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ORIGINAL ARTICLE

Cornerstones and divergencies in the implementation and use of liver hypertrophy techniques: results from a nationwide survey for the set-up of the prospective registry

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Abstract

Background The aim of this national survey on liver hypertrophy techniques was to track the trends of their use and implementation in Italy and to detect analogies and heterogeneities among centers.

Methods In December 2022, Italian centers with liver resection activity were specifically contacted and asked to fill an online questionnaire composed of 6 sections including a total of 51 questions.

Results 46 Italian centers filled the questionnaire. The proportion of major/total number of liver resections was 27% and the use of hypertrophy techniques was required in 6,2% of cases. The most frequent reason of drop out was disease progression in 58.5% of cases. Most frequently used techniques were PVE and ALPPS with an increasing use of hepatic venous deprivation (HVD).

Heterogeneous answers were provided regarding the cutoff values to indicate the need for hypertrophy techniques. Criteria to allocate a patient to different hypertrophy techniques are not standardized.

Conclusions The use of hypertrophy techniques is deep-rooted in Italy, documenting the established value of their role in improving resectability rate. While an evolution of techniques is detectable, still significant heterogeneity is perceived in terms of cutoff values, indications and managing protocols.

Keywords Liver surgery · Liver failure · Survey · Morbidity · Hypertrophy techniques

Introduction

Despite the growing attention to the concept of parenchymal sparing surgery and the ever-increasing efficacy of cytoreductive chemotherapy programs, the need to perform major liver resections with extensive parenchymal demolitions and consequent drastic reduction of hepatic functional reserve to obtain radical treatment of primary and secondary liver tumors is a constant in all centers with a program of liver surgery [1–5]. Consequently, the need to deal with the

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issue of the quantity and quality of the residual liver (Future Liver Remnant, FLR) is equally constant: these factors have indeed a significant impact on the risk of postoperative liver failure, which is the most life-threatening complication in hepatic surgery, still representing a challenging issue in current clinical practice [5–10].

Within this perspective, liver surgeons—often in synergy with interventional radiologists—have worked over the last 30 years to refine and expand the pool of procedures available to induce parenchymal hypertrophy of the residual liver, dealing with the limit of a still incomplete knowledge about the molecular mechanisms underlying liver regeneration and addressing the risk of drop-out linked to disease progression while waiting for volumetric gain [10–17]. Indeed, portal vein embolization and portal vein ligation—alone or as part of a two-stage hepatectomy (TSH) program—were described as the gold standard techniques for hepatic hypertrophy [11, 12, 18], while more recently ALPPS and hepatic venous deprivation (HVD) have trod the stage thanks to promising results in terms of drop-out rate reduction and faster FLR growth [13, 19–23]. The overall scenario, therefore, sees a multiplicity of techniques available to induce liver hypertrophy [11, 18–23]—moreover in constant and continuous evolution—and an equally vast multiplicity of attitudes, which vary according to personal preference and available resources. The underlying rationale is widening resectability while maintaining safety.

Recognizing the importance of recording trends and outcomes of new procedures, both to monitor the quality of the interventions performed and to carry out large-scale analyses, the need to create a registry dedicated to ALPPS was immediately perceived in Italy, where this initiative was born in 2013 and saw the active and enthusiastic participation of many centers [23].

The purpose of this study is to report the results of a survey conducted on a national scale and which involved centers with an active program of liver surgery that were specifically questioned about the volumes of activity, the percentages of use of hypertrophy techniques and finally characteristics and indications to each hypertrophy technique. The main objective was to track the trends of their use and implementation in Italy and to detect analogies and heterogeneities among centres in terms of preferred techniques, changes of strategy over time and indications to detect practice variations, which may improve available indications and guidance for the whole community.

Data source and study population

Italian centers with an activity of liver resection, regardless of the volume of activity, were specifically contacted through a personal email and the existence of the survey was advertised through the communication channels of Italian surgical societies and the AICEP (Italian Association of Hepatopancreatobiliary Surgeons) mailing lists. The willingness of surgeons to participate in a survey on the topic of liver hypertrophy techniques was requested, explaining the main aim of tracing this activity in Italy and investigating the perception of the need to create a national prospective registry on hypertrophy techniques.

