cancer) lived in Italy in 2011.⁸

The most important risk factors for HCC are cirrhosis due to chronic hepatitis B and chronic hepatitis C, alcoholic cirrhosis, or nonalcoholic steatohepatitis, high body mass index, and diabetes mellitus.^{9–11}

Worldwide, the most important risk factor for liver cancer is chronic hepatitis B or hepatitis C virus. People infected with both viruses have a high risk of developing chronic hepatitis, cirrhosis, and liver cancer. The risk of developing liver cancer is higher if patients are also heavy drinkers.¹² The vast majority of patients developing liver cancer already have some evidence of cirrhosis. Obesity increases the risk of developing liver cancer, probably because it can result in fatty liver disease and cirrhosis. Type 2 diabetes is associated with an increased risk of liver cancer, usually in patients who also have other risk factors (eg, heavy alcohol use, chronic viral hepatitis).¹² This risk may be increased as type 2 diabetes patients tend to be overweight or obese, which can cause liver problems.¹² Although HCC patients can benefit from radical resection, transplantation, or radiofrequency ablation thanks to preliminary

screening and diagnosis, tumors in some patients (those with background cirrhosis in particular) still progress rapidly because of local spreading or metastases.

The Barcelona Clinic Liver Cancer Classification (BCLC) correlates stages of the disease with treatment modalities, and identifies five stages of HCC (0, A, B, C, and D) according to preestablished prognostic variables and treatment modalities for each stage of the disease, thus providing both prognostic prediction and treatment allocation recommendations.¹³ The American Association for the Study of Liver Disease (AASLD) guidelines 2010,¹⁴ the European Association for the Study of the Liver (EASL) guidelines 2012,¹⁵ and the Italian Association for the Study of the Liver (AISF 2012)¹⁶ are the most updated guidelines for the treatment of HCC and include staging and prognostic–therapeutic stratification (EASL–BCLC guidelines) (Figure 1).

In the intermediate stage (BCLC B), patients with asymptomatic tumors (without an invasive pattern) survive 16 months on average;^{2,17,18} chemoembolization prolongs the survival of these patients up to 19–20 months, according to randomized controlled trial and meta-analysis of pooled data.¹⁷

HCC exhibits intense neoangiogenic activity during its progression. The rationale for transarterial chemoembolization (TACE) is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels

