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ORIGINAL ARTICLE

Hepatocellular carcinoma surgical and oncological trends in a national multicentric population: the HERCOLES experience

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Abstract

Liver surgery is the first line treatment for hepatocarcinoma. Hepatocarcinoma Recurrence on the Liver Study (HERCOLES) Group was established in 2018 with the goal to create a network of Italian centres sharing data and promoting scientific research on hepatocellular carcinoma (HCC) in the surgical field. This is the first national report that analyses the trends in surgical and oncological outcomes. Register data were collected by 22 Italian centres between 2008 and 2018. One hundred sixty-four variables were collected, regarding liver functional status, tumour burden, radiological, intraoperative and perioperative data, histological features and oncological follow-up. 2381 Patients were enrolled. Median age was 70 (IQR 63–75) years old. Cirrhosis was present in 1491 patients (62.6%), and Child-A were 89.9% of cases. HCC was staged as BCLC0-A in almost 50% of cases, while BCLC B and C were 20.7% and 17.9% respectively. Major liver resections were 481 (20.2%), and laparoscopy was employed in 753 (31.6%) cases. Severe complications occurred only in 5%. Postoperative ascites was recorded in 10.5% of patients, while posthepatectomy liver failure was observed in 4.9%. Ninety-day mortality was 2.5%. At 5 years, overall survival was 66.1% and disease-free survival was 40.9%. Recurrence was intrahepatic in 74.6% of cases. Redo-surgery and thermoablation for recurrence were performed up to 32% of cases. This is the most updated Italian report of the national experience in surgical treatment for HCC. This dataset is consistently allowing the participating centres in creating multicentric analysis which are already running with a very large sample size and strong power.

Keywords Hepatocellular carcinoma · Liver surgery · HERCOLES · Hepatocarcinoma recurrence · Redo surgery

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and the third leading cause of cancer-related death [1]. This high incidence has led to the development of several clinical studies on HCC, including the effectiveness of available treatments for patients at the primary diagnosis and for patients with HCC recurrence. Indeed, the rate of HCC recurrence is still very high, being reported approximately 70% at 5 years [2].

Currently, there is no centralisation of hepatobiliary surgery in Italy. This means that HCC is treated with disparate experiences and results across the nation. To date, there isn't

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a national register on the surgical treatment and follow-up of HCC. Therefore, high-volume centres specialising in liver surgery or teaching hospitals are the major sources of studies on this topic, thus losing data from centres with lower volumes and without the possibility to concretely depict the real Italian state of the art. In this setting, a national register has the crucial role to evaluate the real situation with regard to hepatic resections for HCC, without the biases coming from the literature produced by few and selected high volume centres. Moreover, a national register may allow not only to summarise the Italian surgical experience but also to create a substrate for more powerful analysis.

This is the background that led to the realisation of the Hepatocarcinoma Recurrence on the Liver Study (HERCOLES) Group, a framework for HCC treatment and its recurrence in Italian reality with the goal to set up a data hub and projects on a national basis, creating the basis for works that fully represent the state of the art with regard to the surgical approach to HCC, since there is evidence that the measurement and monitoring of outcomes associated with auditing and feedback from surgeons specialising in liver surgery led to an improvement in the quality of care. This paper is the first attempt to depict the HERCOLES Group dataset and its potential in the clinical and experimental setting.

Methods

Register information, study design and inclusion criteria

This retrospective study evaluated patient data enrolled in the Italian Register of HCC, promoted by the HERCOLES Group, which is composed of 30 Italian liver surgery centres. The participation is open to Italian centres performing curative liver surgery to treat HCC, without restriction criteria based on the number of procedures.

The register is divided between two principal studies. The "Phase 1" study (HERCOLES1) is a retrospective data collection between January 2007 and December 2018. The data of this manuscript are a snapshot of this project. The "Phase 2" study (HERCOLES2) is a prospective data collection, which started in September 2019; the study protocol was registered at clinicaltrial.gov (ID NCT04053231). Both studies followed the ethical guidelines of the 1975 Declaration of Helsinki, as revised in Brazil 2013. The Ethical Committee of the Coordinating Centre (San Gerardo Hospital, Monza, Italy, "Monza e Brianza Ethical Committee") reviewed and approved the protocol on 21 December 2018. Inclusion criteria for enrolment in HERCOLES1 were: (1) first diagnosis of HCC without any previous hepatocarcinoma-related treatment; (2) no age limit; (3) hepatocarcinoma diagnosis confirmed at histological specimen; and (4) patients treated between 2007 and 2018. Exclusion criteria were: (1) surgery as a downstaging therapy for transplant; (2) patients who were treated with liver transplantation; (3) histopathological specimen of combined liver primary neoplasms (e.g., 'hepatocholangiocarcinoma'); and (4) patients with other tumours in the previous past. The register database collected 163 variables related to patient comorbidities, underlying liver function, radiological and intraoperative findings, postoperative course, histological evaluation and follow-up information for each patient enrolled. Particularly, all data about the treatment of recurrences were recorded. All data were submitted by local researchers and anonymized prior to submission to the Coordinating Centre. Data collection was performed using an electronic database system in all centres. The submitted data were then checked centrally at San Gerardo Hospital and when important missing data were identified, the local investigator was contacted and asked to complete the records. If the data were not available at the local centre, the record was considered missing. Once examined, the record was accepted into the dataset for analysis. Data were processed and disseminated in anonymous form. Data management and statistical analysis were managed by the Bicocca Clinical Research Office (BiCRO), which actively participated and supported the study Group. The subject has the right at all times to obtain confirmation of the existence or otherwise of such data, know their content and origin, check their accuracy and ask for data additions or updating or rectification. More information about the HERCOLES Project may be found at https://www.hercolesgroup.eu.

