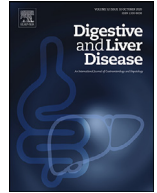




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Liver, Pancreas and Biliary Tract

Current management of hepatobiliary malignancies between centers with or without a liver transplant program: A multi-society national survey

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ABSTRACT

Background: Availability of liver transplantation (LT) as a treatment for hepatocellular carcinoma (HCC) and other liver malignancies may determine heterogeneity of therapeutic strategies across different centers.

Aims: To investigate the practice between hepato-biliary centers without (HB centers) and with a LT program (LT centers), we launched a 38-item web-based national survey, with directors of centers as a target.

Methods: The survey, including 4 clinical vignettes, collected data on their approach to HCC and transplant oncology.

Results: After duplicates removal, 75 respondents were considered. Respondents from LT centers ($n = 22$, 29.3 %) were more in favor of LT in the case of HCC outside Milan criteria (90.9 % vs. 67.9 %, $p = 0.037$), recurrent HCC (95.5 % vs. 50.9 %, $p = 0.002$) and other malignancies such as cholangiocarcinoma or neuroendocrine tumors. No significant difference was observed concerning the proportion of centers favorable to LT for unresectable colorectal liver metastases (100 % vs. 88.7 %, $p = 0.100$).

Conclusion: This national survey showed how management of HCC and awareness of transplant oncology may differ between HB and LT centers. Effective networking between HB and LT centers is crucial to provide optimal treatment and access to LT.

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1. Introduction

Liver transplantation (LT) has emerged as a crucial therapeutic option for patients suffering from primary or secondary liver tumors, especially hepatocellular carcinoma (HCC) [1]. Once considered as formal contraindications to LT, unresectable colorectal cancer liver metastases, as well as intra- and perihilar cholangio-

carcinoma are nowadays broadening the landscape of LT indications. As transplant oncology is evolving at a fast pace, a multidisciplinary team (MDT) approach [2] including transplant and hepato-biliary (HB) surgeons, is mandatory to select the most appropriate treatment for these patients. [3] Treatment of recurrent HCC after liver resection has been demonstrated to be different between HB centers with or without liver transplant activity [4], suggesting differences also in the overall management of HB malignancies.

We therefore decided to launch a national survey with three objectives: (1) to take a reliable snapshot of the distribution and type of activity of the centers that carry out oncological hepato-biliary surgery and LT in Italy; (2) to describe the current referral patterns and management strategies for HCC; (3) to gauge the awareness and perception of transplant oncology comparing the attitudes of surgeons from centers with or without an active LT program.

2. Material and methods

2.1. Participants and survey design

In August 2023, directors or co-directors of LT and HB centers across Italy were contacted through personal emails and invited to fill out a 38-item web-based survey using the Google Forms platform (Supplementary File). HB centers were defined as those performing at least ≥ 10 LR in 2022 and not including a LT program. To maximize reach, the survey was also sent to the general membership of 3 Italian surgical societies, AICEP (Italian Association of Hepato-Bilio-Pancreatic Surgery), SITO (Italian Organ Transplant Society) and CCTF (Committee of Liver Transplant Surgeons), as part of their regular newsletters. Only one response directly from or on behalf of center directors was considered. The survey collected data on the demographics of surgical directors and the centers where they worked, as well as their current approaches to liver malignancies and transplant oncology, including four clinical vignettes with case-based scenarios on the management of HCC. The survey was conducted according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [5]. A reminder email was sent two weeks after initial distribution to encourage participation and the survey was closed after three weeks (September 2023). Participation was on a voluntary basis and participants were blind to study hypotheses. Given the nature of this study, it was exempt from ethical board approval.

2.2. Statistical Analysis

Descriptive statistics were expressed as median and interquartile range (IQR). Mann-Whitney U test explored differences

between HB and LT centers for data that was not normally distributed. Categorical variables were compared using the chi-square test. All statistical tests were two-tailed, and differences were considered significant at a p-value of ≤ 0.05 . The statistical software used for all analyses was Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

3. Results

3.1. Demographics and center characteristics

In total, 86 respondents completed the survey. Eleven questionnaires were duplicates and were removed resulting in 75 final respondents. Overall response rate was 89.6 % (86/96) when calculated from direct distribution and it was 100 % (22/22) among LT centers.

