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ORIGINAL ARTICLE

Survival benefit of second line therapies for recurrent hepatocellular carcinoma: repeated hepatectomy, thermoablation and second-line transplant referral in a real life national scenario

Simone Famularo[1,2,3*], Umberto Cillo[4,*], Andrea Lauterio[5,*], Matteo Donadon[1,2], Alessandro Vitale[4], Matteo Serenari[6], Federica Cipriani[7], Federico Fazio[8], Mario Giuffrida[9], Francesco Ardito[10], Tommaso Dominioni[11], Mattia Garancini[12], Quirino Lai[13], Daniele Nicolini[14], Sarah Molfino[15], Pasquale Perri[16], Enrico Pinotti[17], Simone Conci[18], Cecilia Ferrari[19], Matteo Zanello[20], Stefan Patauner[21], Giuseppe Zimmitti[22], Paola Germani[23], Marco Chiarelli[24], Maurizio Romano[25], Michela De Angelis[26], Giuliano La Barba[27], Albert Troci[28], Valentina Ferraro[29], Francesco Izzo[30], Adelmo Antonucci[31], Andrea Belli[30], Riccardo Memeo[29], Michele Crespi[28], Giorgio Ercolani[27], Luigi Boccia[26], Giacomo Zanus[25], Paola Tarchi[23], Moh'd Abu Hilal[22], Antonio Frena[21], Elio Jovine[20], Guido Griseri[19], Andrea Ruzzenente[18], Mauro Zago[17,24], Gianluca Grazi[16], Gian L. Baiocchi[15], Marco Vivarelli[14], Massimo Rossi[13], Fabrizio Romano[12], Marcello Maestri[11], Felice Giuliante[10], Raffaele D. Valle[9], Alessandro Ferrero[8], Luca Aldrighetti[7], Luciano De Carlis[5], Matteo Cescon[6], Guido Torzilli[1,2] HE.RC.O.LE.S. Group Contributors

[1]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy, [2]Department of Hepatobiliary and General Surgery, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, [3]Surgical Data Science Team, Research Institute Against Digestive Cancer (IRCAD), Strasbourg, France, [4]Department of Surgical, Oncological and Gastroenterological Sciences (DiSCOG), University of Padova, Second General Surgical Unit, Padova Teaching Hospital, Padua, Italy, [5]Department of General and Transplant Surgery, Grande Ospedale Metropolitano Niguarda, School of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy, [6]Hepato-biliary Surgery and Transplant Unit, Policlinico Sant'Orsola IRCCS, Department of Medical and Surgical Sciences, University of Bologna, Italy, [7]Hepatobiliary Surgery Division, "Vita e Salute" University, Ospedale San Raffaele IRCCS, Milano, Italy, [8]Department of General and Oncological Surgery, Mauriziano Hospital "Umberto I", Turin, Italy, [9]Department of Medicine and Surgery, University of Parma, Parma, Italy, [10]Hepatobiliary Surgery Unit, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of the Sacred Heart, Rome, Italy, [11]Unit of General Surgery 1, University of Pavia and Foundation IRCCS Policlinico San Matteo, Pavia, Italy, [12]School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy, [13]General Surgery and Organ Transplantation Unit, Sapienza University of Rome, Umberto I Polyclinic of Rome, Rome, Italy, [14]HPB Surgery and Transplantation Unit, Department of Clinical and Experimental Medicine, Polytechnic University of Marche, Ancona, Italy, [15]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [16]Division of Hepatobiliarypancreatic Unit, IRCCS - Regina Elena National Cancer Institute, Rome, Italy, [17]Department of Surgery, Ponte San Pietro Hospital, Bergamo, Italy, [18]Division of General and Hepatobiliary Surgery, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy, [19]HPB Surgical Unit, San Paolo Hospital, Savona, Italy, [20]Alma Mater Studiorum, University of Bologna, AOU Sant'Orsola Malpighi, IRCCS at Maggiore Hospital, Bologna, Italy, [21]Department of General and Pediatric Surgery, Bolzano Central Hospital, Bolzano, Italy, [22]Department of General Surgery, Poliambulanza Foundation Hospital, Brescia, Italy, [23]Division of General Surgery, Department of Medical and Surgical Sciences, ASUGI, Trieste, Italy, [24]Department of Emergency and Robotic Surgery, ASST Lecco, Lecco, Italy, [25]Department of Surgical, Oncological and Gastroenterological Science (DISCOG), University of Padua, Hepatobiliary and Pancreatic Surgery Unit - Treviso Hospital, Italy, [26]Department of General Surgery, Ospedale Carlo Poma, Mantua, Italy, [27]General and Oncologic Surgery, Morgagni-Pierantoni Hospital, Department of Medical and Surgical Sciences - University of Bologna Forlì, Italy, [28]Department of Surgery, L. Sacco Hospital, Milan, Italy, [29]Department of Hepato-Pancreatic-Biliary Surgery, Miulli Hospital, Bari, Italy, [30]Division of Epatobiliary Surgical Oncology, Istituto Nazionale Tumori IRCCS Fondazione Pascale-IRCCS di Napoli, Naples, Italy, and [31]Department of Surgery, Monza Policlinic, Monza, Italy

Abstract

Background: Despite second-line transplant(SLT) for recurrent hepatocellular carcinoma(rHCC) leads to the longest survival after recurrence(SAR), its real applicability has never been reported. The aim was to compare the SAR of SLT versus repeated hepatectomy and thermoablation(CUR group).

Methods: Patients were enrolled from the Italian register HE.RC.O.LE.S. between 2008 and 2021. Two groups were created: CUR versus SLT. A propensity score matching (PSM) was run to balance the groups.

Results: 743 patients were enrolled, CUR = 611 and SLT = 132. Median age at recurrence was 71(IQR 6575) years old and 60(IQR 53-64, $p < 0.001$) for CUR and SLT respectively. After PSM, median SAR for CUR was 43 months(95%CI = 37 – 93) and not reached for SLT($p < 0.001$). SLT patients gained a

* These authors contributed equally to this work.

survival benefit of 9.4 months if compared with CUR. MilanCriteria(MC)-In patients were 82.7% of the CUR group. SLT(HR 0.386, 95%CI = 0.23 – 0.63, p < 0.001) and the MELD score(HR 1.169, 95%CI = 1.07 – 1.27, p < 0.001) were the only predictors of mortality. In case of MC-Out, the only predictor of mortality was the number of nodules at recurrence(HR 1.45, 95%CI= 1.09 – 1.93, p = 0.011).
Conclusion: It emerged an important transplant under referral in favour of repeated hepatectomy or thermoablation. In patients with MC-Out relapse, the benefit of SLT over CUR was not observed.