Variables and follow-up

Age, sex, Charlson Comorbidity Index and liver function at presentation were recorded and evaluated at the first visit. In particular, the presence of cirrhosis and its severity was evaluated by expert hepatologists during the disease workup. BCLC grade was estimated after radiological evaluation. Model for end-stage liver disease (MELD) score and Child–Pugh score were calculated on the basis of preoperative serum biochemical values and clinical examination. Biochemical tests, including albumin and total bilirubin, were collected at the time of recovery. The number and diameter of nodules were assessed through preoperative radiologic imaging and confirmed by intraoperative ultrasound either during the staging procedures at the first diagnosis or during the follow-up time in case of recurrence. The extension of liver resection was defined as minor ≤ 3 segments and major > 3 segments, as based on Brisbane nomenclature [3]. Complications were registered according to the Clavien–Dindo classification. Postoperative liver ascites was defined as ≥ 500 ml in drainage or the presence of ascites at US scan in case of no drains for three consecutive days

[4, 5]. Post-hepatectomy liver failure (PHLF) was defined according to the 50–50 criteria [6]. Length of hospital stay was measured from the day of surgery to the date of discharge.

All patients were followed using a local protocol, including measurement of serum α-fetoprotein, abdominal ultrasound, contrast computed tomography (CT) or magnetic resonance imaging (MRI), and office visits as suggested in European guidelines [2]. Briefly, each patient was followed up every 3 months for the first 2 years and then every 6 months. Overall survival (OS) was defined as the time interval between the first diagnosis of HCC to death. Disease-free survival (DFS) was defined as the time interval in months from the date of surgery to recurrence or death. In case of no recurrence or death, data were censored at the date of the last available follow-up. Survival after recurrence (SAR) was defined as the time interval between the date of relapse to death. Treatment of recurrences was at the surgeon's will and each centre declared to discuss all cases at their own multidisciplinary meeting, involving hepatologists, oncologists and interventional radiologists. Treatment allocation was the sum of different evaluations about underlying liver function, tumour burden and comorbidities, creating tailored treatment for each case. Briefly, treatment allocation was founded on comorbidities, previous surgical history, underlying liver damage and presence of bilobar disease. Each case had been separately discussed, and consequently, each candidate for specific treatment. Patient surveillance was closed at the end of March 2019.

Statistical analysis

Sample description was performed using medians and interquartile ranges (IQRs) for numeric variables and numbers and proportions for categorical variables. OS, DFS and treatment-specific SAR over time were estimated using the Kaplan–Meier method, and the log-rank test was used to compare groups. Median follow-up was estimated by reverse Kaplan–Meier method. All statistical tests were two-tailed and a 5% significance level was considered. All the analyses were carried out using R software version 3.6.0.

Results

Thirty centres are registered in the HERCOLES Group, and 22 of them correctly submitted data in the register for "HERCOLES1" at the end of November 2019. Between January 2007 and December 2018, a total of 2381 patients were enrolled. The number of enrolments increased progressively with an almost linear trend over time, as depicted in Fig. 1.

Median age was 70 years old (IQR 63–75), and 568 (23.9%) patients were female. Comorbidities were measured by the Charlson Comorbidity Index, which had a median score of 6 (IQR 5–7) among the whole cohort.

Liver function and tumour burden

Cirrhosis was present in 1491 (62.6%) cases, and liver function was deteriorated in 101 (6.8%) cases that were classified as Child class B. Liver damage was related to HCV infection in 1151 (48.3%) cases, while HBV was the driver in 452 (19.0%) cases. Chronic excessive alcohol consumption was recorded in 472 (19.8%) patients. Steatosis was diagnosed in 528 (22.2%) cases. In 390 (16.4%) patients, collateral veins and gastroesophageal varices were not considered contraindications for surgery. Considering the first presentation of the tumour, the indication for surgery had been made according to radiological imaging, in which the median number of nodules in the liver was 1 (IQR 1–2), while the median size was 4.0 cm (IQR 2.5–6.0). The BCLC staging system was employed to stratify patients and very early and early stages accounted for 50.7% ($n = 1208$) of the cases. Intermediate (BCLC B)