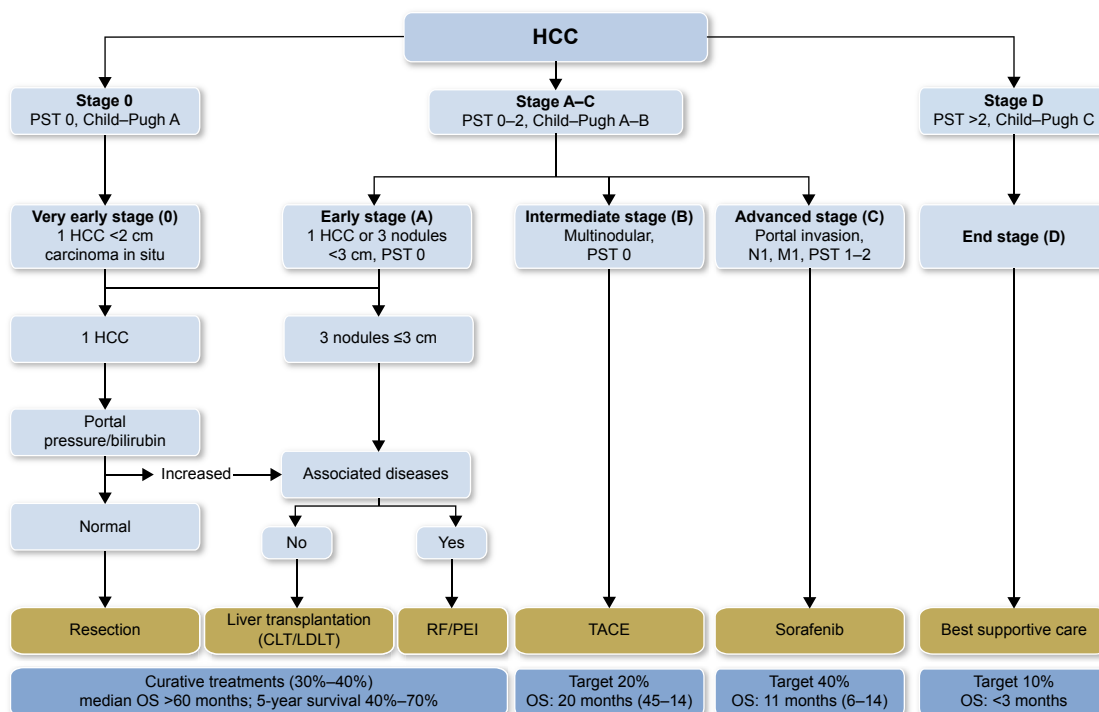


Figure 1 Updated staging system and treatment strategy.

Notes: Reprinted from the Journal of Hepatology, Volume 56, European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer, EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. Pages 908–943. Copyright 2012, with permission from Elsevier.¹⁵

Abbreviations: HCC, hepatocellular carcinoma; PST, performance status test; CLT, cadaveric liver transplantation; LDLT, liver donor liver transplantation; RF, radio frequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; OS, overall survival.

will result in a strong cytotoxic and ischemic effect. This procedure combines transcatheter delivery of chemotherapy emulsified with lipiodol, followed by vascular stagnation achieved with embolic agents. Chemoembolization achieves partial responses in 15%–55% of patients and significantly delays tumor progression and macrovascular invasion. Overall, the median survival for intermediate HCC cases is expected to be approximately 16 months, whereas after chemoembolization, the median survival is ~20 months.^{15,19,20}

Patients in the advanced stage of the disease (BCLC stage C) (cancer-related symptoms and/or macrovascular invasion and/or extrahepatic spread) have poorer prognosis, and the expected median survival without treatment is ~6 months,^{18,21} or 25% at first year,¹⁹ which is extended to 11 months by treatment with sorafenib.²⁰

Sorafenib, a multikinase inhibitor, is the standard systemic therapy suggested by guidelines for HCC BCLC stage C or for intermediate stage after failure of or ineligibility for locoregional therapies (treatment-stage migration strategy).¹³

Efficacy and safety of sorafenib were evaluated in several clinical studies;²² the Phase III SHARP study²³ demonstrated that sorafenib significantly increased overall survival by 44% vs placebo (10.7 vs 7.9 months, respectively; $P < 0.001$) and almost doubled median time to progression (5.5 vs 2.8 months, respectively; hazard ratio [HR]: 0.58, $P < 0.001$).

These results were confirmed by a Phase III study conducted in the Asia-Pacific region;²⁴ in this trial, sorafenib significantly increased the overall survival by 47% vs placebo (6.5 vs 4.2 months, respectively; HR: 0.68; $P = 0.014$) and doubled the median time to progression vs placebo (2.8 vs 1.4 months, respectively; HR: 0.57, $P = 0.0005$).

In both Phase III studies, the safety profiles of sorafenib were predictable and manageable, and the benefits of sorafenib were consistent across subgroups by etiology, tumor burden, tumor stage, and prior therapy. Based on these results, international and national guidelines recommended sorafenib as the treatment of choice for advanced HCC (level of evidence IA^{15,25}/positively strong). A few studies^{26–31} reported the economic burden of HCC worldwide, and while sorafenib cost-effectiveness analyses have been published,^{32,33} to our knowledge no data exist on the cost-effectiveness of TACE for HCC. The objective of the present analysis is to investigate treatment pathways and related health care costs for HCC BCLC stage B and stage C patients.

Material and methods

The aim of the present survey is to investigate the current patterns of treatment, health care resource consumption, and costs related to the treatment of HCC in the intermediate and

advanced stages of the disease, through an analysis of the therapeutic pathways followed in four Italian centers. The survey was conducted through structured interviews involving gastroenterology and interventional radiology units. Ethical approval for this study was obtained from Policlinico Umberto I Roma, AOU Seconda Università di Napoli, Policlinico Paolo Giaccone Palermo, and AO Brotzu Cagliari. Informed consent was obtained from all patients.