The survey was built and conducted according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [24] and technical functionality of the electronic questionnaire was tested before sending out the invitation. Participation was voluntary, no incentives for participation were offered and surgeons were asked to complete one questionnaire per center. Centers and respondents identity was not blinded and was explicitly required, to avoid overlapping data (contact data from the respondent were required to consider the questionnaire valid). The survey was open and shared on Google Forms, hence the results were automatically exported in Excel for storage and subsequent analysis. Access to responses was possible only for survey principal investigators (FR, MS, LA, EJ). Check for completeness was not available for respondents but was performed from investigators after the questionnaire has been submitted. The survey was sent out on 12 December 2022. Surgeons were asked to complete it within 15 days, but a further deadline extension of one week was provided and a reminder email was sent to encourage participation. The survey was then closed on December 31, 2022. No minimal threshold regarding case volume was set for survey inclusion, enabling centers to be considered irrespectively of their experience. The survey included a 51-questions questionnaire (time for questionnaire completion ≈ 15 min), organized in five different sections, each displayed on a different page. Specifically, the first section, consisting of nine questions, addressed the centers' annual volume of activity in liver surgery, in major liver resections and in hypertrophy techniques, together with drop-out rates and general reasons for drop out. Furthermore, preoperative planning resources were examined. The second section, consisting of 19 questions, focused on general availability of hypertrophy techniques, along with indications to hypertrophy (cutoff volumes of FLR according to characteristics of liver parenchyma) and methods to calculate FLR volume and evaluate liver function. The third section, consisting of 12 questions, covered the topic of PVE and HVD (indications, technical features and drop-out rate). The fourth section, consisting of 8 questions, assessed the issue of two stage hepatectomy and ALPPS (indications, technical features and drop-out rate). The fifth session, including two questions, assessed the use of radioembolization as a technique for hepatic hypertrophy. The final question—in a separate session—addressed the topic of perceived need and eventual participation to the

prospective national registry I GROWtoH (Italian Group of Regenerative and Occlusive Worldwide-used techniques of hepatic Hypertrophy).

The work has been reported in line with the STROCSS criteria [25].

Statistical analysis

All statistical analyses were performed using the statistical package SPSS version 24 (IBM, Armonk, New York, USA). Only completed questionnaires coming from Italian centers were included. Categorical variables were expressed as frequencies and percentages. Median values and interquartile ranges were used for continuous variables. When required, the weighted mean was used instead of an arithmetic mean. The weighted mean considers the proportional relevance of each sample (i.e. data from each center had a different relevance according to the number of performed cases), rather than treat each sample equally. $P < 0.05$ was considered statistically significant for all parameters.

Results

48 respondents from an equal number of centers filled the questionnaire. Two questionnaires were excluded from analysis since coming from centers outside Italy. The estimated Italian response rate was 85.2%, considering an estimate of 54 centers performing liver surgery in Italy and specifically invited to participate and 46 final responses. The degree of representativeness was hence considered adequate.

The recruitment rate (ratio of centers who declared their agreement to participate/number of responses) was 100%. The completion rate (ratio of respondents who finished the survey/respondents who started the survey) was 100%. Completeness check was performed by survey investigators and detected < 5% questionnaire items blank.

Figure 1 provides a breakdown of ratios of activity across centers. Within 46 respondent centers, a median of 79 (range 10–345) liver resections per year was performed: among these, 29 (range 0–83) were major liver resections including a median of 9 (range 0–50) right hepatectomies/trisectionectomies. A median of 5 (range 0–27) patients/year per center were candidates to liver hypertrophy techniques. The weighted mean number of patients submitted to liver hypertrophy techniques was 8.92 per center. The raw ratio of patients receiving hypertrophy techniques/total number of liver resections was 6.1% (254/4184), while the ratio calculated according to weighted mean was 9.8%. The ratio of patients who dropped out from surgical program after being submitted to hypertrophy techniques was 20.1% (51/254). The weighted mean number of drop out per center was 1.87. Table 1 reports data regarding hypertrophy techniques within the annual caseload of activity. Reported