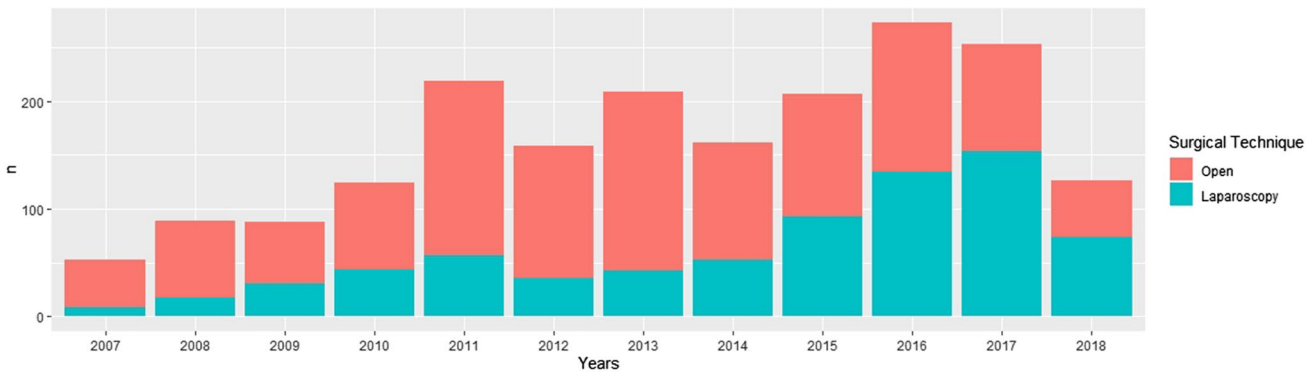

Fig. 1 Trends in patient enrolment during the period of the study. The different surgical approaches were summarised per year, depicting the relative percentage of patients treated by laparoscopy rather than open approach

and advanced (BCLC C) stages were 20.7% and 17.9% of the cohort, respectively. Data are summarised in Table 1. Underlying liver function and tumour features are also depicted in Fig. 2.

Table 1 Baseline characteristics of the whole sample in the register

	n/median (*n* = 2381)	%/IQR	Missing (%)
Age (years)	70.00	63.00, 75.00	127 (5.3)
Sex			
Female	568	23.9	0 (0.0)
Charlson Comorbidity Index	6	5, 7	401 (16.7)
Cirrhosis			
Yes	1491	62.6	54 (2.3)
Steatosis			
Yes	528	22.2	160 (6.7)
Metabolic syndrome			
Yes	248	10.4	885 (37.2)
Child–Pugh grade[a]			
A	1342	89.9	48 (3.2)
B	101	6.8	
HBV			
Yes	452	19.0	70 (2.9)
HCV			
Yes	1151	48.3	69 (2.9)
Potus			
Yes	472	19.8	97 (4.1)
Esophageal varices and/or collateral circulation			
Yes	390	16.4	449 (18.9)
Splenomegaly			
Yes	405	17.0	247 (10.4)
Total bilirubin (mg/dl)	0.87	0.60, 1.20	109 (4.5)
Platelet (10^3/mm^3)	171.00	120.25, 227.00	151 (6.3)
INR	1.10	1.03, 1.22	137 (5.7)
αFP (ng/ml)	14.85	4.50, 119.47	1510 (63.4)
Bilobar disease			
Yes	244	10.3	227 (9.5)
Extra-hepatic disease			
Yes	122	5.1	179 (7.5)
BCLC stage			
0	259	10.9	250 (10.5)
A	949	39.9	
B	492	20.7	
C	427	17.9	
Nodules number, *n*	1.00	1.00, 2.00	96 (4.0)
Size (cm)	4.00	2.50, 6.00	85 (1.0)

HBV hepatitis B virus, *HCV* hepatitis C virus, *INR* international normalised ratio, *αFP* alfa-feto-protein, *BCLC* Barcelona Clinic Liver Cancer

[a] Child Pugh Score is calculated only for cirrhotic patients

First operation data, postoperative course and histological specimen

All the patients underwent liver surgery. Minor (≤ 3 segments) resections were performed in 1900 (79.8%) cases, and the anatomic removal of the liver segment had been made in 1506 (63.3%) cases. Laparoscopy was employed in 752 (31.6%) cases, but conversion was needed in 116 (15.4%) of these cases. In Fig. 1, open and laparoscopic approaches are compared across the time of enrolment and the employment of the latter technique has slightly increased in recent years. Median length of surgery was 250 min (IQR 180–320), and median blood loss was 300 ml (IQR 150–500).

Complications occurred in 858 cases (36.0%), but they were severe (Clavien–Dindo 3–4) in 119 (5.0%). Postoperative ascites complicated the course in 249 (10.5%) cases, but it responded to diuretic therapy in 237 (95.2%) cases. PHLF was observed in 117 (4.9%) patients. Ninety-day mortality occurred in 59 patients (2.5%). Data are reported in Table 2.

With regard to the histological specimen, microvascular invasion (MVI) was found in 665 (27.9%) cases, while satellite nodules were evident in 305 (12.8%) cases. Histological grading was G1 in 262 cases (11.0%), G2 in 1386 cases (58.2%), G3 in 551 cases (23.1%) and G4 in 33 cases (1.4%). A radical resection (R0) was achieved in 1812 (76.1%) cases, while a positive surgical margin (R1) was evident in 206 (8.6% cases).