Accordingly, 22 respondents (29.3 %) worked in LT centers and 53 (70.7 %) in HB centers without a LT program; 18 respondents (24 %) worked in high-volume centers for liver surgery (≥ 100 LRs per year [6]); 9 respondents (12 %) worked in both high-volume and LT centers; 8 respondents (10.6 %) worked in both high-volume and HB centers. The proportion of centers according to the volume of liver surgery and the type of specialty is shown in Supplementary Figure 1. The median age of surgical directors was 58 years (IQR 52-62), and 74 (99 %) were males (Table 1).

A total of 5713 liver resections (LRs) were performed in 2022 at participating centers as declared by respondents, of which 2830 were performed by a minimally invasive (MI) approach (49.5 %) and 1987 were performed for HCC (34.8 %) (Fig. 1a). The median number of LR performed in LT centers was 93 (IQR 33-127) compared to 50 (IQR 29-85) in HB centers ($p = 0.104$). The proportion of MLR was 50.1 % in LT centers compared to 49.2 % in HB centers whereas the proportion of HCC cases was 40.8 % in LT centers compared to 31 % in HB centers.

A total of 1479 liver transplantations were performed in 2022 as stated by respondents working in LT centers, of which 700 (47.3 %) for HCC and 43 (2.9 %) for oncological indications different from HCC (Fig. 1b). The median number of LT performed was 50 (IQR 32-108).

Twelve out of 22 LT centers (54.5 %) reported to have performed at least 1 LT for oncological indications different from HCC in 2022: 8 (36.4 %) performed at least 1 LT for perihilar cholangiocarcinoma (PHCC), 9 (40.9 %) for intrahepatic cholangiocarcinoma (IHCC), 12 (54.5 %) for colorectal liver metastases (CRLM) and 10 (45.4 %) for metastatic neuroendocrine tumor (NET).

Table 1
Demographics of respondents and characteristics of the centers according to specialty.

Variable	Total (n = 75)	LT (n = 22)	HB (n = 53)	p-value
Age of director, median (IQR), yrs	58 (52-62)	60 (54-65)	58 (50-61)	0.056
Gender of director M/F	74/1 (99)	22/0 (100)	52/1 (98.1)	0.517
Volume, n (%)				0.027
High	18 (24)	9 (40.9)	8 (15.1)	
Mid-Low	57 (76)	13 (59.1)	45 (84.9)	
Center, n (%)				0.016
Academic	35 (46.7)	15 (68.2)	20 (37.7)	
Non-academic	40 (53.3)	7 (31.8)	33 (62.3)	
Geographical area, n (%)				0.464
North	45 (60)	12 (54.5)	33 (62.3)	
Center	14 (18.7)	6 (27.3)	8 (15.1)	
South and Islands	16 (21.3)	4 (18.2)	12 (22.6)	

F = female; IQR = interquartile range; M = male.