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Correspondence
Simone Famularo, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. E-mail: simone.famularo@gmail.com (S. Famularo)

Correspondence
Guido Torzilli, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy. E-mail: guido.torzilli@hunimed.eu (G. Torzilli)

Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common malignancy and the second most frequent tumour-related cause of death worldwide.[1] Liver resection (LR) and primary liver transplantation (PLT) have been considered potentially curative options, with PLT remaining the most effective treatment thanks to the possibility of simultaneously eliminating both the HCC and the underlying liver disease.[2–4] Anyway, considering the organ shortage and the consequent waiting list drop-out rate,[5] LR has been promoted as a first-line curative option for resectable tumors with no underlying liver decompensation.[6] Despite that, long-term prognosis remains unsatisfactory with more than half of patients experiencing recurrence at 5-year from curative LR.[7,8] In case of HCC recurrence, second-line liver transplant (SLT) has been proposed as curative treatment of a first recurrence, showing results comparable to PLT in terms of disease-free survival (DFS) and overall survival (OS).[9–11] The SLT strategy was also proposed to overcome the organ shortage issue, limiting the transplant procedure only in case of recurrence after a first curative treatment.

Nevertheless, a number of causes lead to reduced access to transplantation as clinical contraindications or lack of referral. Therefore, repeated hepatectomy for HCC recurrence has been adopted with acceptable results even though inferior to those achieved with SLT.[12,13]

The indication for transplant has been modified several times, reflecting the progression of the clinical studies in this field, however the Milan Criteria (MC) remained, particularly in the literature, a good and simple (although too simplistic also) score to define the tumor burden, and to define those who could be surely optimal candidates for transplant. Thus, it was adopted in this study to estimate the rate of those patients who were surely eligible for SLT, in order to account the real life rate of SLT indications versus repeated hepatectomy or thermoablation in a national cohort over time. Although the various scientific evidences available in literature on how to treat the recurrence, "how the things go" in the reality has never been reported.

The aims of this study were to show the rate of repeated curative treatment or second line LT for recurrent HCC, and to detail their corresponding rates of survival after recurrence (SAR) based on a multicentric real-life experience.

Methods

Registers information

This retrospective study evaluated data prospectively collected by the Italian registers on HCC, the HE. RC.O.LE.S. (Hepatocarcinoma Recurrence on the Liver Study). Patients were enrolled between 2008 and 2021 by 30 centers.[14] The register is based on spontaneous collaborations across Italian centers that desired to participate after acceptance of the study protocol, without restriction on the number of patients treated per year. The study protocols followed the ethical guidelines of the 1975 Declaration of Helsinki (as revised in Brazil 2013). The HE. RC.O.LE.S. protocol was approved by the Ethical Committee of San Gerardo Hospital (Monza, Italy, "Monza e Brianza Ethical Committee") on 21/12/2018, and afterwards by all centers (clinicaltrial.gov registration number: NCT04053231). Nearly 170 variables are collected, related to patient comorbidities, underlying liver function, radiological and intraoperative findings, postoperative course, histological evaluation, and follow-up information. All

data were collected by local researchers and anonymized before their submission to the coordinating center.

Study overview, patient selection, and study design

Results are reported according to principles of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[15] All consecutive adult (age ≥18 years) patients with a radiological and/or histological proven recurrent HCC after a first curative approach by liver resection from January 2008 to December 2021 were evaluated. Inclusion criteria were: 1) patients treated for HCC recurrence by repeated hepatectomy (RH) and/or thermoablation (TA) versus SLT; 2) HCC recurrence limited to the liver. Exclusion criteria were the following: 1) extra-hepatic tumor spread; 2) macrovascular intrahepatic involvement of the recurrent disease; 3) missing data on the follow-up. Selected patients were then divided into those who were treated by RH or TA (CUR) and those who underwent SLT. The recurrent episode was sub-stratified according to the Milan Criteria[2] (MC, 1 nodule >5 cm or up to 3 nodules<3 cm).

Study endpoint

The primary endpoint was the survival after recurrence (SAR) across the groups. The secondary endpoint was the rate of recurrent patients who were within and without the MC criteria and the relative survival benefit when treated with one of the two treatments considered. The tertiary end-point was to identify the factors that were independent predictors of mortality after recurrence.

Patients follow-up

All patients were followed up by using local protocols, which included periodical outpatient visits, measurement of serum alpha-fetoprotein (AFP) and abdominal ultrasound, computed-tomography (CT) or magnetic resonance imaging (MRI). SAR was defined as the time interval in months between the date of recurrence to any cause of death. In case patients were alive, data were censored at the date of the last available follow-up visit. Patient surveillance was closed at the end of August 2021.

Treatments

The indication for recurrent treatments was provided by the multidisciplinary board of each center that included surgeons, hepatologists, oncologists, radiologists, interventional radiologists, infectivologists and pathologists. The board decision took into account several factors, such as liver function, tumor burden (size and number of lesions, uni/bilobar disease, residual liver volume after resection), comorbidities, previous surgical history, patient's opinion and level of available scientific evidence to provide a patient-tailored treatment in line with the precision medicine approach. In case of potential indication to SLT, if the local center could not provide a transplant programme, the patient was referred according to the regional agreements. Not all centers had a transplant surgeon or transplant hepatologist included in their multidisciplinary board.

Definitions

Comorbidities were summarized by the Charlson Comorbidity Index.[16] Eastern ECOG-PS was measured at the first outpatient visit.[17,18] The presence of cirrhosis was established prior to the treatment choice by hepatologists according to clinical, biochemical, endoscopic and, if available, pathological information. The presence of oesophageal varices was assessed by upper gastrointestinal endoscopy. Liver function was estimated using both the model for end-stage liver disease (MELD) score[19] and Child-Pugh score.[20] Biochemical variables were obtained within two weeks from the assigned treatment. The number and size of recurrent nodules was assessed by multiphase contrast computed tomography (CT) or magnetic resonance imaging (MRI) and each center declared that images were scrutinized by expert and dedicated radiologists. Histological grading of the primary HCC was assessed in the resected specimen, together with the presence of microvascular invasion and satellitosis. The extension of liver resection was defined as minor or major, based on the Brisbane nomenclature.[21]