Survival and recurrence

Median follow-up was 43 months (95% CI 40.45–45.54), and by the end of the study, 559 (25.2%) patients had died. Median OS was 141 months (95% CI 111.05–170.94), and 1-, 3- and 5-year OS were 92.8%, 77.0% and 66.1%, respectively. Recurrence was experienced by 1093 (45.9%) patients during follow-up. Median DFS was 38 months (95% CI 33.47–42.52), and 1-, 3- and 5-year DFS were 77.3%, 51.7% and 40.9%, respectively. The median number of recurrent nodules was 2 (IQR 1.0–3.0), while the median size of nodules was 2.0 cm (IQR 1.5–3.0). Additionally, the relapse was single in 417 (37.3%) cases. Intrahepatic recurrence was the most frequent event, accounting for 815 (74.6%) cases, but synchronous extrahepatic spread was observed in 97 (8.9%) cases, while only extrahepatic relapse was evident in 59 patients (5.4%). Local recurrence, defined as recurrence on the surgical edge, was documented in 185 (16.9%) cases. Patterns of recurrence are summarized in Table 3. Data were available on the treatment of recurrences for 871 (79.6%) patients. Redo surgery was performed for 142 (16.3%) of these patients, while thermoablation (TA) was executed in 145 (16.6%) patients. Chemoembolization (TACE) was performed in

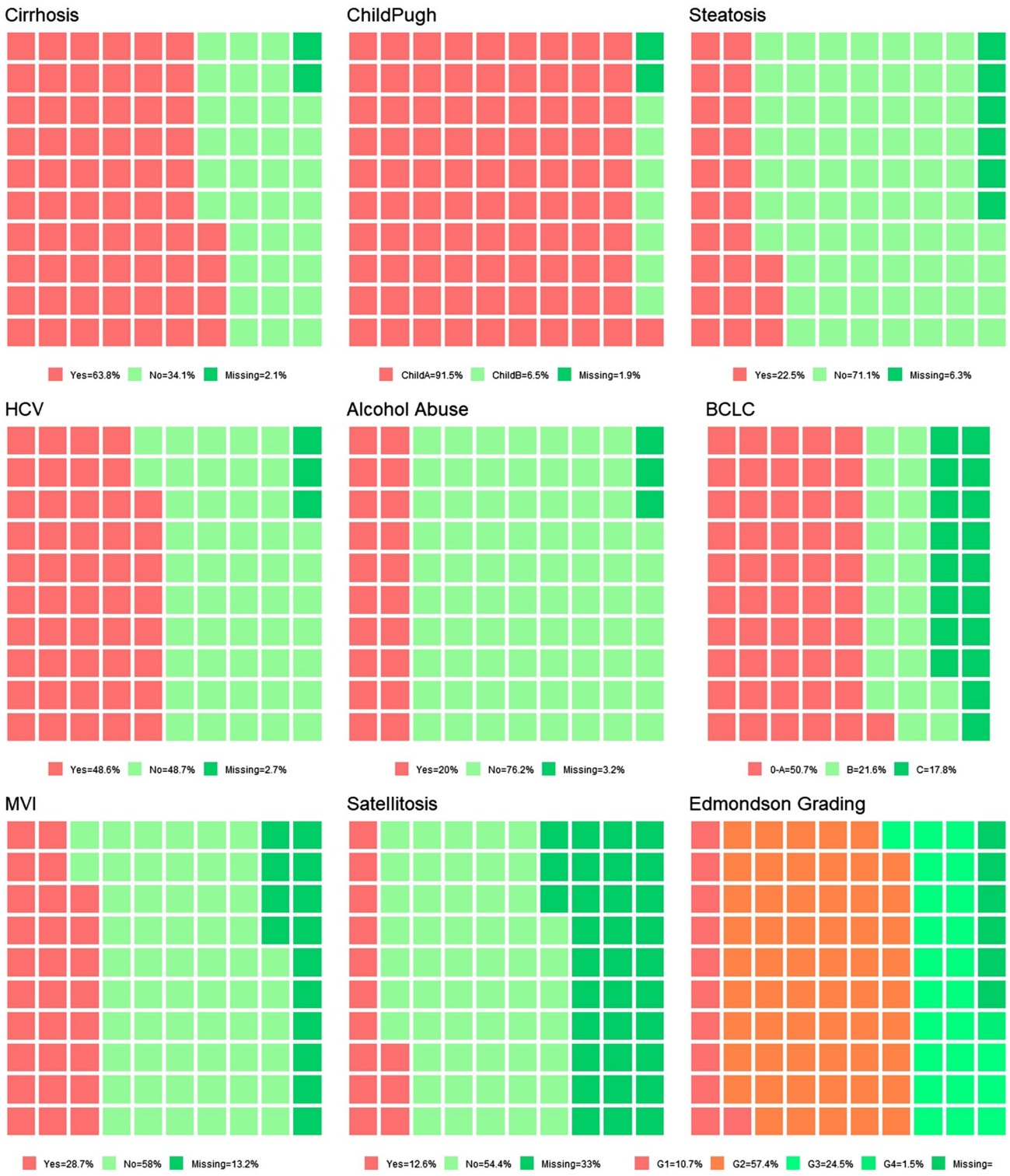

Fig. 2 Underlying liver function, tumor stage and histological characteristics of the sample

225 (25.8%) patients, while systemic therapy (ST) was administered in 221 (25.3%) patients. A total of 110 (12.6%) patients underwent watchful-waiting, transarterial embolization (TAE), radiotherapy or other treatments (others group). The differences between all these groups are reported in Table 4. The median SAR was not reached for redo surgery and the TA sub-population, while it was 38 months (95% CI 26.0–48.1) for the TACE group and