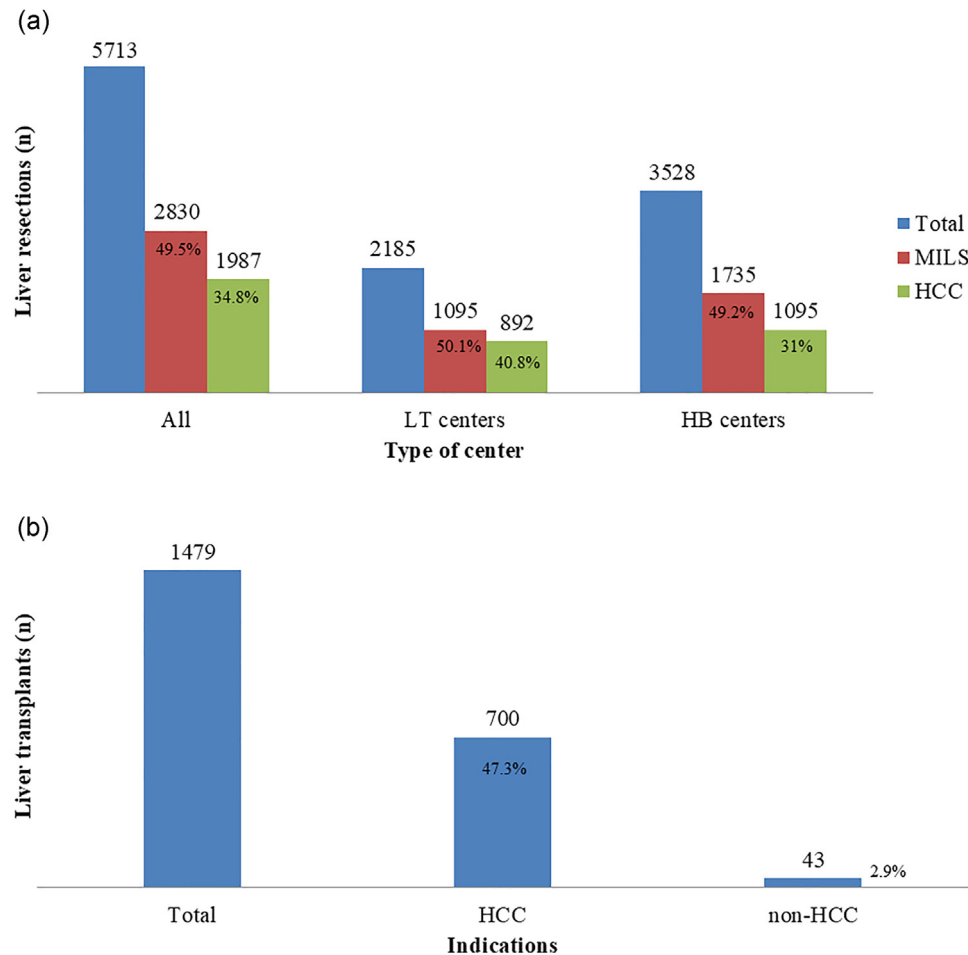


Fig. 1. Total number of liver resections (LR), minimally invasive liver resections (MILR) and LR for hepatocellular carcinoma (HCC) performed in 2022 as reported by respondents according to the type of specialty (a). Total number of liver transplantations (LT), LT for HCC and for oncologic indications different from HCC performed in 2022 (b).

3.2. Management strategies for HCC

For the treatment of HCC, all the therapeutic options reported in the corresponding section of the questionnaire (i.e. radiofrequency ablation -RFA-, trans-arterial chemoembolization, trans-arterial radioembolization -TARE-, anti-vascular endothelial growth factor, tyrosine kinase inhibitors, stereotactic body radiation therapy) were stated to be available by the 54.5 % (n = 12) of the respondents working in LT centers compared to 41.5 % (n = 22) of those working in HB centers (p = 0.302). The largest difference was observed for TARE which was available in 72.7 % (n = 16) of LT centers compared to 50.9 % (n = 27) of HB centers. Fig. 2 shows the percentage of respondents according to the type of therapy and specialty.

When directors of HB centers were asked about the presence of a transplant expert in the multidisciplinary therapeutic decision process for HCC, 60.4 % (n = 32) responded that a transplant surgeon or hepatologist was always involved.

3.2.1. Case 1 - Early HCC (BCLC A, single nodule)

In case of early HCC (BCLC A, single nodule) on compensated cirrhosis with mild clinically significant portal hypertension and a superficial nodule of 2.5 cm in S6 in patient ECOG 0, < 65 years, with nodule visible on ultrasound, what is the FIRST therapeutic option that you would consider in your center.

The preferred (88 %, n = 66) primary treatment modality for early HCC in the presence of compensated cirrhosis and mild significant portal hypertension was MILR for both LT (86.4 %, n = 19) and HB centers (88.7 %, n = 47). RFA was indicated by 9 % (n = 2) and 4 % (n = 2) of the respondents working in LT and HB centers, respectively. Overall, no significant differences were found between them (p = 0.297) (Fig. 3a). No significant differences (p = 0.512) were found also when comparing centers according to the presence or not of a transplant physician in the decision making.