Statistical analysis

The sample description was done using median and interquartile range (IQR) for numeric variables and number and proportion for categorical variables. Mann–Whitney and Fisher tests were used to compare baseline patient characteristics between the two treatment groups, respectively. The issue of unmeasured values in some covariates (due reasonably to a "missing at random" (MAR) mechanism[22]) was handled by using the multiple imputation method, and final estimates of the coefficients and standard errors were obtained by pooling model results on ten imputed datasets.[23] After the univariate comparison of baseline characteristics, further analyses were made to make CUR and SLT groups comparable: all variables showing a p value < 0.10 and with a known prognostic role were considered as confounders and included in a 1:1 nearest neighbour propensity score matching (PSM) with a caliper of 0.1 SD. After PSM, two new and balanced groups were further compared. Standardized mean differences of confounders were calculated in both the original and matched populations to check the balance between treatment groups, and a "Love" plot was generated. Survival was estimated by the Kaplan–Meier method, and comparisons were performed by the Log Rank test and Robust test before and after PSM respectively. The survival benefit has been defined as the area under the survival curve, calculated by the restricted mean method, with an upper limit setted at 60 months: the difference between the benefit of each treatment was defined as the absolute survival benefit across groups. An univariate Cox regression analysis was done to evaluate the prognostic role of baseline variables. Variables that were associated with SAR by a p value < 0.05 were included in the multivariate model, together with other well-known factors related to mortality. These data were reported as hazard ratio (HR) and 95% confidence interval (CI). As subgroup analyses, the association between treatment

and SAR was tested among CUR and SLT in specific subgroups as follows: 1) patients with a recurrence within the MC criteria; 2) patients with a recurrence outside the MC, 3) patients treated after 2016, 4) patients managed in a transplant center (excluding the HPB-purely centres). All statistical tests were two-tailed and a 5% significance level was adopted. All the analyses were computed by using the open-source R software (v4.0.2).

Results

Between 2008 and 2021, 4757 patients with a first diagnosis of HCC were correctly recorded in the HE. RC.O.LE.S. database (version 12.22.2021). Two thousand five hundred and seventy-six patients were excluded because they did not experience a recurrence after surgery. Further, 683 patients were excluded because the recurrence treatment was classified as "other" (e.g. watchful waiting, symptoms support etc.). Those who were treated by TACE or systemic therapies were excluded too (PAL group, n = 716). Forty-two patients were excluded because of missing data about the follow-up. Finally, 743 patients were correctly enrolled in the present study and further divided, according to their treatment, between those who underwent RH (n = 247) or TA (n = 364) (CUR group, n = 611) and those who were submitted to SLT (n = 132). A baseline comparison among patients submitted to CUR vs SLT vs PAL was reported in supplementary table 1.

Comparison among CUR versus SLT patients

Comparing CUR vs. SLT, we noted that the first group had a median age at recurrence of 71 years old (IQR 65–75) versus 60 years old (IQR 53–64, $p < 0.001$) in the latter. One hundred nine (17.8%) patients and 13 (9.8%) were female in the CUR and SLT groups respectively ($p = 0.034$). Median Charlson Comorbidity Index was 6 (IQR 5–7) for CUR and 5 (IQR 5–6) for SLT ($p < 0.001$). Patients in the SLT group were more frequently cirrhotics (87.1% vs 71.2%, $p < 0.001$), with the presence of collateral veins (29.1% vs 16.5%, $p = 0.003$), with a higher median number of recurrent nodules (2 IQR 1–2 vs 1 IQR 1–2, $p = 0.003$) and a shorter median time to recurrence from the first hepatectomy (12.50 months IQR 5.0–21.7 versus 16 months for CUR, IQR 7.0–34.0, $p = 0.004$). This comparison was reported in Table 1. Other information about the surgical treatment and the primary tumor before the recurrence were reported in supplementary table 2. Median SAR for CUR group was 46 months (95%CI = 41–56), while it was 120 months (95% CI = 101-NA) for the SLT group ($p < 0.001$). The corresponding survival curve was depicted in Fig. 1a. The survival benefit of CUR was 40.8 months (SE 0.932) while for SLT was 52.3 months (SE 1.419), and the absolute survival benefit was 11.5 months in favour of SLT. Furthermore, the recurrence presentation was classified according to the Milan Criteria. After this subgrouping, CUR patients were Milan–in in 505 (82.7%) of the cases, while SLT patients were 105 (79.5%). When age<70 years old was added to the MC, patients who were MC(age)-in were 198 (32.4%) and 99 (75.0%) for CUR and SLT respectively ($p < 0.001$).

Comparison among CUR and SLT after PSM

The following significant factors were then employed for 1:1 nearest neighbour propensity score matching among the CUR and SLT groups: sex, age at recurrence, cirrhosis, presence of collateral veins, splenomegaly, platelet count, Charlson Index, number of recurrent nodules and presence of multiple recurrence. After the PSM, 240 patients were correctly matched, 120 per group. The baseline comparison after the PSM was reported in Table 1, reflecting a good balancing for all the considered variables, while a love plot to summarize the mean differences before and after the adjustment was reported in Fig. 2. After the matching, median SAR for CUR was 43 months (95% CI = 37–93) while for S-OLT was not reached ($p < 0.001$). One, three and five years SAR were 92.8%, 61.3% and 45.3% for CUR and 95.7%, 85.0% and 74.7% for SLT. Survival curves were depicted in Fig. 1b. CUR showed a survival benefit of 42.4 months (SE 2.03) and SLT of 52.1 (SE 1.53), while the absolute survival benefit was 9.4 months in favour of SLT. A multivariate Cox regression analysis (with Robust test) revealed that being treated by SLT (HR 0.386, 95%CI = 0.23–0.63, $p < 0.001$), and the MELD score (HR 1.169, 95%CI = 1.07–1.27, $p < 0.001$) were the only factors impacting mortality prediction after recurrence in the matched cohort. The univariate and multivariate regressions are reported in Table 2.

Factors predicting mortality after recurrence among patients with recurrence within MC

After PSM, 137 (57.1%) patients had a recurrence within the MC, 78 (65.0%) in the CUR group and 59 (49.1%) in the SLT one ($p = 0.234$). Factors independently associated with the risk of mortality after recurrence were being treated by SLT (HR 0.41, 95%CI = 0.21–0.79; $p = 0.008$), a time to recurrence $\geq$ 24 months from the first treatment (HR 0.25, 95%CI = 0.11–0.61; $p = 0.002$), size of recurrent nodules (HR 1.61, 95% CI = 1.02–2.52; $p = 0.039$) and the presence of satellitosis at the histology of the primary tumor (HR 3.51, 95%CI = 1.60–7.68; $p = 0.002$). The multivariate analysis was reported in Table 3.