The data collected in the project remained the property of each facility provider and were managed in aggregate and anonymous form, without access to individual patient data.

The following information was collected:

- Number of patients with HCC by stage
- Distribution of patients by treatment options (TACE, transarterial radioembolization [TARE] systemic treatment) and line of treatment (first- and second-line treatment)
- Treatments administered (frequency, average number of locoregional therapies, and duration of treatment for systemic therapies)
- Diagnostic procedures and laboratory tests associated with each treatment
- Specialist visits and follow-up associated with each treatment (percentage of patients undergoing examinations/visits and frequency)
- Consumption of medical and nonmedical supplies associated with treatments (type of consumables, quantity, and unitary costs)
- Cost of medical, nursing, and technical staff involved in patient management during the treatment.

Unit costs considered in this analysis and related sources are reported in Table 1.

As for drugs, the cost per milligram was estimated as the average cost of different packs at the maximum price reimbursed by the Italian National Health Service.

In order to estimate the average cost per month of therapy, an 80% adherence to treatment was considered for sorafenib, along with published data on oral antineoplastic treatments.³⁴ The reference year of the present survey was 2013.

Results

The present survey involved 137 patients with intermediate and advanced stage HCC, BCLC stage B, and BCLC stage C among a cohort of 285 patients (mean age: 66 years, 74% males) treated in four Italian centers specialized in the treatment of patients with HCC (Policlinico Umberto I Roma, AOU Seconda Università di Napoli, Policlinico Paolo Giaccone Palermo, AO Brotzu Cagliari). In the overall population, 20% of patients were in the very early stage of the disease (HCC BCLC stage 0), 17% in the early stage (HCC

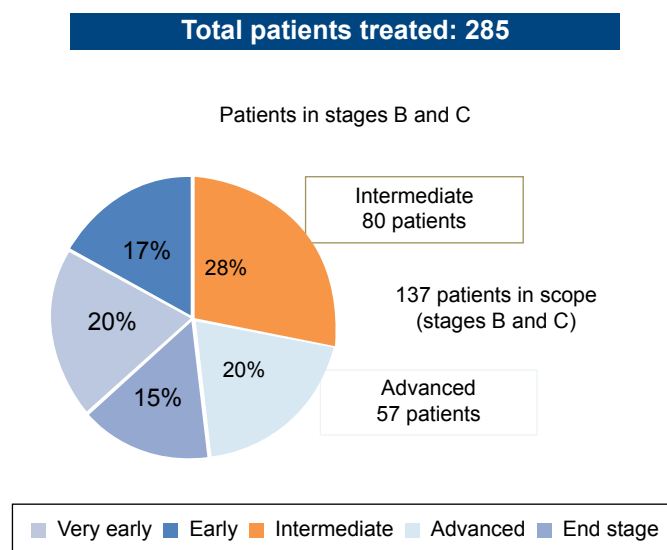
Table I Resources consumption and costs

Item	Description	Unit cost (€)	References
Professional resources	Interventional radiologist	74.20/h	Conferenza Stato-Regioni 21/11/2014 – Rapporto STEM ⁴⁰
	Hepatologist	74.20/h	
	Anesthetist	74.20/h	
	Nuclear medicine physician	74.20/h	
	Nurse	34.03/h	
	Radiology technician	34.03/h	
	Hospital pharmacist	61.42/h	
Drugs	Doxorubicin	0.83/mg	Italian Medicines Agency ⁴¹
	Fluorouracil	1.39/mg	
	Ethiodized oil	2.40/vial	
	Sorafenib	28.70/tablet	
Consumables	Angiographic sterile field	39.96	Selection of public tenders data in 23 relevant Italian hospitals; prices include VAT
	Angiographic introducer	161.33	
	Catheter	87.22	
	Microcatheter	764.25	
	Guide	80.55	
	Microguide	439.06	
	DC Beads®	822.60	
	Hemostasis system	17.78	
	Spiral	592.90	
	Technetium	1,245.95	
Overheads	SIR-Spheres microspheres	11,000.00	Setacci et al ⁴²
	Gastroenterology admission	522.17/day	
	Nuclear medicine admission	600.50/day	
	Angiographic room	7.50/min	

BCLC stage A), 28% in the intermediate stage (HCC BCLC stage B), 20% in the advanced stage (HCC BCLC stage C), and the remaining 15% in the terminal stage (HCC BCLC stage D) (Figure 2).