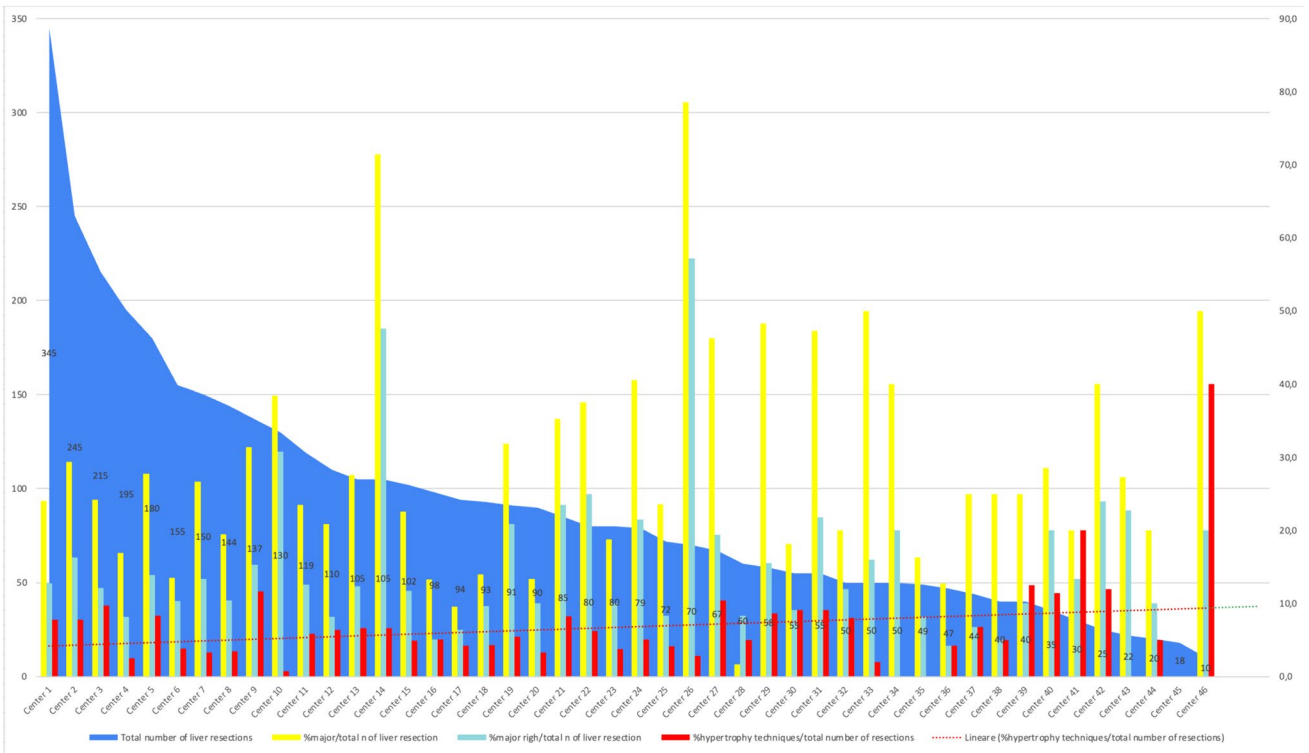

Fig. 1 Distribution of cases among participating centers

Table 1 Hypertrophy techniques within annual caseload of activity

Total number of liver resections	Median (range)	79 (10–345)
Total number of major liver resections	Median (range)	21(0–83)
Total number of right major liver resections	Median (range)	9 (0–50)
Total number of patients submitted to hypertrophy techniques	Median (range)	5 (0–27)
Total number of patients who dropped out	Median (range)	1 (0–5)
% of patients receiving hypertrophy techniques/total number of resections		6.2
% of patients receiving hypertrophy techniques/major liver resections		22.7
% of patients receiving hypertrophy techniques/major right liver resections		41.4
% drop out from surgical program after hypertrophy techniques		20.1

most frequent reasons for dropout were disease progression (57.1% of respondents) and inadequate hypertrophy (21.4%). Other reasons mentioned were surgical complications and general conditions of the patient.

93.5% of respondents stated that all patients were submitted to multidisciplinary discussion, while 6.5% discussed only selectively. 56.5% of centers had a specific institutional protocol of management for patients submitted to hypertrophy techniques.

Data regarding availability of each technique, as well as preferred and eventually abandoned techniques are reported in Table 2 and Fig. 2. Briefly, while 10 years ago PVE (54.3%) and PVL (52.2) were declared among preferred techniques by respondents, 5 years ago an increasing trend in ALPPS as preferred technique was reported (37% of respondents). Currently—while PVE maintains the role among preferred techniques in 73.9% of centers—an increasing rate of ALPPS (50%) and HVD (26.1%) among preferred techniques was registered. PVE, PVL and ALPPS are anyway currently available in > 85% of centers; HVD and radioembolization were available in 60.9% and 41.3% of centers, respectively. 30.4% of centers have abandoned the use of PVL. Figure 3 reports annual use of each single technique within the last year.