Factors predicting mortality after recurrence among patients with recurrence outside MC

After PSM, 103 (42.9%) patients were classified as MC-out, 42 (35.0%) in the CUR group and 61 (50.8%) in the S-OLT one. At the multivariate Cox regression, only the number of recurrent nodules (HR = 1.45, 95%CI = 1.09–1.93, $p = 0.011$) was independently associated with the risk of mortality after recurrence. Results were reported in Table 3.

Patients fully managed in a transplant hospital

Three hundred and eighty patients were fully managed by centres that have a transplant centre: from their first treatment (liver

Table 1 Baseline characteristics of the cohort before and after the propensity score matching

	PRE-PSM			POST-PSM		
	CUR	**SLT**	**p**	**CUR**	**SLT**	**p**
n	**611**	**132**		**120**	**120**	
Age at recurrence, years (median [IQR])	71.00 [65.00, 75.00]	60.00 [53.00, 64.00]	<0.001	58.50 [53.25, 66.00]	60.00 [54.25, 64.00]	0.479
Female (%)	109 (17.8)	13 (9.8)	0.034	10 (8.3)	13 (10.8)	0.661
Charlson Index (median [IQR])	6.00 [5.00, 7.00]	5.00 [5.00, 6.00]	<0.001	5.00 [4.00, 6.00]	5.00 [5.00, 6.00]	0.426
MELD (median [IQR])	8.00 [7.00, 9.00]	8.00 [7.00, 10.00]	0.107	8.00 [7.00, 9.00]	8.00 [7.00, 10.00]	0.762
Platelet count (median [IQR])	165.50 [123.00, 207.25]	122.50 [82.00, 180.50]	<0.001	137.50 [98.00, 180.75]	129.00 [80.25, 183.50]	0.378
ECOG PS (%)			0.268			0.301
0	497 (84.2)	119 (90.8)		105 (88.2)	107 (89.9)	
1	81 (13.7)	11 (8.4)		14 (11.8)	11 (9.2)	
2	12 (2.1)	1 (0.8)		0 (0.0)	1 (0.8)	
Cirrhosis (%)	428 (71.2)	115 (87.1)	<0.001	101 (84.2)	103 (85.8)	0.857
Steatosis (%)	124 (21.1)	24 (18.8)	0.637	22 (18.8)	22 (19.0)	1
Child-B grade (%)	29 (5.7)	9 (7.3)		12 (11.2)	9 (8.1)	NaN
HBV + (%)	119 (19.8)	29 (22.3)	0.729	27 (22.7)	26 (22.0)	NaN
HCV + (%)	284 (47.2)	63 (48.1)	0.925	64 (53.8)	56 (47.1)	0.364
Alcohol consumption (%)	132 (21.9)	31 (23.7)	0.751	21 (17.6)	27 (22.7)	0.419
Collateral veins or varices (%)	91 (16.5)	34 (29.1)	0.003	25 (22.7)	32 (30.2)	0.276
Splenomegaly (%)	115 (19.9)	49 (41.9)	<0.001	39 (33.3)	42 (39.6)	0.403
N recurrent nodules (median [IQR])	1.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.003	1.00 [1.00, 3.00]	2.00 [1.00, 2.00]	0.877
Size recurrent nodules, cm (median [IQR])	2.00 [1.50, 2.60]	1.60 [1.20, 2.90]	0.099	2.00 [1.40, 2.50]	1.60 [1.20, 2.73]	0.281
AFP at recurrence (median [IQR])	6.95 [3.00, 31.75]	7.10 [4.00, 26.50]	0.809	9.00 [2.80, 35.20]	7.10 [3.85, 28.75]	0.867
MVI (%)	236 (42.7)	43 (34.4)	0.11	50 (46.3)	37 (32.7)	0.054
Satellitosis (%)	93 (18.5)	20 (15.9)	0.579	17 (16.5)	18 (15.8)	1
Multiple recurrence (%)	228 (37.3)	61 (52.1)	0.004	59 (49.2)	54 (50.9)	0.894
Bilobar recurrence (%)	101 (18.7)	26 (23.2)	0.467	30 (26.5)	23 (22.8)	0.190
Time to recurrence, months (median [IQR])	16.00 [7.00, 34.00]	12.50 [5.00, 21.75]	0.004	12.00 [5.00, 27.25]	13.00 [5.00, 22.75]	0.874
Milano In at recurrence (%)	505 (82.7)	105 (79.5)	0.472	93 (77.5)	63 (80.8)	0.71
Milano In at recurrence + age<70 y.o. (%)	198 (32.4)	99 (75)	<0.001	80 (66.7)	99 (82.5)	<0.001

PSM, propensity score matching; MELD, model for end stage liver disease; ECOG-PS, eastern cooperative oncologic group – performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; N, number; AFP, alfa-feto-protein; MVI, microvascular invasion.