First- and second-line treatments for patients in the intermediate and advanced stages of the disease are reported in Figures 3 and 4.

Among the 80 patients in the intermediate stage of the disease treated with first-line therapies, 63% (minimum 50% to maximum 80%) were treated with TACE, 15% with sorafenib (range, 10%–17%), 14% (range, 5%–30%) with radiofrequency ablation, and the remaining 10% with other therapies (best supportive care, TARE, and liver resection).

**Figure 2** Distribution of total patients treated.

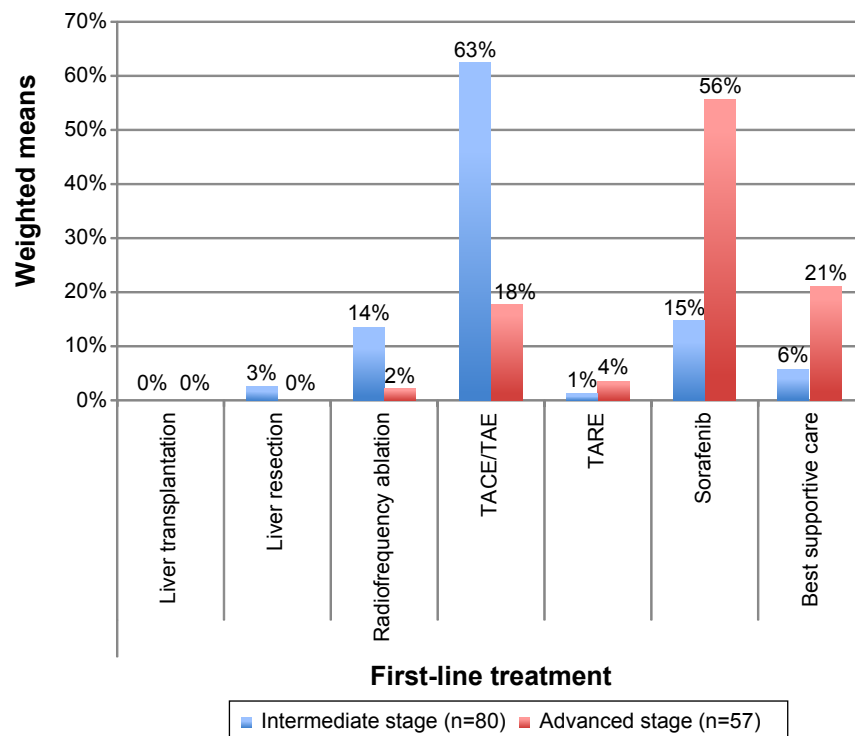


Figure 3 First-line treatments of patients with intermediate and advanced HCC.

Abbreviations: TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; HCC, hepatocellular carcinoma.