Table 3 reports cutoff volumes of FLR according to characteristics of liver parenchyma: heterogeneous answers were provided regarding the cutoff values to indicate the need for hypertrophy techniques in the healthy, steatotic and cholestatic liver (none of options getting > 50% of responses), while 86.7% of respondents indicated 40% as a safe cutoff volume in cirrhosis—see Fig. 4 for details. In 39.1% of centers volumetric evaluation was performed by radiologists, in 21.7% of centers by surgeons and in 37% of centers by both. Most frequently used formula to calculate FLR is FLR/mTLV (Total Liver Volume manually measured). Volumetric evaluations are performed both before hypertrophy technique and before surgery by 100% of centers, while functional evaluation is performed in both moments by 71.7% of respondents (15.2% perform functional evaluation only before surgery). While functional evaluation is performed from most centers (86.7%), the method of evaluation is heterogeneous (ICG, scintigraphy, MRI), as reported in Table 3. Biopsy of FLR is selectively performed to evaluate characteristics of liver parenchyma by 52.2% of centers. 56.5% of centers standardly perform an evaluation of the nutritional status of patients, 17.4% of centers do it selectively and 26.1% do not perform it at all.

Criteria to indicate PVE and HVD are reported in Table 4. 60.9% of centers perform segment 4 embolization in candidates to right trisectionectomy in selected patients. 31.8% of centers report a drop out rate < 20% after portal vein embolization and 52.9% a drop out rate between 0 and 5% after hepatic vein deprivation. Most centers (52.2%) report an interval of 4 weeks between portal vein embolization and surgery, while an interval HVD-surgery of 2 or 3 weeks is reported by 34.2% and 31.6% of centers, respectively.

Criteria to indicate TSH and ALPPS are reported in Table 5. 35.7% of centers report a drop out rate < 20% from TSH program and 33.3% a drop out rate between 0 and 5% during ALPPS. Within TSH program, technique for portal vein occlusion is PVE in 40% and PVL in 48.9% of centers; within ALPPS program, technique for portal vein occlusion is PVL in 56.8%, PVE in 13.6% of centers while it is defined case by case in 27.3% of centers. 46.7% of centers define an indication to complete or partial parenchymal transection on a case by case discussion, while complete and partial transection are standardly performed by 24.4% and 28.9% of centers, respectively. While minimally invasive approach is not reported from 55.6% of centers, 15.6% of centers consider it only for stage 1 and 28.9% for both stages.

Radioembolization is used as a bridge to surgery technique to induce liver hypertrophy in 41.3% of centers.

100% of respondents acknowledge the need and express their willingness to participate in the prospective national registry about hypertrophy techniques.

Table 2 General preferences and time-trends

		N	%
Multidisciplinary discussion	Always	43	93.5
	Only selected patients	3	6.5
	No	0	0
Internal protocol for patient management	Yes	26	56.5
	No	20	43.5
Available techniques	PVE	43	93.5
	PVL	41	89.1
	ALPPS	41	89.1
	HVD	28	60.9
	Radioembolization	19	41.3
	Other variants	3	6.6
Preferred technique	PVE	34	73.9
	PVL	13	28.3
	ALPPS	23	50
	HVD	12	26.1
	Radioembolization	2	4.3
	Other variants	4	8.6
Preferred technique 5 years ago	PVE	38	82.6
	PVL	23	50
	ALPPS	17	37
	HVD	0	0
	Radioembolization	2	4.3
	None	3	6.5
	Other variants	0	0
Preferred technique 10 years ago	PVE	25	54.3
	PVL	24	52.2
	ALPPS	0	0
	HVD	1	2.2
	Radioembolization	0	0
	None	7	15.2
	Other variants	0	0
Abandoned techniques	PVE	2	4.5
	PVL	14	31.8
	Two stage hepatectomy	3	6.8
	ALPPS	1	2.3
	HVD	0	0
	Radioembolization	1	2.3
	None	28	63.6

Discussion

The Italian national survey shows the consolidated role of hypertrophy techniques as an integral part of the clinical practice of centers with dedicated activity of liver surgery, regardless of the annual caseload. The availability of surgical and interventional radiology techniques throughout the country witnesses the constant attention to the issue of controlling the risk of postoperative liver failure. In fact, this issue concerns a significant proportion of patients—mainly undergoing major or extended right-sided resections—and overall 6.2% of patients undergoing liver resections in 2022. Although PVE remains the standard preferred by 73.9% of centres, more recently described techniques such as ALPPS and HVD are available in most centers. A significant heterogeneity is instead found both in terms of indications for the use of the techniques (cutoff volumes depending on the characteristics of the parenchyma), in the choice of the technique to be used (and in particular there are heterogeneities in the criteria identified as significant in the choice) and use of liver function study methods.