Table 2 Description of the surgical, perioperative and histological variables in the whole dataset

	n/median (*n* = 2381)	%/IQR	Missing (%)
Extension of surgery			131 (5.5)
Major resection	481	20.2	
Type of surgery			23 (1.0)
Anatomical resection	1506	63.3	
Parenchymal sparing resection	852	35.8	
Surgical procedure			46 (1.9)
Wedge resection	787	33.1	
Segmentectomy	741	31.1	
Right hepatectomy (S5–6–7–8)	220	9.2	
Left hepatectomy (S2–3–4)	177	7.4	
Right anterior sectionectomy (S5–8)	45	1.9	
Right posterior sectionectomy (S6–7)	83	3.5	
Left lateral sectionectomy (S2–3)	120	5.0	
Right trisectionectomy (S1–S4–5–6–7–8)	21	0.9	
Left trisectionectomy (S1–S2–S3–S4–S5–S8)	6	0.3	
Other	135	5.7	
Laparoscopy			348 (4.6)
Yes	753	31.6	
Converted			13 (1.7)
Yes	116	15.4	
Pringle manoeuvre			37 (1.6)
Yes	1639	68.8	
Total Pringle time (min)	43.00	30.00, 60.00	21 (1.2)
Length of surgery (min)	250.00	180.00, 320.00	111 (4.6)
Blood loss (ml)	300.00	150.00, 500.00	157 (6.5)
Length of stay (days)	9.00	7.00, 12.00	700 (29.3)
Complication			55 (2.3)
Yes	858	36.0	
Clavien–Dindo classification			28 (3.3)
CD1–2	633	26.6	
CD3–4	119	5.0	
Post-operative ascites			23 (1.0)
Diuretic responder	237	10.0	
Non responder	12	0.5	
PHLF			21 (0.9)
Yes	117	4.9	
90 day mortality			16 (0.7)
Dead	59	2.5	
Microvascular invasion			333 (14.0)
Positive	665	27.9	
Satellitosis			835 (35.1)
Positive	305	12.8	
Edmondson grading			149 (6.3)
G1	262	11	
G2	1386	58.2	
G3	551	23.1	
G4	33	1.4	

PHLF post hepatectomy liver failure

Table 3 Survival and pattern of recurrence

	n/Median	%	Missing (%)
Death			52 (2.2)
Yes	559	25.2	
Recurrence			47 (2.0)
Yes	1093	45.9	
No. of recurrent nodules, *N*	2	1.00, 3.00	411 (37.6)
Recurrence size (cm)	2.0	1.50, 3.00	201 (18.3)
Single vs multiple recurrence[a]			167 (15.3)
Single	417	38.2	
Multiple	509	46.6	
Recurrence localisation[a]			122 (11.1)
Intra-hepatic	815	74.6	
Extra-hepatic	59	5.4	
Both	97	8.9	
Local recurrence[a]			323 (29.5)
Yes	185	16.9	

[a]Percentages are calculated on the total recurrent number of patients

14 months (95% CI 12.0–21.0) for the ST group. The SAR is depicted in Fig. 3.

Discussion

This work aims to introduce the HERCOLES Registry, which represents the first Italian national database on the surgical treatment of HCC. The increasing number of participating centres between January 2018 (when the project was born) and now demonstrates the enthusiasm for the proposal to create a network of national data to investigate the surgical indications, treatment and follow-up of HCC.

The population of our study was 76.1% men and had a median age of 70 years; these data are similar to those already present in the literature on the epidemiology of HCC, confirming the prevalent incidence of the disease among the male population in Italy [7, 8]. The relative older age of the cohort when compared with the median age of presentation of HCC was explained by its exclusion from the dataset of the transplanted patients, which are commonly younger. In fact, elderly patients are currently not candidates for organ transplantation, since the lack of internationally accepted survival benefit [9]; consequently, they are prevalently treated with liver surgery if the underlying comorbidities and tumour burden allow this approach.

Cirrhosis is the prevalent liver environment in which HCC can be developed [10], and in our series, 62.6% of patients are cirrhotic. The relatively high rate of patients without cirrhosis is in line with the recent reports on the changing epidemiology of this tumour. Thanks to the new available therapies for viral infection and greater attention on new metabolic liver disorders [11–13], such as NASH and NAFLD [14], that are spreading according to population lifestyle changes. The diagnosis of metabolic syndrome rather than NAFLD was considered in the dataset, but more than half of the data were missing. The recognition of the incidence of these syndromes in patients with HCC, which may benefit from surgery, is one of the challenges of the prospective phase of this study. The proportion of patients that were HBV- and HCV-positive in our cohort were 19.0% and 48.3%, respectively. The latter remains the main predisposing factor for cirrhosis (and therefore for HCC) in our country [15, 16], as it agrees with the incidence in the Western world where 20% of HCC can be attributed to HBV infection, while HCV infection appears to be a major risk factor [17]. Even if the severity of liver damage has been a deterrent to surgery for several years, our report recognized a small but evident effort in pushing the surgical boundaries beyond the classical limits. In fact, in selected patients (accounting for 6.8% of cases), Child class B was not a contraindication for surgery. Portal hypertension was also not considered an exclusion criteria. In fact, splenomegaly was present in 17.0% of cases, while the presence of varices accounted for 16.4% of the whole cohort. The surgical indications for these patients is a very old and controversial debate, with different opinions also in international guidelines, and the surgical indications remain variable without real global agreement [18–20].