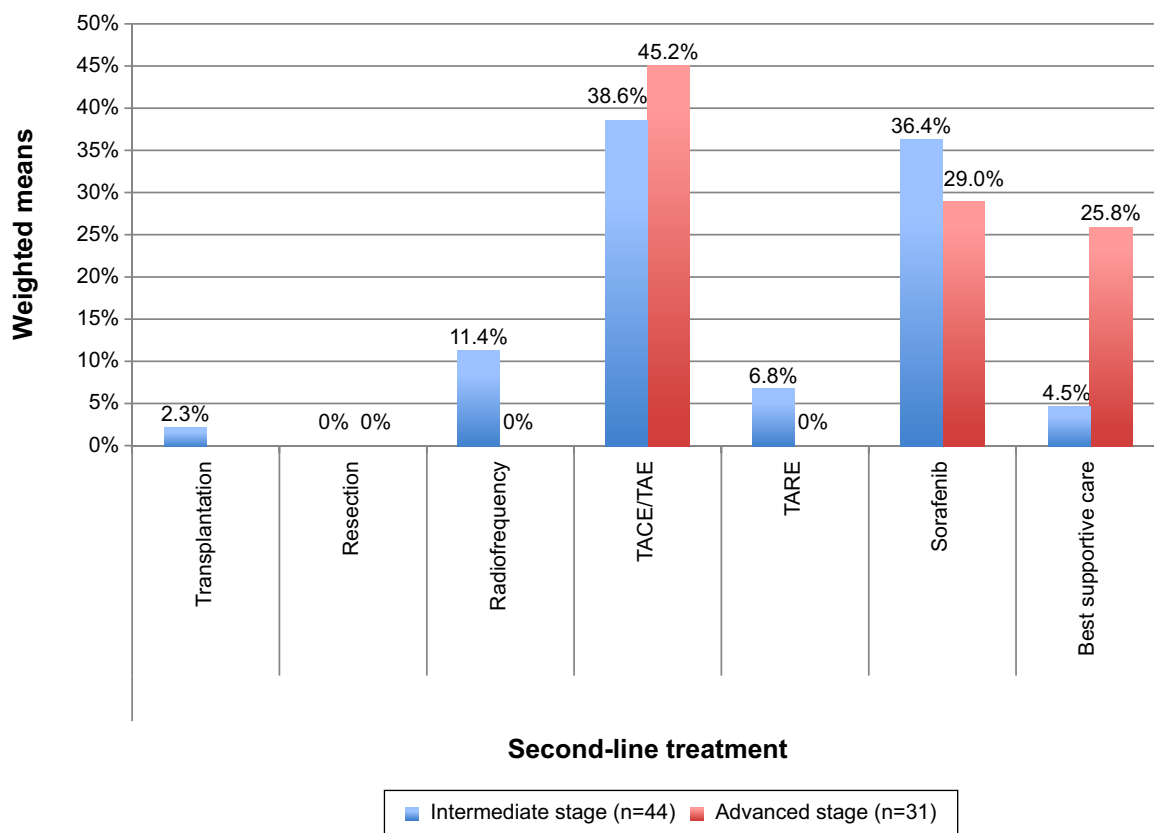


Figure 4 Second-line and subsequent treatments for patients with intermediate and advanced HCC.

Abbreviations: TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; HCC, hepatocellular carcinoma.

Table 2 Resources according to type of treatment

Resource/treatment	Sorafenib	TACE	TARE
Specialist visit (hepatologist)	× (outpatients)	× (outpatients)	× (inpatients)
Diagnostic procedures	× (outpatients)	× (outpatients)	× (inpatients)
Prehospitalization workup			
Hepatic scintigraphy			× (inpatients)
Radiopharmaceutical evaluation			× (inpatients)
Drug distribution	× (outpatients)		
Patient preparation		× (inpatients)	× (inpatients)
Complete angiography		× (inpatients)	× (inpatients)
Medical device (ie, DC Beads®) or contrast medium (ethiodized oil) injection		× (inpatients)	× (inpatients)
Chemotherapy drug injection		× (outpatients)	

Notes: ×, all resource used for each specific treatment.

Abbreviations: TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Of these, 55% (n=44) were treated with second-line or subsequent therapies. The most frequent second-line or subsequent therapies were TACE – 39% (range, 5%–60%) and sorafenib – 36% (range, 9%–40%).

Among the 57 patients in the advanced stage of the disease treated with first-line therapies, sorafenib was the most frequently used first-line treatment: 56% (range, 12%–79%). Best supportive care was used in 21% of patients (range, 15%–24%) as the first-line option.

Of these, 54.4% (n=31) were then treated with second-line or subsequent therapies. TACE was the most frequent second-line option in the advanced stage – 45% (range, 0%–80%), followed by sorafenib – 29% (range, 0%–60%), and best supportive care – 26% (range, 0%–30%).

The mean duration of treatment with sorafenib in 137 patients with intermediate and advanced stage HCC was 6.1 months in all treatment lines combined.

The average number of TACE was 2.5 procedures/patient, and patients treated with TARE received an average of 1.5 procedures/patient.

The health care resources used in association with each type of therapy are reported in Table 2.

Mean resource consumption related to the different treatments, and related costs of consumables and professional resources are reported in Tables 3 and 4.