3.2.2. Case 2 - Non-single HCC within the Milan criteria (multi-nodular BCLC A)

In the case of non-single HCC but within Milan criteria (multi-nodular BCLC A) on compensated cirrhosis in a patient < 65 years old, what is the FIRST therapeutic option you would consider in your center?

Liver transplantation in the case of multinodular HCC but within Milan Criteria (BCLC A) was the preferred therapeutic option for 64.2 % of respondents (n = 34) working in HB centers and 63.6 % in LT centers (n = 14). MILR was also considered as a valid option for 22.7 % (n = 5) and 17 % (n = 9) of LT and HB centers, respectively. Overall, no significant differences were found between the two groups (p = 0.735) (Fig. 3b). No significant differences (p = 0.838) were found also when comparing centers according

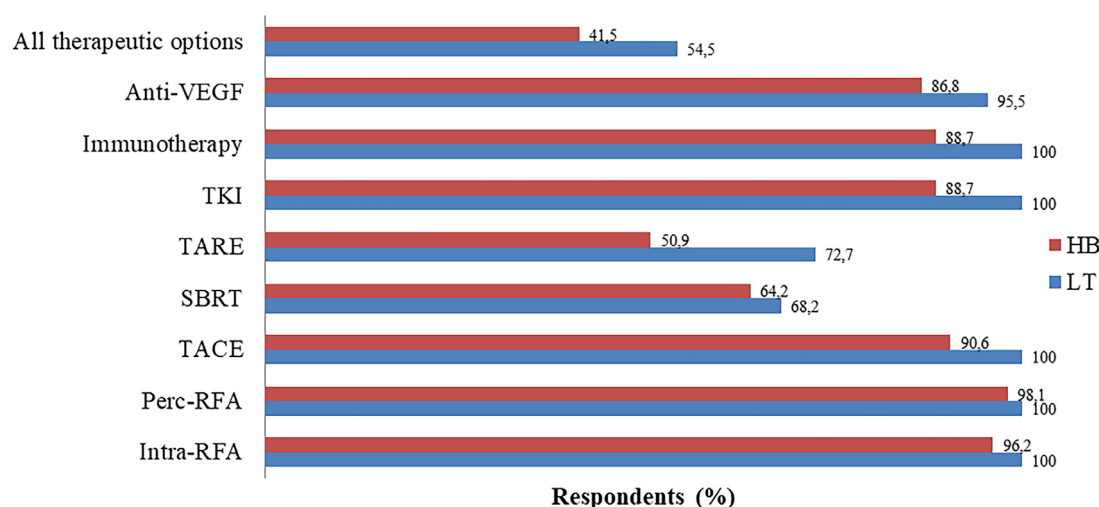


Fig. 2. Therapeutic options reported to be available at their institutions by respondents. VEGF = vascular endothelial growth factor; TKI = Tyrosine kinase inhibitors; TARE = trans-arterial radioembolization; SBRT = Stereotactic Body Radiation Therapy; TACE = transarterial chemoembolization; perc-RFA = percutaneous radiofrequency ablation; intra-RFA = intraoperative radiofrequency ablation.