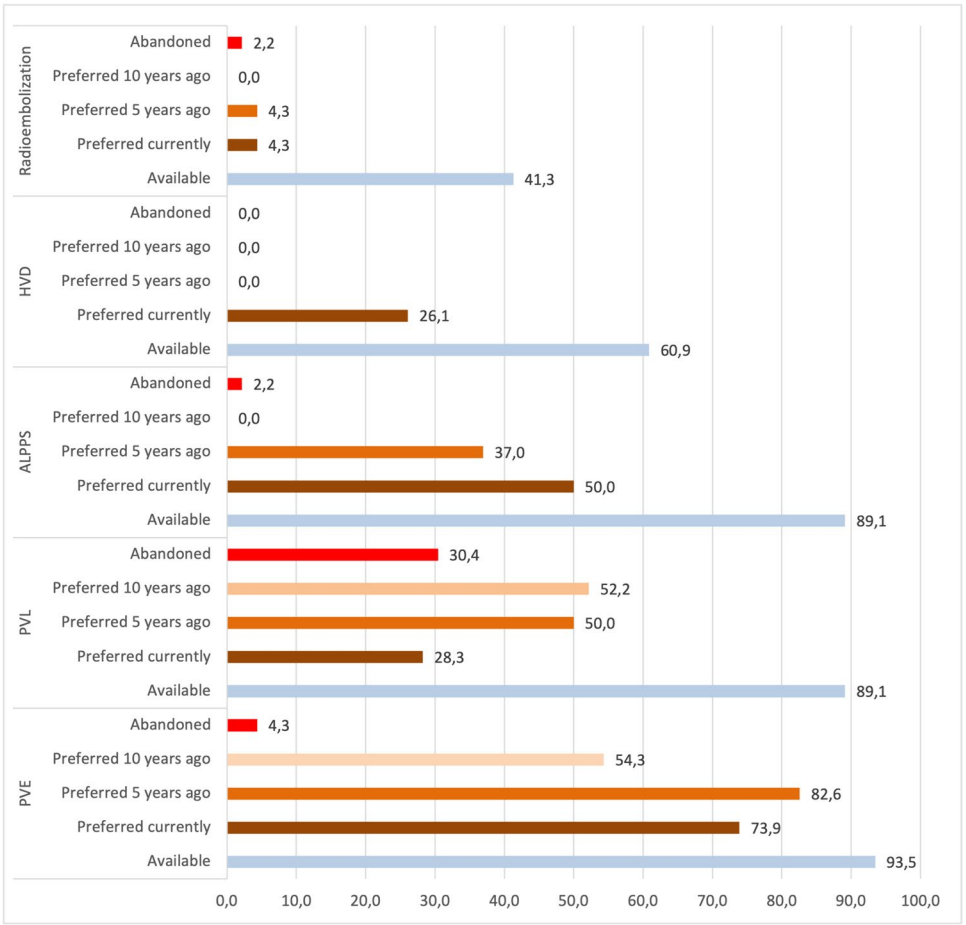

Fig. 2 Answers provided regarding preferred and abandoned techniques

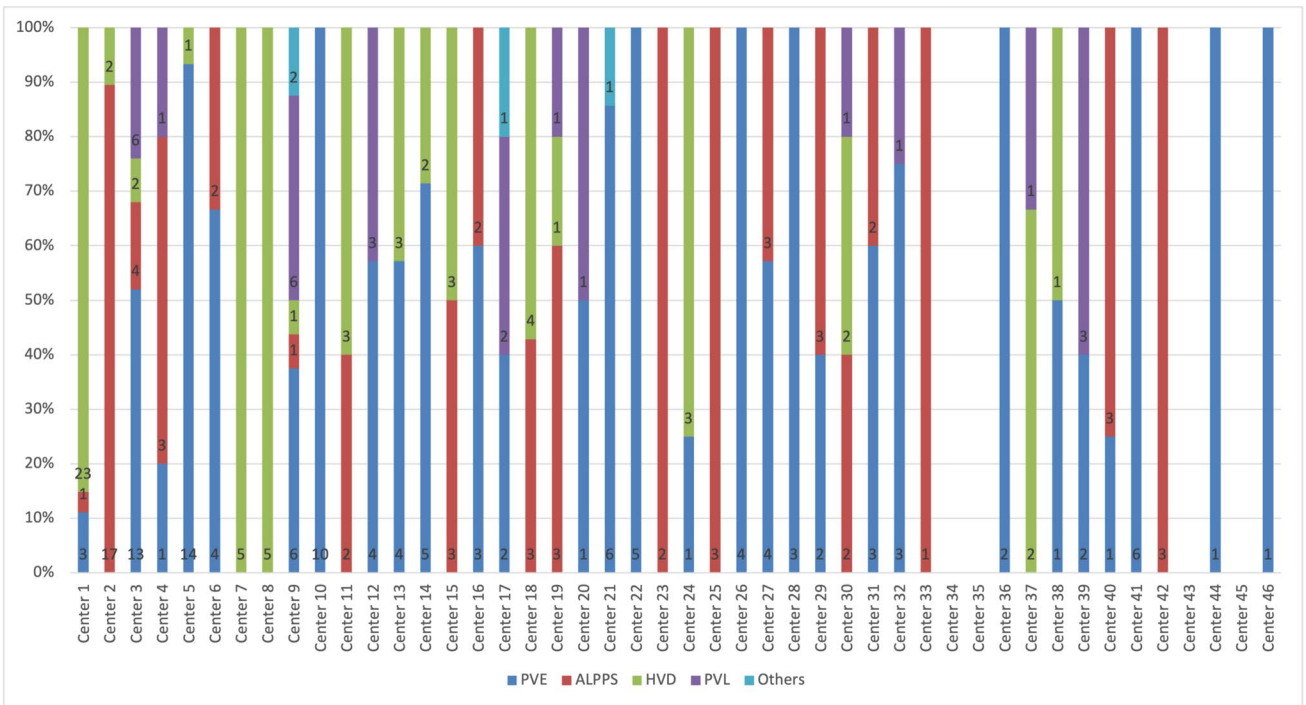

Fig. 3 Use of techniques among participating centers

Table 3 Indications for hypertrophy techniques

		N	%
Cutoff in healthy liver	> 20%	5	11.1
	> 25%	18	40
	> 30%	17	37.8
	> 35%	5	11.1
	> 40%	18	40
Cutoff in liver with steatosis/CALI	> 20%	0	0
	> 25%	1	2.2
	> 30%	16	34.8
	> 35%	20	43.5
	> 40%	9	19.6
Cutoff in liver with cirrhosis	> 20%	0	0
	> 25%	0	0
	> 30%	1	2.2
	> 35%	5	11.1
	> 40%	39	86.7
Cutoff in liver with cholestasis	> 20%	0	0
	> 25%	0	0
	> 30%	13	28.9
	> 35%	17	37.8
	> 40%	15	33.3
Formula used to measure FLR	FLR/sTLV	4	8.7
	FLR/mTLV	29	63
	FLR/BW	12	26.1
	Unknown	1	2.2
Evaluation of liver function	No (Only blood tests)	15	32.6
	ICG	17	37
	Hepatobiliary scintigraphy	7	15.2
	Functional MRI	5	10.9
	Other	2	4.3

It is reasonable that—precisely because of this heterogeneity and the lack of a uniform attitude—100% of the Italian liver surgery centers consider it useful to develop and implement a prospective registry dedicated to hypertrophy techniques, which also underpins the creation of a network.

A recent meta-analysis specifically targeting the topic of comparison between HVD and PVE in terms of achievement of resectability in the setting of colorectal liver metastases concluded that HVD seems to perform better than PVE, allowing faster and higher volume increase while maintaining a comparable safety profile [11]. These results—although based on a moderate/low level of evidence—seem to be perceived in Italian centers where, in a relatively short distance compared to the first reports in the literature (it was in fact described by Guiu in 2016 [19] and the first series only appeared from 2017 onwards [26] 60.9% of the centers currently have this interventional radiology technique available, although it is counted among the preferred techniques only by 26.1% of the centres. This could at least partially explain a still significant dropout rate (20.1%)—linked as the main reason to disease progression before surgery: it is instead possible that with the large-scale diffusion of hypertrophy methods that induce rapid parenchymal growth, this drop out can shrink. Indeed, in the first Italian report of the ALPPS Registry—published in 2016—the completion rate of the surgical program was 100%: however this series still belongs to an initial phase of the ALPPS technique, when the indications were in an exploratory phase and the morbidity and mortality still significant (major morbidity 54%, mortality 20%) [23]. In the period following these data—albeit within variations related to the experience of individual centers—the perioperative outcomes described for ALPPS have globally improved, especially in high-volume centers [27].