Regarding the systemic treatment, the average cost per tablet (200 mg) of sorafenib to public health care structures (including the two 5% transient price reductions, as per Italian law at the time of the analysis)^{35,36} accounted for €28.70.

Considering the overall mean daily dosage (612 mg) and an estimated 80% of adherence to therapy,³⁴ the average per-month cost of treatment with sorafenib amounted to €1,986.36.

On the basis of the unitary cost per procedure/month of treatment and the duration of each therapy, the calculated average total costs of the different treatments are reported in Table 5.

Discussion

The results of the present analysis, aimed at evaluating the patterns of treatment and the costs related to HCC treatments,

Table 3 Per-patient resource consumption and costs of consumables by procedure

Consumables ^a	Unitary costs (€)	TACE		TARE	
		Average number/patient	Cost/patient/procedure (€)	Average number/patient	Cost/patient/procedure (€)
Angiographic sterile field	39.96	1.00	39.96	1.00	39.96
Angiographic introducer	161.33	1.00	161.33	1.10	177.47
Catheter	87.22	1.15	100.31	1.10	95.95
Microcatheter	764.25	1.05	802.46	1.10	840.68
Guide wire	80.55	0.74	59.61	1.10	88.61
Microguide wire	439.06	0.57	250.27	–	–
DC Beads®	822.60	1.06	871.96	–	–
Hemostasis system	17.78	0.56	9.96	1.00	17.78
Metal spiral	592.90	–	–	10.00	5,929.00
Technetium	1,245.95	–	–	0.03	41.54
SIR-Spheres microspheres	11,000.00	–	–	0.50	5,500.00
Total consumables	–	–	2,295.86	–	12,730.99

Note: ^aSorafenib is not included in this table because, as it is an oral treatment, no consumables are necessary to deliver the treatment.

Abbreviations: TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Table 4 Per-patient resource consumption and costs of professional resources by treatment

Professional resources	Hourly costs (€)	Sorafenib		TACE		TARE	
		Hours/patient/prescription (mean)	Cost/procedure/patient (€)	Hours/patient/prescription (mean)	Cost/procedure/patient (€)	Hours/patient/prescription (mean)	Cost/procedure/patient (€)
Interventional radiologist	74.20	–	–	1.90	141.11	2.83	210.25
Hepatologist	74.20	0.17	12.37	–	–	–	–
Anaesthetist	74.20	–	–	0.49	36.15	–	–
Nuclear medicine physician	74.20	–	–	–	–	0.33	24.74
Nurse	34.03	–	–	1.71	58.34	2.50	85.09
Radiology technician	34.03	–	–	0.85	28.96	–	–
Hospital pharmacist	61.42	0.17	10.24	–	–	–	–
Total professional resources		0.34	22.61	4.95	264.56	5.66	320.08

Abbreviations: TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Table 5 Overall cost per patient by type of treatment

Costs (€)	Sorafenib	TACE	TARE
Total consumables/procedure/patient		2,295.86	12,730.99
Angiographic sterile field	–	39.96	39.96
Angiographic introducer	–	161.33	177.47
Catheter	–	100.31	95.95
Microcatheter	–	802.46	840.68
Guide wire	–	59.61	88.61
Microguide wire	–	250.27	–
DC Beads®	–	871.96	–
Hemostasis system	–	9.96	17.78
Metal spiral	–	–	5,929.00
Technetium	–	–	41.54
SIR-Spheres microspheres	–	–	5,500.00
Total drugs/procedure month/patient	1,986.36	68.26	–
Ethiodized oil (per procedure)	–	1.44	–
Doxorubicin (per procedure)	–	42.01	–
Farmorubicin (per procedure)	–	24.81	–
Sorafenib (month of therapy)	1,986.36	–	–
Total professional resources/procedure month/patient	22.61	264.56	320.08
Interventional radiologist	–	141.11	210.25
Hepatologist	12.37	–	–
Anesthetist	–	36.45	–
Nuclear medicine physician	–	–	24.74
Radiology technician	–	28.96	–
Nuclear medicine technician	–	–	–
Nurse	–	58.34	85.09
Hospital pharmacist	10.24	–	–
Overheads/procedure/patient	–	2,675.07	4,352.98
Occupation of angiographic room ^a	–	604.19	750.00
Gastroenterology ward admission ^b	–	2,070.88	–
Nuclear medicine admission ^b	–	–	3,602.98
Total cost per procedure-month of treatment/patient	2,008.97	5,303.75	17,404.05
Average number of treatments	6.08	2.53	1.50
Average total cost of treatment/patient	12,214.54	13,418.49	26,106.08