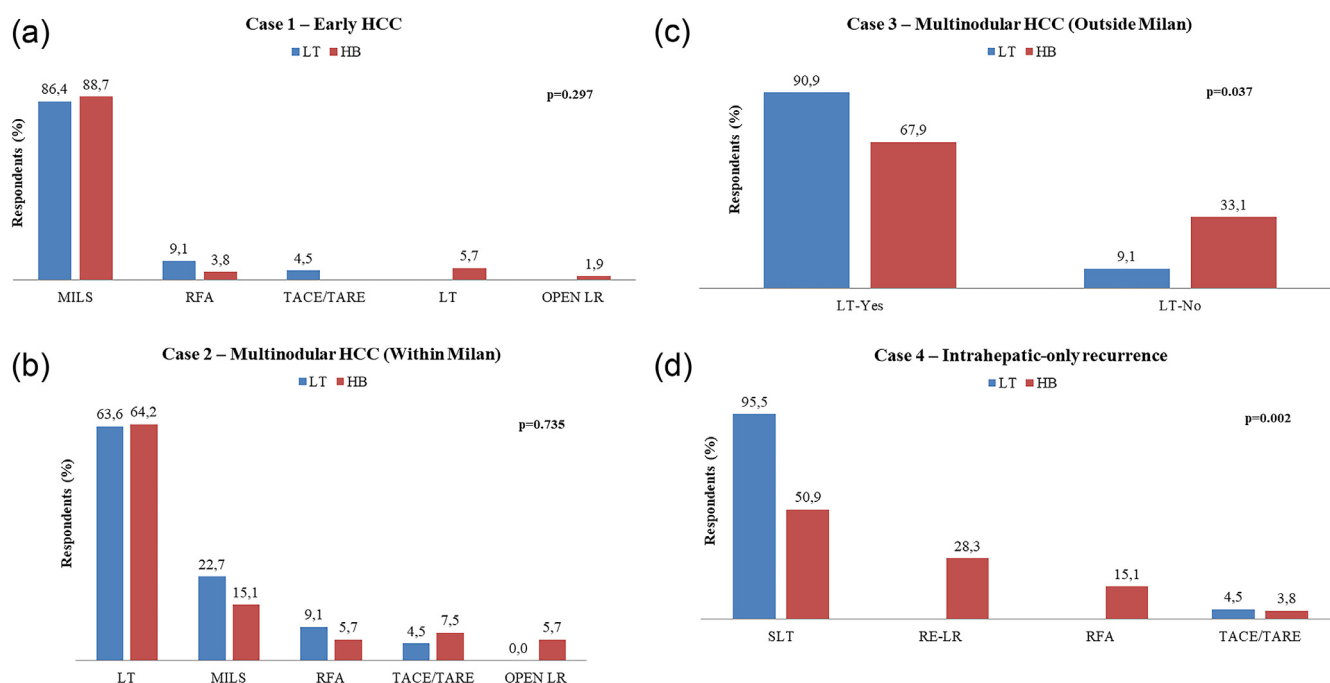


Fig. 3. Clinical vignette with case-based scenario. On the vertical axis is reported the % of respondents (a) Case 1: In the case of early HCC (BCLC A, single nodule) on compensated cirrhosis with mild clinically significant portal hypertension and a superficial nodule of 2.5 cm in S6 in patient ECOG 0, < 65 years, with nodule visible on ultrasound, what is the FIRST therapeutic option that you would consider in your center? (b) Case 2: In the case of non-single HCC but within Milan criteria (multi-nodular BCLC A) on compensated cirrhosis in a patient < 65 years old, what is the FIRST therapeutic option you would consider in your center? (c) Case 3: In the case of HCC outside Milan criteria (but without extrahepatic disease and macrovascular invasion), would you consider liver transplant a viable therapeutic option? (d) Case 4: In the case of intrahepatic-only recurrence (within Milan criteria) after resection in a cirrhotic patient < 65 years, what is the FIRST therapeutic option you would consider in your center?

MILS = minimally invasive liver surgery; RFA = radiofrequency ablation; TARE = trans-arterial radioembolization; TACE = trans-arterial chemoembolization; LT = liver transplantation; SLT = salvage liver transplantation.

to the presence or not of a transplant physician in the decision making.

3.2.3. Case 3 - HCC outside Milan criteria

In the case of HCC outside Milan criteria (but without extrahepatic disease and macrovascular invasion), would you consider liver transplant a viable therapeutic option?

Liver transplantation in the case of HCC outside Milan Criteria was considered the preferred treatment modality by 90.9 % (n = 20) of LT centers while this option was contemplated less frequently in HB centers (67.9 %, n = 36) (p = 0.037) (Fig. 3c). A sig-

nificant difference (p = 0.006) was found when comparing centers according to the presence of a transplant physician: in particular, 18 out of 32 (56.2 %) of HB centers involving a transplant physician would proceed with LT compared to 18 out of 21 (85.7 %) of HB centers without a LT physician and 20 out of 22 (90.9 %) of LT centers.