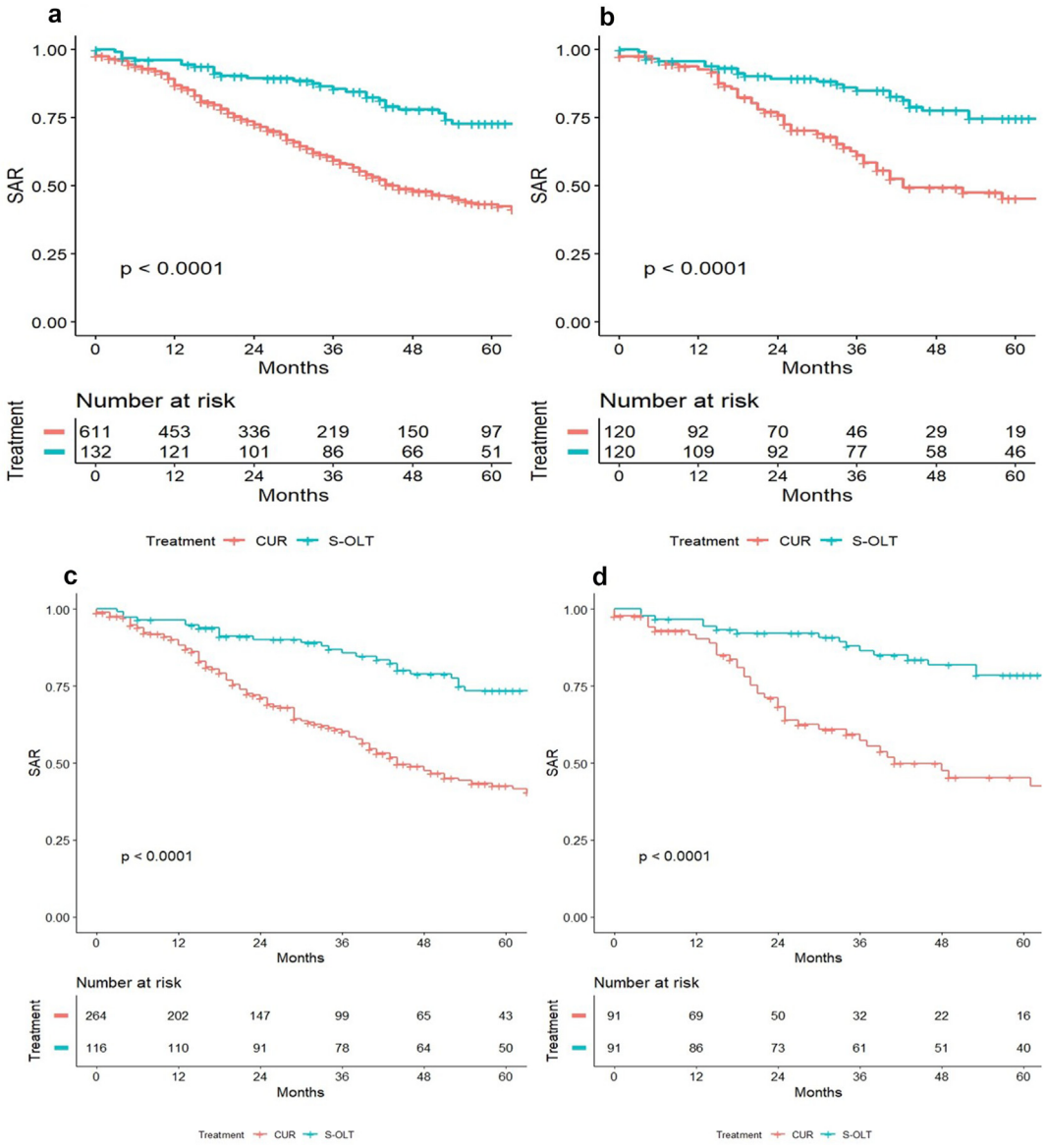

Figure 1 Survival after recurrence a) before and b) after propensity score matching among the two groups. Figures c and d showed the survival after recurrence before and after propensity score matching (respectively) in the subgroup of patients treated in a transplant centre. CUR curative; SLT second line liver transplant

resection) for the first diagnosis of HCC to the recurrence episode and the relative treatment (either with CUR or SLT). Those patients were treated by CUR in 264 cases (69.5%) and SLT in 116 (30.5%). At the baseline, median age was 68 years (IQR 62–73) and 59 (IQR 53–63) for CUR and SLT respectively ($p < 0.001$). Median Charlson Index was 6 (IQR 5–7) for CUR and 5 (IQR 5–6) for SLT (p: 0.003). Cirrhosis was present in 87.9% among SLT, and in 74.2% in the CUR group (p: 0.004). SLT patients had more frequently oesophageal varices (29.3% vs 15.9%, p: 0.004), splenomegaly (44.0% vs 23.5%, $p < 0.001$), but they showed a lower rate of presence of microvascular invasion at the first specimen (36.2% vs 51.1%, p: 0.010). These and other data were summarized in supplementary table 3. Patients treated by CUR were MC-In in 38.3% of cases, while 73.3% were the same in the SLT group ($p < 0.001$).

One, three and five years SAR were 88.4%, 60.2% and 42.5% for CUR group, and 96.6%, 85.8% and 73.5% for the SLT group ($p < 0.001$, Fig. 1c). CUR showed a survival benefit of 40.5 months (SE 1.40) and SLT of 52.6 (SE 1.46), while the absolute survival benefit was 12.1 months in favour of SLT.

All the preoperative variables significantly different at the baseline of the two groups were retained to match the two groups with a propensity-score matching analysis, and 91 patients were correctly matched. After PSM, 1-3-5 years SAR was 90.4%,

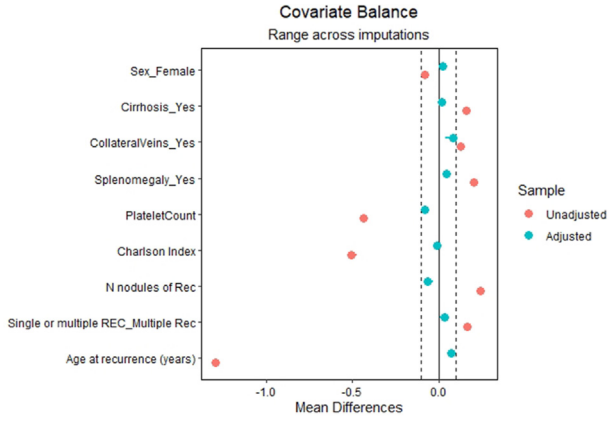

Figure 2 Loveplot demonstrating the mean differences among the variables that have been matched by 1:1 nearest neighbour propensity score matching

57.4%, 45.3%, 96.7%, 86.5%, 78.5% for CUR and SLT respectively ($p < 0.001$); the survival benefit of CUR was 40.3 months and for SLT it was 53.6 months (Fig. 1d). At the Cox multivariate regression, SLT (HR 0.33, 95%CI: 0.19–0.57, $p < 0.001$), MELD score (HR 1.19, 95%CI: 1.07–1.32, p: 0.001), AFP at recurrence (HR 1.00, 95%CI: 0.98–0.99, p: 0.010) and macrovascular invasion (HR 3.47, 95%CI: 1.54–7.83, p: 0.003) were independent predictors of mortality after recurrence (Table 4).

Patients treated between 2016 and 2021

Since the large period considered in this real-life analysis, in which several technical and oncologic updates were risen in the field of this study, a sub-analysis on patients treated more recently (from January 2016 to December 2021) were considered (n = 225). In this timespan, 200 (88.8%) patients were treated by CUR and 25 (11.2%) by SLT. MC-In patients in the CUR group were 62 (31.0%) while in SLT were 19 (76.0%). The same rates were observed if the age criterion was considered. Median SAR was 37 months (95%CI: 29-NA) for CUR, while it was not reached by SLT. At 5 years, SAR was 38.1% and 91.3% for CUR and SLT respectively ($p < 0.001$). CUR showed a survival benefit of 36.8 months (SE 2.24) and SLT of 55.6 (SE 2.97), while the absolute survival benefit was 18.8 months in favour of SLT. At the multivariate Cox regression, SLT (HR 0.23, 95%CI: 0.06–0.97, p: 0.045) and MELD score (HR 1.13, 95%CI: 1.03–1.24, p: 0.007) were the only factors independently associated with the risk of mortality after recurrence. The multivariate was reported in supplementary table 4.