The register included also several patients with intermediate (BCLC B) and advanced tumours (BCLC C), accounting for nearly 20% of cases in each. Surgery is the main therapeutic approach for HCC, while other therapies, such as chemoembolization or ST, have only palliative roles. This simple evidence led several centres to also consider surgery in more advanced cases, with excellent survival reported in the literature when compared with the theoretically appropriate treatments [21–24]. These differences are at the centre of an international debate, with strong different approaches between the West and East, as reflected in the relative national guidelines. A few years ago, Torzilli et al. [25] reported the rate of agreement with treatment guidelines in intermediate and advanced stages, stating very low adhesion worldwide, with surgery being the preferred first option in the absence of severe liver damage. As a consequence, recent EASL guidelines [2] clarified that, if technically feasible, patients classified as having intermediate HCC (BCLC B) with borderline liver conditions (i.e., Child B7, moderate pH or bilirubin around 2 mg/dl) may benefit from surgical resection, and they should be re-classified as BCLC A [2, 26, 27]. Considering patients with BCLC C in our series, this group is composed prevalently of tumours presenting with portal or hepatic vein thrombi, with good ECOG status and almost compensated liver function. Even though EASL guidelines

Table 4 Baseline characteristics compared between the different recurrent treatments

	Surgery [142]	TA [145]	TACE [225]	ST [221]	Others [110]	*p*
Age (median [IQR])	70.00 [63.50, 73.00]	71.00 [64.00, 75.00]	70.50 [64.75, 76.00]	70.00 [62.00, 75.00]	70.50 [62.00, 76.00]	0.429
Sex (%)						
Male	109 (76.8)	116 (80.0)	179 (79.6)	167 (75.6)	85 (77.3)	
Female	33 (23.2)	29 (20.0)	46 (20.4)	54 (24.4)	25 (22.7)	
n/a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Charlson Comorbidity Index (median [IQR])	6.00 [4.25, 7.00]	7.00 [5.00, 8.00]	6.00 [5.00, 8.00]	5.00 [4.00, 7.00]	6.00 [5.00, 7.00]	0.002
Cirrhosis (%)						0.004
Yes	103 (72.5)	108 (74.5)	144 (64.0)	143 (64.7)	71 (64.5)	
n/a	2 (1.4)	7 (4.8)	2 (0.9)	1 (0.5)	3 (2.7)	
Child–Pugh grade (%)						
A	97 (68.3)	108 (74.5)	165 (73.3)	142 (64.3)	72 (65.5)	
B	8 (5.6)	4 (2.8)	12 (5.3)	10 (4.5)	6 (5.5)	
n/a	37 (26.1)	33 (22.8)	48 (21.3)	69 (31.2)	32 (29.1)	
HBV (%)						0.161
Yes	28 (19.7)	25 (17.2)	40 (17.8)	53 (24.0)	25 (22.7)	
n/a	3 (2.1)	7 (4.8)	1 (0.4)	6 (2.7)	3 (2.7)	
HCV (%)						0.195
Yes	77 (54.2)	63 (43.4)	111 (49.3)	106 (48.0)	45 (40.9)	
n/a	3 (2.1)	6 (4.1)	1 (0.4)	6 (2.7)	3 (2.7)	
Single vs multiple recurrence (%)						< 0.001
Single	108 (76.1)	100 (69.0)	76 (33.8)	49 (22.2)	47 (42.7)	
Multiple	34 (23.9)	41 (28.3)	128 (56.9)	159 (71.9)	53 (48.2)	
n/a	0 (0.0)	4 (2.8)	21 (9.3)	13 (5.9)	10 (9.1)	
Recurrence localization (%)						< 0.001
Intra-hepatic	127 (89.4)	133 (91.7)	205 (91.1)	149 (67.4)	78 (70.9)	
Extra-hepatic	6 (4.2)	4 (2.8)	1 (0.4)	18 (8.1)	18 (16.4)	
Both	7 (4.9)	6 (4.1)	11 (4.9)	45 (20.4)	10 (9.1)	
n/a	2 (1.4)	2 (1.4)	8 (3.6)	9 (4.1)	4 (3.6)	
Local recurrence (%)						< 0.001
No	97 (68.3)	100 (69.0)	106 (47.1)	150 (67.9)	60 (54.5)	
Yes	30 (21.1)	23 (15.9)	42 (18.7)	33 (14.9)	28 (25.5)	
n/a	15 (10.6)	22 (15.2)	77 (34.2)	38 (17.2)	22 (20.0)	
No. recurrent nodules (median [IQR])	1.00 [1.00, 2.00]	1.00 [1.00, 2.00]	2.00 [1.00, 5.00]	3.00 [2.00, 5.00]	2.00 [1.00, 3.00]	< 0.001
Size recurrent nodules (median [IQR])	2.00 [1.50, 2.68]	1.70 [1.40, 2.00]	2.00 [1.50, 3.42]	2.10 [1.50, 3.52]	2.00 [1.40, 3.68]	< 0.001

TA thermoablation, *TACE* trans-arterial chemo-embolization, *ST* systemic therapies, *HCV* hepatitis C virus, *HBV* hepatitis B virus

suggest submitting these patients to ST, several studies (prevalently from the East) [28–33] have reported excellent survival after surgery when compared with drugs. Those studies are prevalently retrospective, with several potential biases; however, the ITA.LI.CA. study [22] also demonstrated this advantage in selected patients in a national cohort. Consequently, the approach to tumour thrombus remains controversial, but not completely unaccepted by the majority of Italian liver surgeons. Another consideration is that our data shows how adherence to the European guidelines is not strong. In fact, one of the future focuses for our group will be to transform these recognitions in several experimental studies to evaluate the impact of these variables on short- and long-term outcomes, appreciating the goodness of fit of the European statement on surgical indication in the setting of a large national dataset.