3.2.4. Case 4 - Intrahepatic recurrence of HCC (within Milan criteria)

In the case of intrahepatic-only recurrence (within Milan criteria) after resection in a cirrhotic patient < 65 years, what is the FIRST therapeutic option you would consider in your center?

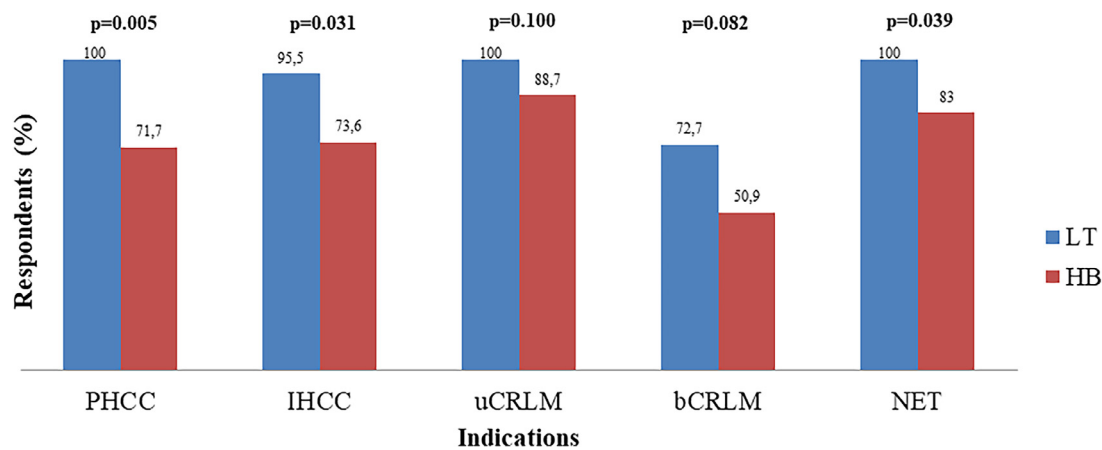


Fig. 4. Percentage of respondents who would consider liver transplantation in case of different hepatobiliary diseases. PHCC = perihilar cholangiocarcinoma; IHCC = intra-hepatic cholangiocarcinoma; uCRLM = unresectable colorectal liver metastases; bCRLM = borderline colorectal liver metastases; NET = neuroendocrine tumor.

Salvage LT was the most preferred therapeutic option for limited hepatic recurrence after LR by 95.5 % (n = 21) of LT centers and 50.9 % (n = 27) of HB centers. Thirty percent (n = 16) of the respondents working in HB centers also considered repeated resection a valid option. A significant difference was found between LT and HB centers (p = 0.002) (Fig. 3d). A significant difference (p = 0.009) was also found between HB centers involving or not a transplant physician and LT centers: 56.2 % (n = 18) of HB centers with LT physician preferred in case of recurrence salvage LT compared to 42.9 % (n = 9) of HB centers without LT physician and 95.5 % (n = 21) of LT centers.

3.3. Transplant oncology for non-HCC tumors

Respondents were then asked about the perception of transplant oncology to treat different malignant HB diseases (Fig. 4). All respondents working in LT centers (100 %, n = 22) would consider LT in case of unresectable perihilar cholangiocarcinoma (PHCC) compared to 71.7 % (n = 38) of those of HB centers (p = 0.005). Similarly, all but one LT center director (95.5 %, n = 21) would take into consideration LT in the case of intra-hepatic cholangiocarcinoma (IHCC) compared to 73.6 % of HB centers (p = 0.031). LT was considered in the case of the metastatic neuroendocrine tumor (NET) by all LT centers compared to 83 % (n = 44) of HB centers (p = 0.039). No significant differences (p = 0.100) were found between LT (100 %, n = 22) and HB centers (88.7 %, n = 47) when asked if they would consider LT for unresectable CRLM. The rate of both LT (72.7 %, n = 16) and HB centers (50.9 %, n = 27) in favor of transplantation decreased when respondents were asked if LT would be considered to be appropriate also in case of borderline CRLM but still resulting not significant (p = 0.082). When asked about the effectiveness of the networking with medical oncologists to recruit candidates for LT, surgical directors of LT centers responded to be satisfied in 40.9 % (n = 9) of cases.