Discussion

In case of HCC recurrence after a first surgical approach, SLT was confirmed to be superior when compared to other treatments, specifically when considering other curative alternatives, such as RH or TA.[9,24] SLT therefore, confirms its role as the best therapeutic choice after first HCC recurrence. Patients who were candidates for SLT were more frequently with a more decompensated underlying liver, which may have driven the treatment allocation. The superiority of SLT, however, has been confirmed even after propensity score matching, where all the preoperative factors that could modify the survival have been balanced among the curative and the transplant group, as confirmed in previous studies.[12,25]

Table 2 Univariate and multivariate Cox regression analysis to estimate the risk of overall mortality

	Univariate Cox				Multivariate Cox			
	HR	95%CI low-up		p	HR	95%CI low-up		p
SLT (vs CUR)	0.367	0.218	0.619	<0.001	0.386	0.235	0.634	<0.001
Age at rec (per year)	1.014	0.984	1.045	0.3638	1.014	0.985	1.044	0.3727
Cirrhosis (vs not)	1.114	0.443	2.804	0.8237				
Varices (vs not)	1.064	0.637	1.776	0.8146				
Splenomegaly (vs not)	1.277	0.765	2.133	0.3577				
Charlson Index (per point)	0.981	0.859	1.121	0.7812				
N recurrent nodules (per unit)	1.059	0.902	1.244	0.4943				
Size rec nodules (per cm)	0.985	0.931	1.043	0.6154				
Multiple recurrence (vs single)	1.106	0.685	1.786	0.6833				
Bilobar recurrence (vs unilobar)	1.356	0.785	2.344	0.2858				
Local recurrence (vs not)	0.96	0.572	1.611	0.8774				
MVI (vs absence)	1.148	0.664	1.985	0.628				
Satellitosis (vs absence)	1.598	0.975	2.617	0.0683	1.674	0.968	2.893	0.0723
MELD score (per point)	1.169	1.081	1.264	<0.001	1.169	1.071	1.277	<0.001
Time to recurrence (per month)	0.988	0.971	1.006	0.2168				

SLT, second line liver transplant; N, number; MVI, microvascular invasion; MELD, model for end stage liver disease.

Table 3 Univariate and multivariate Cox regression analysis to estimate the risk of overall mortality among patients with a recurrence within and beyond the Milan Criteria

	MILAN–IN		MILAN-OUT	
	HR (95%CI) univariable	HR (95%CI) multivariable	HR (95%CI) univariable	HR (95%CI) multivariable
Age at recurrence (per year of increase)	0.99 (0.96–1.02, p = 0.581)	–	1.02 (0.96–1.08, p = 0.481)	–
Time to recurrence>24 months (vs < 24)	0.34 (0.18–0.65, p = 0.001)	0.25 (0.11–0.61, p = 0.002)	0.29 (0.10–0.85, p = 0.024)	0.36 (0.05–2.47, p = 0.300)
Charlson Index (per point of increase)	0.92 (0.77–1.11, p = 0.400)	–	1.18 (0.81–1.71, p = 0.383)	–
SLT (vs CUR)	0.41 (0.23–0.73, p = 0.002)	0.41 (0.21–0.79, p = 0.008)	0.21 (0.06–0.78, p = 0.020)	0.26 (0.02–3.03, p = 0.284)
MELD_score	1.18 (1.07–1.30, p = 0.001)	1.13 (0.96–1.34, p = 0.153)	1.03 (0.79–1.35, p = 0.840)	–
Anatomic resection (vs wedge)	0.71 (0.42–1.19, p = 0.191)	–	2.01 (0.64–6.32, p = 0.233)	–
N nodules of recurrence (per nodule)	1.12 (0.80–1.57, p = 0.489)		1.22 (1.00–1.48, p = 0.049)	1.45 (1.09–1.93, p = 0.011)
Size of recurrence (per cm of increase)	1.31 (0.96–1.78, p = 0.085)	1.61 (1.02–2.52, p = 0.039)	0.99 (0.93–1.05, p = 0.741)	–
AFP at recurrence	1.00 (1.00–1.00, p = 0.674)	–	1.00 (1.00–1.00, p = 0.075)	1.00 (1.00–1.00, p = 0.060)
Macrovascular invasion (vs not)	1.77 (0.80–3.93, p = 0.161)	–	2.42 (0.67–8.73, p = 0.176)	–
ECOG PS 1 (vs 0)	1.34 (0.63–2.83, p = 0.444)	–	0.77 (0.10–6.00, p = 0.806)	–
Cirrhosis (vs not)	0.54 (0.23–1.27, p = 0.160)	–	0.78 (0.22–2.80, p = 0.700)	–
Splenomegaly (vs not)	1.51 (0.88–2.60, p = 0.133)	–	0.73 (0.25–2.14, p = 0.569)	–
Varices or collaterals (vs not)	1.09 (0.60–1.99, p = 0.776)	–	1.00 (0.27–3.69, p = 0.995)	–
INR	5.55 (1.24–24.91, p = 0.025)	0.66 (0.06–7.50, p = 0.734)	0.05 (0.00–8.72, p = 0.249)	–
MVI + (vs neg)	1.27 (0.73–2.22, p = 0.393)	–	0.99 (0.31–3.13, p = 0.988)	–
Satellitosis (vs absence)	4.22 (2.16–8.24, p < 0.001)	3.51 (1.60–7.68, p = 0.002)	0.44 (0.09–2.09, p = 0.302)	–

SLT, second line liver transplant; N, number; MVI, microvascular invasion; MELD, model for end stage liver disease.