Notes: ^aAverage occupation of angiographic room per procedure was 80.6 minutes for TACE and 100 minutes for TARE. ^bThe average length of stay in the gastroenterology ward was 4 days for TACE, and the average length of stay in the nuclear medicine ward was 6 days for TARE.

Abbreviations: TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

show a high variability among centers concerning procedures used in both the intermediate and advanced stages, first-line and subsequent lines. TACE was the treatment of choice in intermediate HCC, as suggested by the guidelines, but ~38% of patients were treated with alternative therapies. Sorafenib was the most frequently used first-line therapy in advanced HCC as recommended by international and Italian guidelines, although ~45% of these patients received other first-line treatments. A potential role of the combined approach of these therapies in intermediate HCC patients, as suggested by recent publications,³⁷ is still experimental and needs further confirmatory trials. The cost of HCC treatment amounted to ~€12,200/patient for sorafenib, €13,400/patient for TACE, and €26,100/patient for TARE.

The unitary costs of the treatments that were used in the calculations originate from tariffs and average acquisition costs at the national level (determined on a benchmark of 23 tenders). This methodology allows a comparison among treatment strategies based on the same evaluation criteria. From the perspective of health care cost of treatment, some facts should be taken into consideration. Treatment guidelines recommend TACE for intermediate HCC. The costs sustained by the centers for this procedure are, however, only partially covered by their diagnosis-related group's (DRG)³⁸ tariff (€5,304 vs a reimbursement tariff of €4,085; DRG 203: malignancy of hepatobiliary system or pancreas).³² Regarding TARE, which is not recommended by treatment guidelines either in intermediate stage or in advanced stage HCC, the costs sustained by the centers are relevant (~€17,400/patient/procedure), while at the national level, the DRG's reimbursement tariff for TARE is DRG 409 (radiotherapy),³⁸ reimbursed at €1,471. Among the centers involved in the present study, only one performs this kind of procedure.

Sorafenib, recommended by national and international guidelines as the treatment of choice for advanced HCC, is dispensed in Italy by hospital pharmacies and registered in the "file F" that is used for specific categories of drugs distributed by NHS health care structures not covered by DRGs or tariffs (sorafenib cost is directly reimbursed to hospitals by local health care units or regions). We note, however, that this evaluation is only a cost analysis and does not take into account unplanned hospitalization, cost of side effects, and their treatment. The inclusion of these "shadow costs" could change the final cost of HCC treatment. Furthermore, we did not find any cases of HCC surgical treatments. Recent literature,³⁹ for example, showed that surgical therapies could also give the best results in patients with intermediate or advanced HCC. A limitation of the present study is that the centers that participated in this analysis may not accurately

mirror the situation of the entire Italian territory, although they are centers experienced in the treatment of HCC, selected among hospitals with a wide volume of activity in this field. To our knowledge, this is the first study that evaluates the costs of treatment patterns for intermediate/advanced HCC patients in a real-life setting in Italy.

Conclusion

Sorafenib is recommended by international and Italian guidelines (level of evidence IA/strong positive) as the treatment of choice for advanced HCC. It was the most frequently used treatment in this setting; the associated cost of treatment was €12,200/patient. TACE was the most widely used treatment in intermediate HCC, and its associated costs of €13,400/patient are only partially covered by the DRG's reimbursement tariffs. TARE, which is not indicated as a treatment choice in HCC management guidelines, was performed in one of the participating centers with an associated average cost of €26,100/patient that is not covered by the national reference DRG. The present study highlights the need for additional analyses of the national health care system resources that are being used routinely for the treatment of HCC and the associated outcomes, and can be the basis for future research and analysis of the cost-effectiveness of TACE, alone or combined with sorafenib, for the treatment of HCC.

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Disclosure

The authors report no conflicts of interest in this work.

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