3.4. Networking between LT and HB centers

When directors of HB centers were asked, 96.2 % (n = 51) of them reported having an effective patient referral network with LT centers. In particular, 33 centers (44 %) stated that they had referred at least one patient with malignant hepatobiliary disease different from HCC to a LT center. Of these, 47.2 % (n = 25) were CRLM, 32.1 % (n = 17) PHCC, 32.1 % (n = 17) NET and 15.1 % (n = 8) were IHCC. No significant differences were found when comparing

HB centers according to the presence of a transplant physician in the decision making (59.4 % vs. 66.7 %, p = 0.592).

3.5. Clinical outcomes

The last question asked which clinical outcome was considered to be the most important in evaluating the indication for the surgical treatment of a liver tumor. Survival benefit (SB) and overall survival (OS) were equally preferred among LT surgeons (each n = 10, 45.5 %). Among HB surgeons, OS and SB were selected by 23 (43.4 %) and 20 (37.7 %) respondents, respectively (Fig. 5).

4. Discussion

This national survey showed how the management of HCC and other malignant HB diseases might differ between HB centers with and without a LT program despite the reported existing networking between them. In particular, the respondents working in LT centers were more in favor of LT in the case of HCC outside Milan criteria, recurrent HCC or other HB malignancies, except for CRLM where the perception of LT seemed generally favorable on both sides.

Patients with liver cancer may be managed in either LT or HB centers and studies showed that the type of treatment might also be dependent on the type of hospital where the patient was initially referred. In particular, LT has been demonstrated to be more frequently proposed in case of recurrence of HCC after LR when patients were treated in LT centers [4]. In keeping with previous findings, our data showed that only half of HB centers would propose salvage LT for recurrent HCC, as compared to the vast majority of LT centers. Additionally, other differences in HCC management emerged from clinical scenarios. First, nearly one-third of respondents working in HB centers would not offer LT to their patients in case of multinodular HCC outside Milan criteria. Considering that the definition of Milan-OUT did not include extra-hepatic disease, this could exclude from LT a significant number of potentially curable patients, probably due to a lack of up-to-date knowledge about most recent and generally accepted transplant criteria [7,8,9]. However, we are aware that case 3 could have been prone to bias since there was no mention of any other details in the question such as AFP level, tumor size/number information or any possible downstaging therapy which may have probably changed the number of respondents centers in favor or not of LT. On the other hand, no significant differences were found when comparing HB and LT centers in managing early HCC or multinodular HCC

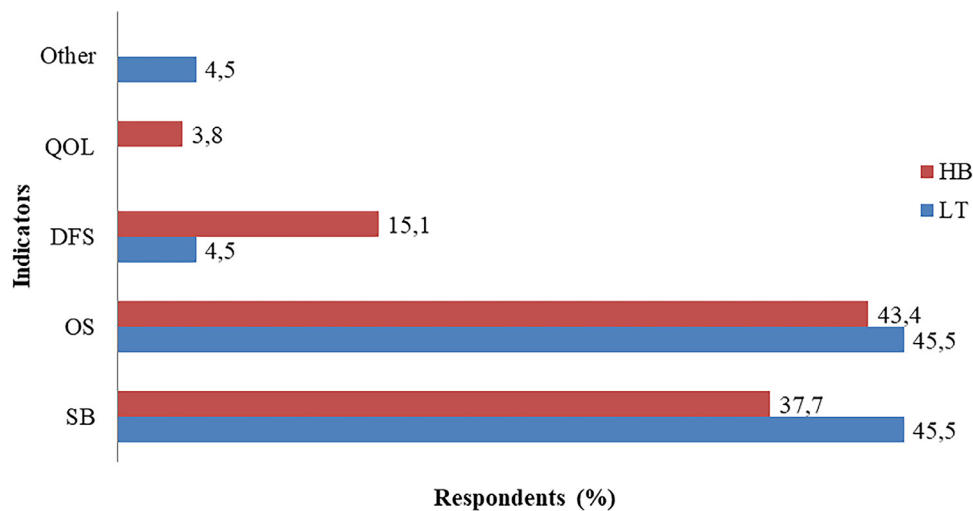


Fig. 5. Percentage of respondents according to the clinical outcome considered to be the most important in evaluating the indication for the surgical treatment of a liver tumor. QOL = quality of life; DFS = disease-free survival; OS = overall survival; SB = survival benefit.