Even though the superiority of SLT on other curative approaches for recurrent HCC is well established, the effective transplant benefit calculation in a real life matched population has never been previously published to our knowledge. In our propensity score matched analysis, SLT patients gained 9.7 life months at five years after recurrence if compared to the CUR ones. This benefit remained almost similar even when we considered the results of the transplant centres only, where those who were treated by SLT gained 13.3 life months at five years. These advantages are significant, but not as sharp as expected. This similarity among transplant and non transplant hospitals depicts the good level of care delivered in Italy for hepatocellular carcinoma. Recently, Serenari M. *et al.* reported that the differences in Italy among centres with a transplant programme and the others HPB hospitals were about the short terms outcomes, but not in terms of survival or risk of recurrence.[26] However, the advantage of SLT has been confirmed, thus these data open relevant considerations on availability, patient selection methodology and clinical paths to access transplantation in presence of a first recurrence. Considering the best results obtained after SLT, we should expect that this treatment has been widely adopted as the first choice, or at least as the most frequent. Indeed, the choice to resect transplantable HCC patients in first line may be justified to reduce transplant center engagement, in view of the fact that some patients may not recur or in case of recurrence may still have a future transplant option. In the previous past, organ shortage also drove some centers to propose transplant only in case of recurrence after surgery or ablation.[27] However, in Italy the rate of dropped-out patients listed for HCC has been reported at 7%, which is quite low. Nevertheless, after first recurrence, excluding patients from transplantation may have relevant implications in terms of potential loss of patient life

Table 4 Univariate and multivariate Cox regression analysis to estimate the risk of mortality among patients with a recurrence that were managed by a centre with an available transplant programme

	HR (95%CI) univariable	HR (95%CI) multivariable
Age at recurrence (per year of increase)	1.01 (0.98–1.04, p = 0.680)	–
Time to recurrence>24months (vs < 24)	0.70 (0.37–1.31, p = 0.261)	–
Charlson Index (per point of increase)	1.05 (0.91–1.22, p = 0.483)	–
SLT (vs CUR)	0.30 (0.18–0.51, p < 0.001)	0.33 (0.19–0.57, p < 0.001)
MELD score (per point of increase)	1.19 (1.08–1.32, p = 0.001)	1.19 (1.07–1.32, p = 0.001)
N nodules of recurrence (per n of increase)	1.09 (0.98–1.21, p = 0.129)	1.45 (1.09–1.93, p = 0.011)
Size of recurrence (per cm of increase)	0.92 (0.80–1.06, p = 0.258)	–
AFP at recurrence (per point of increase)	1.00 (1.00–1.00, p < 0.001)	1.00 (1.00–1.00, p = 0.010)
Macrovascular invasion (vs not)	3.46 (1.57–7.62, p = 0.002)	3.47 (1.54–7.83, p = 0.003)
ECOG_PS 1 (vs 0)	1.06 (0.48–2.32, p = 0.891)	–
Cirrhosis	1.06 (0.54–2.08, p = 0.866)	–
Splenomegaly	1.42 (0.86–2.36, p = 0.175)	–
Varices or collaterals (vs not)	1.10 (0.62–1.94, p = 0.745)	–
INR	1.59 (0.43–5.92, p = 0.490)	–
MVI + (vs neg)	1.32 (0.80–2.15, p = 0.274)	–
Satellitosis	1.80 (1.02–3.16, p = 0.043)	1.84 (1.02–3.31, p = 0.044)

SLT, second line liver transplant; N, number; MVI, microvascular invasion; MELD, model for end stage liver disease.

months due to an exclusion from the best therapeutic option. Furthermore, according to recent evidence, LT in third and fourth line may not warrant the same expected good long term survivals as observed as PLT and SLT.

Looking at the real-life data, an interesting result is the rate of patients effectively submitted to a curative rather than a salvage transplant approach. For this study, MC was adopted to select candidates for transplant. These criteria are now considered too restrictive, and currently others indications were spread out (e.g. AFP TTV,[28] METROTICKET 2.0,[29] French AFP Score,[30] UCSF,[31] ASAN Criteria,[32] PADOVA-TORONTO Criteria[33]), enlarging the population which could benefit from transplant. Most of the Italian centers now adopt one of these criteria. However, even considering the "simplified old conventional" parameters such as MC, patients who were submitted to CUR who were MC-IN were almost 83% before PSM, and 77% after it. Likely, these rates could be higher when adopting those new criteria for transplant.

Even though some of these patients may have been excluded from transplant due to relevant comorbidities, consent denial to transplantation or unavailability of transplant centers, our data suggest a relevant amount of transplant under referral, which could be accounted as the physiologic time span in which SLT has been established and widely accepted. In fact, when considering patients from 2016 to 2021, the amount of those who were eligible to SLT but treated by CUR dropped from 83% (overall) to 31%. Thus, being managed in a transplant centre showed to reduce, although not drastically, the number of patients submitted to CUR but potentially transplantable up to 69%. The higher rate of SLT allocation among transplant centres when compared to HPB ones was recently reported.[26] However, although a stringent tendency to candidate patients to SLT, the rate of those who were treated in the CUR group but were oncologically feasible for transplant was still very high, reflecting in the last decade a weak tendency to delivery SLT in case of recurrence, at least in Italy, regardless the availability of a transplant programme.

Such phenomena could be due to different complex reasons, in a phase of progressively changing transplant scenarios, but this changement during years could be considered the time a novel strategy to deal with HCC recurrence takes to become philosophically predominant. Furthermore, the absence, in many instances, of a transplant surgeon or transplant hepatologist routinely involved in multidisciplinary territory case discussions may have played an important role. Such an absence may have led to addressing patients to the therapeutic choice more easily available and deliverable.[26]

For several years, old age was considered a contraindication for transplant. In our series, arbitrarily adopting a cut-off of 70 years old, the number of recurrent patients who could be within MC and have been treated by CUR dropped to 32%, which still represents a high rate of under referral. However, in the last years, age *per se* was demonstrated to be not an absolute contraindication for any types of treatment,[34] including transplant: other parameters, such as comorbidities, frailty,[35] body weights variations could better drive the risk evaluation.[36,37] In fact, while we evaluated the impact of age at recurrence in a multivariate model, this was never a

risk factor, either in the whole cohort, in the MC-IN subgroup and in the MC-OUT one. This means that older patients should not be excluded from SLT automatically without careful expert evaluation in a transplant setting. More than 10% of waitlist transplant inclusions nowadays refer to patients $\geq$ 70 years of age in Europe and United States with a progressively increasing trend. Such a trend is particularly evident in HCC patients. Even though for these patients reported long term survivals are slightly inferior to younger, still 5 years survival ranges from 55 to 65%.[38] However, age adjusted data on life years lost, representing the best metrics to address the issue, are still lacking. These and other reports, referring to thousands of patients >70 years of age, show an increased waitlist dropout for these patients but still a similar transplant benefit if compared to younger recipients.[39]

This evidence should discourage patient non-referral to transplantation simply according to MC unless a transplant expert formalizes such an exclusion. In this view, any *ex pre* age cutoff, even in presence of a donor scarcity context, is to be considered discriminatory and ethically arguable. The figures here reported should drive a deep reflection, since they may reflect the absence of a well-established network, in Italy, among HPB centers and the transplant ones, which may have driven a potential under-treatment for those patients. This approach, indubitably demanding from the logistic point of view, has evidently lacked in this real life national experience.