In Italy—where ALPPS is indicated among the techniques preferred by a growing proportion of centers—this trend is confirmed, in parallel with the refinement of technique and technology. In fact, currently 46.7% of the

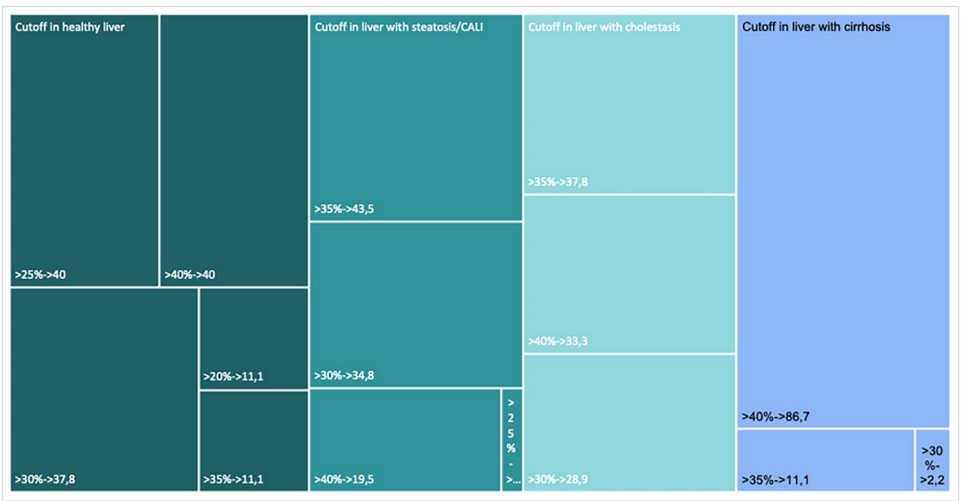

Fig. 4 Cutoffs used to indicate the need for liver hypertrophy techniques according to characteristics of the liver parenchyma

Table 4 Portal vein embolization, hepatic deprivation and radioembolization

PVE			
		N	%
Criteria for indication	Diagnosis	11	23.9
	Lesions distributiom	27	58.7
	FLR volume	44	95.7
	Proximity of lesions to FLR	10	21.7
	Failure of other techniques	3	6.5
	Others	2	4.4
Access for PVE	Ipsilateral	30	65.2
	Controlateral	5	10.9
	Ileocolic	0	
	Unknown	11	23.9
Embolization of Sg4 before right trisectionectomy	Always	7	15.2
	Selectively	28	60.9
	Never	11	23.9
Drop out risk estimation after PVE	0		
	0–5%	2	4.5
	5–10%	8	18.2
	< 20%	14	31.8
	20–40%	5	11.4
	> 40%	5	11.4
HVD			
Criteria for indication	Diagnosis	5	12.5
	Lesions distributiom	13	32.5
	FLR volume	26	65
	Proximity of lesions to FLR	6	15
	Failure of other techniques	17	42.5
	Others	2	5
Drop out risk estimation after HVD	0		
	0–5%	9	52.9
	5–10%	6	35.3
	< 20%	1	5.9
	20–40%	1	5.9
Radioembolization as a bridge to resection	Yes	19	41.3
	No	27	58.7

centers define the need to use a complete rather than a partial parenchymal transection on a case-by-case basis, while 28.9% of the centers use the partial transection technique in a standard way, described to reduce the biological load of the first surgical time by reducing therefore the risk of morbidity without paying the price in terms of hypertrophy, as documented also in a meta-analysis published in 2019 on 4 studies including a total of 124 patients [28]. Furthermore—again aiming to increase protection from surgical stress and control the risk of morbidity—in Italy, there is an increasing use of the minimally invasive technique (from the data of this survey, it emerges that 15.6% of the centers reserve the laparoscopic or only in the first surgical stage, while 28.9% of the centers use it for both stages): in a series from the Italian ALPPS registry and including only the data relating to hepatocellular carcinoma, it already appeared that the minimally invasive approach—even if only applied in the first surgical phase—manages to reduce the overall risk of liver failure [29].