BCLC-A, reflecting an acceptable homogeneity of approach in this setting. Importantly, the rate of MILR, as well as indication for MILR in case of limited disease was comparable between HB and LT centers, confirming that the diffusion of MI approach is deeply rooted in Italy [10]. Conversely, almost two-thirds of directors of HB centers stated that a transplant physician is always involved in the multidisciplinary therapeutic decision process of HCC patients. This topic is highly relevant since a timely referral and multidisciplinary discussion between HB and LT teams would be necessary for patients who need to be discussed early with the intent to not lose any chance of receiving LT whenever indicated. This was also in part demonstrated in our study when analyzing overall results according to the presence or not of a transplant physician in the HCC decision making.

Although LT has long been considered to be a curative strategy for HCC [11], more recently, also favored by the decrease in other indications such as HCV [12], LT has been increasingly adopted to treat other malignant HB malignancies [13]. In particular, LT is emerging as a potentially successful treatment for patients with unresectable CRLM since it has been demonstrated to provide long survival rates and a significant survival benefit if performed within selected criteria and standardized protocols [14]. As expected, in our survey, transplant oncology practice appeared to be more widespread among respondents from LT centers especially when considering diseases such as cholangiocarcinoma (intra or perihilar) or metastatic NET. This may be however rather troublesome, because some patients may not be offered LT and may misleadingly be presented for palliative approaches only. In contrast, no significant differences were found between HB and LT surgeons when asked about the possibility of LT for unresectable CRLM. In particular, our survey showed that even 90 % of surgeons working in HB centers agreed on the possibility of LT. This finding confirms the growing interest in this strategy, even though few clinical trials have been completed so far. Such a consensus decreased when respondents were asked to be in favor or not of transplanting patients with borderline CRLM. In this regard, a recent paper by Dueland et al. [15] showed that in borderline resectable cases such portal vein embolization are, survival benefit obtained with LT might also be higher compared to LR, a concept which, according to our survey, seems to be widespread also in HB centers even though there are still no robust data on this topic. However, organ availability inevitably limits its wide adoption and further studies are needed to confirm authors' hypothesis.

The numbers of patients submitted to LT for other oncological HB disease besides HCC would be expected to increase also if networking between surgeons and oncologists improved, considering that only 40 % of respondents in LT centers reported to have a proficient and collaborative relationship. Networking between LT and HB centers could also be improved given that only almost half of HB directors reported to have referred patients to LT centers for transplantation.

This study has several limitations which are mainly intrinsic to the nature of surveys. First, conclusions on the real impact on patients' outcomes of an effective networking between LT and HB centers cannot be drawn based on survey results which lacks of important clinical information. However, most centers performing HB surgery in Italy and all LT centers have been captured through this survey, reflecting a real scenario of how surgical liver patients are currently managed in our country. Second, being a low or high-volume center may have influenced the distribution of responses even though stratification based only on the yearly number of liver resections may not reflect the real expertise of the surgeons involved in the management process. Last but not least, we are aware that the results of this study cannot be generalized outside our country due to the unique characteristics of the patient referral system in Italy but it would be interesting to spread our survey to other European and non-European realities and see any difference.

In conclusion, this national survey showed how management of recurrent and multinodular HCC may be different between HB centers with and without a LT program, highlighting differences in the perception of LT as a potential treatment for other HB malignancies, except perhaps for unresectable CRLM, for which a moderate agreement was observed. Our data stress how a close cooperation between medical oncologists and surgeons at HB and LT centers is of paramount importance to provide patients with the best available treatment and, in selected cases, timely access to a potentially life-saving LT.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Supplementary materials

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