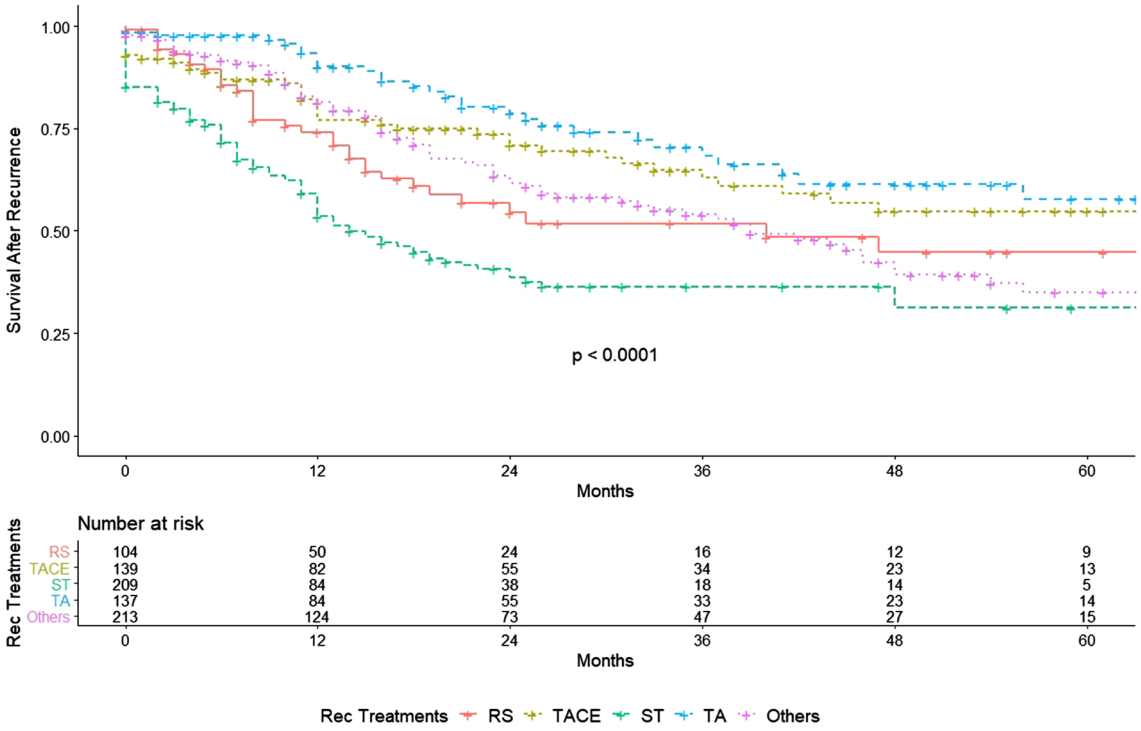

Fig. 3 Overall survival (OS) of the recurrent population for each single treatment recorded in the register. Comparisons were made by Log Rank test. *RS* redo surgery, *TACE* trans arterial chemoembolization, *ST* systemic therapies, *TA* thermoablation

HERCOLES data show that the laparoscopic approach is employed in 31.6% of surgeries for HCC and has been increasing in recent years, as demonstrated by Aldrighetti et al. in their I Go MILS Register on the mini-invasive approach spreading in liver surgery [34]; our conversion rate was 15.4% and is higher than the data presented in the I Go MILS Register, which stands at around 9.4% and is likewise in most representative series existing in the literature [35, 36]. These differences could explain the variety of centres in the HERCOLES Registry (teaching hospitals, district hospitals and specialised centres for liver surgery), which have different levels of expertise in laparoscopic liver surgery. However, the historical trend clearly shows how the laparoscopic approach is becoming more widespread and, in some cases, the technique of choice. Nevertheless, the indication for laparoscopic liver surgery should be carefully evaluated, and, today, should be reserved for selected patients. Even if anatomic resection should be preferred according to guidelines [2], several reports declared comparable outcomes when a parenchyma-sparing approach was employed [37, 38]. In our series, AR remains the principal procedure to treat HCC, but PSR is well represented. These data should be carefully evaluated, because the increase in the laparoscopic approach may have driven an increased use of the PSR [39], enforcing the evidence of superimposable results [35, 40] between AR and PSR. This evidence would be worthy of further future studies.

Looking at the surgical outcomes, the complication rate was still significant, although the general optimisation of the surgical technique and of perioperative management have improved the possibility to manage the consequences of liver surgery. This rate accounted for almost one-third of our patients. However, the rate of severe complication, graduated according to the Clavien–Dindo system, was low (near 5.0% of all the patients). PHLF remains the leading cause of death after liver resection [41], and in our series, it accounted for 4.9% of deaths, while postoperative liver ascites were observed in almost 11% of the cases, with a rate of responsiveness to diuretic therapy of nearly 99% of all the episodes. These data confirm that liver surgery for HCC is a risky surgery, but the improvements in technology and perioperative care guarantee a safe zone in which this risk may be tempered as much as possible, as demonstrated by the low rate of 90-day mortality (only 2.5%). This rate is in line with reports from other countries [42].