The awareness and perception of the importance of the preoperative study of liver function (and not only of the volume) to confirm the indication to induce preoperative hypertrophy is also deep-rooted and widespread. In fact, 86.7% of the centers currently adopt on a standard basis methods for evaluating liver functional reserve, mainly implementing tests based on the use of indocyanine green, hepatobiliary scintigraphy and functional magnetic resonance, with an extremely heterogeneous distribution. In fact, the data currently available in the literature are equally heterogeneous, generally based on comparative evaluation series of

Table 5 Two stage hepatectomy and ALPPS

Two-stage hepatectomy			
		N	%
Criteria for indication	Diagnosis	17	37
	Lesions distribution	37	80.4
	FLR volume	41	89.1
	Proximity of lesions to FLR	14	30.4
	Failure of other techniques	8	17.4
	Others	0	
Drop out risk estimation after PVE	0		
	0–5%	3	7.1
	5–10%	10	23.8
	< 20%	15	35.7
	20–40%	5	11.9
	> 40%	2	4.8
Technique for portal vein occlusion	PVE	18	40
	PVL	22	48.9
	HVD	5	11.1
ALPPS			
Criteria for indication	Diagnosis	17	37
	Lesions distributiom	33	71.7
	FLR volume	42	91.3
	Proximity of lesions to FLR	20	43.5
	Failure of other techniques	20	43.5
	Others	1	2.2
Drop out risk estimation after PVE	0	9	21.4
	0–5%	14	33.3
	5–10%	9	21.4
	< 20%	5	11.9
	20–40%	2	4.8
	> 40%	3	7.1
Technique for portal vein occlusion	PVE	6	13.6
	PVL	25	56.8
	HVD	1	2.3
	Defined case by case	12	27.3
Parenchymal transection in ALPPS	Complete	11	24.4
	Partial	13	28.9
	Defined case by case	21	46.7
Minimally-invasive approach for ALPPS	Not performed	25	55.6
	Considered only for stage 1	7	15.6
	Considered for both stages	13	28.9

one method with respect to another; however, there is still a complete lack of recommendations and guidelines on which tests to use, on indications and on timing [30–33]. Even though ICG was the most used technique reported by centers to measure liver function preoperatively, most of the studies published in this regard all agree on the fundamental role of hepatobiliary scintigraphy to measure sectorial liver function before extended hepatectomies and in particular after hypertrophy techniques [32, 33]. It is possible that in the immediate future surgical community should therefore move in two directions: on one hand further study of the characteristics, limits and cutoffs of each functional study technique, reasonably providing a stratification based on the disease is advisable; on the other hand the definition of a shared attitude that provides guidelines depending on the disease, the residual liver volume and the parenchymal function will represent a watershed for the evolution and implementation of these techniques.

To achieve this second objective, the creation of a national network based on the foundation of a registry to serve as a collector to prospectively develop study projects and for peer-to-peer discussions is certainly a milestone point. In fact, the dissemination and sharing of a specific culture within a community improves clinical results and allows easier achievement of desirable benchmarks.

As reported in methods session, no minimal threshold regarding case volume was set for survey inclusion, enabling centers to be considered irrespectively of their experience. This design was chosen to provide a reliable snapshot of the Italian situation and to pave the way for the establishment of a national registry that should have no defined volume cutoffs and no pre-determined management protocols. The issue of centralization and minimum requirement for annual caseload of activity—as well as a standard ratio between volume of liver resections and percentage of major hepatectomies—is beyond study aims, despite this, it is interesting to underline that the establishment of a prospective national registry may positively contribute to promote the diffusion of cultural background in this setting within the network of liver surgeons, aiming to establish the minimum requirements to perform these procedures safely and to define correct indications to major resections and to hypertrophy techniques as well.

The present study has the limitation of being based on the results of an individual survey, which consequently is unable to follow trends in real time or over short periods of time and to measure changes in the population (unless two or more surveys are done at different points in time).

Unlike the majority of the surveys, however, the population to which the questionnaire was distributed can be easily described and is definitively representative of the Italian scenario: this constitutes a point of strength of the study. The other limitation is the availability of cumulative results coming from the experiences of individual centers, rather than having detailed data available.

In conclusion, the use of liver hypertrophy techniques is now well established in Italy, in consideration of the attention to the issue of increasing the chances of resectability for primary and secondary liver tumors in parallel with the control of the risk of liver failure. The technical and technological evolution is perceptible and documentable, even within the inevitable differences and heterogeneity of attitudes in terms of indications, cutoff values and management protocols.

The present scenario, developed on a history of centers with dedicated expertise, paves the way for the I GROWtoH prospective national registry, contributing to the implementation of a peer network to enhance safety and effectiveness of these approaches, together with the possibility of analyzing specific outcomes on wide cohorts.

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Data availability The data that support the findings of this study are available from the corresponding author, FR, upon reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval All procedures perfomed in studies involving human participants were in accordance with the ethical standards of institutions and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent from subjects was waived.

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