Considering the impact of each treatment on SAR when the recurrence is within or without the MC, we discovered that in case of MC-in recurrence, SLT was confirmed as a protective treatment, reducing the risk of mortality after recurrence by almost 60%, together with the size of recurrent nodules, the time of recurrence and the presence of satellitosis at the first specimen. Nevertheless, in case of MC-out patients, SLT did not reduce the risk of mortality after recurrence when compared with the other curative treatments, and the number of recurrent nodules was the only identified risk factor. This result likely reflects the impact of underlying tumor burden and advanced tumor aggressiveness: in fact, number of nodules and their size indirectly reflects tumor biology,[40] and in all scores they are always considered as predominant risk factors. In such advanced cases, the disease could be already microscopically spread out the liver,[41] determining the comparable results among SLT and CUR. Importantly enough, however, a subgroup analysis on more actual transplant criteria (Metrotiket, AFP score, AFP TTV, Padova-Toronto, Asan score etc) was not conducted thus limiting the capability of the present study to address the superiority of SLT in the context of more recent transplant policies. Of notice, although the higher stage, it's mandatory to remember that even in these cases curative strategies, such the ones considered in this study, can still increase the overall survival of those patients, particularly if compared to other treatments as chemoembolization or systemic therapies,[42] reflecting a well-established treatment hierarchy.[43] Thus, in case of recurrence outside MC, the treatment allocation should be carefully evaluated, and redo-hepatectomy or thermoablation could be considered as alternatives to the SLT in the context of a multidisciplinary setting including transplant experts. These alternative options could be helpful for those conditions in which patient specific expected waitlist times could be too prolonged: the treatment allocation may directly fall to RH or TA, reducing the rate of patients inserted in the waiting list. According to our data, potentially this population accounted for up to 18% of the recurrences recorded in the register. Thus, the tailored evaluation of each patient seems pivotal, and the presence of a strict collaboration among HPB surgeons, transplantologist and the other clinical figures involved in the decision process is fundamental. The risk, in fact, is to under or over indicate the wrong potentially curative treatment to the wrong patient.

The limits of the present study may be several. First, since the retrospective nature of the study, the selection bias cannot be excluded: however, the large dataset from real-life employed, and the propensity-score matching significantly mitigated this risk. Secondly, data about SLT did not include the criteria employed to allocate the organ, the waiting list time or other parameters that could allow considerations about the organ availability and its impact in a real-life scenario. However, the HE. RC.O.LE.S. register, even if it is not a transplant register, recorded the actual treatment that a patient received for his or her relapse, enabling us to make considerations about the effect of the treatment, despite how the patients were transplanted. Another limit is these patients were almost compensated in terms of underlying liver function: this means that all the transplant cases were listed for oncologic reasons, and not because of deteriorated liver functionality. Despite the high number of cases, some analysis showed a reduced sample size, leading to an increased risk of type-II error. Finally, this paper covered a large period of ten years, in which many changes have occurred either in the resection and the transplant fields. We opted to employ the MC since they were the most diffused world-wide until a few years ago, and other modern criteria were not available or considered: it couldn't be realistic to apply the present mentality to an historical series. However, MC today are considered too restrictive, and the transplant benefit has been demonstrated in several different scenarios: our rates regarding the under referral issue could be underpowered.

In conclusion, the indication for SLT or CUR should be carefully evaluated, as the sum of different parameters regarding tumor biology, patients comorbidities and underlying liver function. This real data unprecedented analysis prompts the need for a revision in the standard composition of multidisciplinary teams for HCC decision-making processes, which should always mandatorily include HPB surgeons together with a transplant expert.

Authors contributions

Conceptualization: Simone Famularo, Guido Torzilli, Umberto Cillo, Andrea Lauterio.

Coordination: Guido Torzilli.

Data collection: Matteo Serenari6, Federica Cipriani7, Federico Fazio8, Mario Giuffrida9, Francesco Ardito10, Tommaso Dominioni11, Mattia Garancini12, Quirino Lai13, Daniele Nicolini14, Sarah Molfino15, Pasquale Perri16, Enrico Pinotti17, Simone Conci18, Cecilia Ferarri19, Matteo Zanello20, Stefan Patauner21, Giuseppe Zimmitti22, Paola Germani23, Marco Chiarelli24, Maurizio Romano25, Michela De Angelis26, Giuliano La Barba27, Albert Troci28, Valentina Ferraro29, Francesco Izzo30, Adelmo Antonucci31, Andrea Belli30 & HERCOLES Contributors.

Data analysis: Simone Famularo.

First draft writing: Simone Famularo, Umberto Cillo, Andrea Lauterio, Matteo Serenari6, Federica Cipriani7, Federico Fazio8, Mario Giuffrida9, Francesco Ardito10, Tommaso Dominioni11, Mattia Garancini12, Quirino Lai13, Daniele Nicolini14, Sarah Molfino15, Pasquale Perri16, Enrico Pinotti17, Simone Conci18, Cecilia Ferarri19, Matteo Zanello20, Stefan Patauner21, Giuseppe Zimmitti22, Paola Germani23, Marco Chiarelli24, Maurizio Romano25, Michela De Angelis26, Giuliano La Barba27, Albert Troci28, Valentina Ferraro29, Francesco Izzo30, Adelmo Antonucci31, Andrea Belli30 & HERCOLES Contributors.

Critical revision: Riccardo Memeo29, Michele Crespi28, Giorgio Ercolani27, Luigi Boccia26, Giacomo Zanus25, Paola Tarchi23, Moh'd Abu Hilal22, Antonio Frena21, Elio Jovine20, Guido Griseri19, Andrea Ruzzenente18, Mauro Zago17,24, Gianluca Grazi16, Gian Luca Baiocchi15, Marco Vivarelli14, Massimo Rossi13, Fabrizio Romano12, Marcello Maestri11, Felice Giuliante10, Raffaele Dalla Valle9, Alessandro Ferrero8, Luca Aldrighetti7, Luciano De Carlis5, Matteo Cescon6, Guido Torzilli1,2.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.06.004.