Histopathology is a key feature in determining the risk of relapse, as demonstrated by several studies. The presence of MVI and satellitosis has been reported in up to 40% of cases in some series [43–46], and this evidence drives the debate on the surgical extension. However, in our register, MVI and satellitosis were detected only in 27.9% and 12.8% of cases, respectively. Thus, satellitosis has a very high rate of missing data (almost 35%). This information should be considered as a worrisome feature with regard to the quality

of the evaluations by pathologists and it should drive all the participating centres to improve their relationship with the histologists to create a dedicated team that is able to completely evaluate the oncological hallmarks that are associated with the staging and prognosis.

At 5 years, 66.1% of the patients were alive, and this data is slightly better than other rates reported in literature [27, 47–50]. This should be considered a success driven by the spread of the HPB unit across the country with the consequent improvements in surgical safety and oncological accuracy. At the same time point, 59.9% of patients had a recurrence. This result is of interest and may benefit from deeper analysis, because the reported recurrence rate at 5 years is higher in the comparable literature. In the EASL guidelines [2], this percentage reaches 70%. Most of the studies reporting this data are single-centre [51–54], while our study has the advantage of being a median between dozens of centres. When the recurrence occurred, multiple intrahepatic presentation was the most frequent observation, while extrahepatic spread was observed in nearly 14% of cases, with 59 (5.4%) cases showing only extrahepatic recurrence. This trend suggests a favourable pattern of recurrence for those patients that are candidates for surgery after the first diagnosis and consequently have a favourable disease susceptible to being cured. In fact, the median number of recurrent nodules and the median size of them are within the Milan criteria, reflecting a likely very favourable prognosis even after relapse. Notwithstanding, recurrences were not managed homogeneously across the register and this may reflect the lack of a large consensus on how to treat the relapse after curative intent. In fact, a curative approach (surgery rather than TA) was guaranteed in almost 37% of the patients, while palliative therapies (TACE or ST) were offered to up to 50% of the patients. The register data does not allow for us to know the specific reasons for therapeutic indications; however, our data suggest that the use of palliative treatments does not always seem justified by the tumour burden of the recurrence. It is likely that, for these patients, the curative intent that we have promised at the start of the therapeutic process could still be ensured, even after relapse. However, from the retrospective data, it may be stated that the same oncological indications (tumour burden and bilobarity) drive the choice of a curative rather than palliative approach, and the survival analysis was obviously affected by these different oncological stages. These types of considerations and the consequent analysis that a register, such as HERCOLES, allows are the natural vocation of the group that have created the dataset; in fact, several studies proposed by participating centres in this research line are ongoing.

Several limits of this study should be mentioned. Firstly, multicentric registers should always find a balance between collecting too much data or too little data. In the first case, missing information is frequent, and it may affect the reliability of the dataset, reducing the number of potential studies and, more importantly, the power of the tests. In the second case, the percentage of missing data may be low and adherence to the data entry schedule may be high; however, the potential to investigate several aspects is enormously reduced. We opted for a very large dataset, and by consequence, there are many missing data; however, the local investigator adherence to the data entry was very appreciable and strong, leading to a very low percentage of missing data, in most of the variables less than 10%. For these cases, recent statistical methods, such as multiple imputation, may permit researchers to overcome the risk. Notwithstanding, there are few variables with a very high rate of missing data, which could lead to making these variables unusable.

Although this register is nation-based, not each Italian centre performing liver surgery is now participating. Centres in southern Italy are less represented, missing a very important experience. Due to the nature of the register, which would record the effect of liver resection in HCC care, liver transplantation was excluded, forcing some Italian centres to not participate. Finally, even if the HERCOLES group has two parts of the project, one (HERCOLES1) retrospective and another (HERCOLES2) prospective, each study will be retrospective, with all the consequent well-known bias risk.

Conclusions

The HERCOLES Group created the largest Italian surgical dataset on the impact of liver resection in HCC care. This type of effort will allow researchers to better connect different experiences across the country, enforcing the relationship and allowing the comparison of general outcomes to improve local outcomes. The present snapshot depicts the national trends in the surgical approach for HCC, offering to everybody the possibility to compare their local results with the national trends, and permitting international comparison of the state-of-the-art. Moreover, a large sample size permits the creation of a strong study, which may be the necessary preliminary data to not only generate a RCT but also to enforce the statistical power of each of the centres. In a world where big data are spreading, being connected and sharing our data is mandatory to boost the medical boundaries to a novel horizontal dimension without borders, where each node of the network can produce valuable research.

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Data availability Data are available after study group's approval.Code availability Analysis were performed by R software (v 3.6.2), the script is available upon request.

Compliance with ethical standards

Conflicts of interest None.

Research involving human participants and/or animals The central Ethical Committee review of the protocol deemed that formal approval was not required owing to the retrospective, observational and anonymous nature of this study.

Informed consent Informed consent was obtained by each patient enrolled.

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