Chapter 8

The Role of Ultrasound in Hepatic Surgery

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1. Introduction

The first experiences of ultrasonography (US) during surgical operations dated at the first years of the sixties, when some surgeons employed ultrasound in order to identify urinary or biliary stones [1,2]. These experiences gave birth to 2 important areas of application of ultrasound in the surgical field: intra-operative ultrasonography (IOUS) and interventional ultrasonography.

The first reports concerning the usage of IOUS in liver surgery dated at 1980-81 [3,4].

Hepatic surgery became the most important field of development of IOUS and nowadays the ultrasounds are employed for several goals: the precise localization of lesions and their relationship with surrounding biliary and vascular structures, the examination of the liver anatomy in order to plan the surgical strategy in respect of the oncologic principles, the intra-operative re-staging with identification of new nodules.

In 1968 Gramiak and Shah firstly introduced the ultrasound contrast agents (USCA); later, the introduction of ultrasound contrast agents for the study of the liver in 1999 [5], and then the intra-operative contrast enhanced ultrasound (CEIOUS) [6] offered further development to this important technique.

Nowadays the IOUS is considered an invaluable tool for hepatic surgery and its usage should be considered mandatory. CEIOUS demonstrates great potentialities but its role has not been established yet, even considering recent developments of multi-slice computerized tomography and magnetic resonance with liver-specific contrast agents.

2. IOUS and CEIOUS: Technical aspects

If compared to the trans-abdominal conventional US, IOUS offers several advantages. First, the higher resolution of the ultrasonographyc images, because the probe is in direct contact with the liver avoiding the absorption of acoustic waves by the abdominal wall. Second, during conventional US the liver has to be "spied" within the acoustic windows (es: transcostal), meanwhile during IOUS the proper intra-operative probes [Fig 1] can be placed in contact with the anterior, superior, inferior or posterior liver surface and a lesion can be studied from different point of view; consequently, IOUS performed after liver mobilization offers much more information. Third, during IOUS, information obtained with the ultrasound study and information gained by inspection and palpation can complement each other.

Figure 1. Intra-operative ultrasound probe

The non-panoramic nature of the study represents the main limitation of every US examination, included the IOUS. A great attention should be paid to examine the whole liver parenchyma, avoiding to leave some portion of the liver unexplored. For this reason, information gained by IOUS should always be integrated with the ones obtained from the pre-operative and panoramic study like computerized tomography (CT) and magnetic resonance (MR).

Before IOUS of the liver, partial hepatic mobilization with section of the round and falciform ligaments is always suggested.

Firstly, the liver should be explored using a standard convex (frequencies: 3.75-10 MHz) or micro-convex probe (frequencies: 3.75-10 MHz), in order to obtain a wide ultrasonographyc imaging. The probe should be initially placed between segment 4a and 4b to visualize the hepatic hilum, and then moved on the liver surface evaluating presence of eventual anatomical abnormalities of portal, arterial or biliary pedicles and of sub-hepatic venous system. Then the liver should be explored and mapped searching for focal lesions; precise localization of the lesions detected at pre-operative staging must be confirmed and new lesions must be mapped. A standardized sequential study of each segment is suggested for that, avoiding to leave unexplored portion of liver.

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Afterwards, when indicated, the CEIOUS can be performed; main goals of the CEIOUS are characterization of lesions of uncertain nature and detection of new lesions not previously visualized.

The contrast agent (example: 4.8 ml of Sulfur Hexafluoride) has to be injected in a peripheral vein (cannula of 21 gauge or larger) and the arterial, portal and late phases are monitored (CEIOUS phases are reported in Table 1 and Figure 2); if necessary the USCA can be repeated twice.

Phase	Time (seconds)
Injection	0
Arterial phase	10-45
Portal phase	45-90
Late phase	90-240

Table 1. CEUS and CEIOUS vascular phases

The main advantage of the trans-abdominal contrast enhanced ultrasound (CEUS) and of the CEIUOS is that they allow a continuous real-time imaging; consequently they offer much more information for characterization of nodules than contrast-enhanced CT and MR, whose main limitation is that they are non-continuous techniques.

3. CEIOUS: The contrast agents

The acoustic difference between the intra-vascular gas microbubbles and the surrounding blood and tissues represents the basis for use of ultrasound contrast agents (USCA). The gas content of first-generation USCA (eg: Levovist, Schering AG, Berlin, Germany) is air, and the outward diffusion of air results in a relatively rapid decrease in the acoustic reflection and hence limited clinical utility. The stability of newer USCA like Optison (GE Healthcare, Amersham, Buckinghamshire, England), SonoVue (Bracco, Milan, Italy), and Definity (Bristol-Myers Squibb, Billerica, MA) is achieved by use of highmolecular-weight gases, and the slower outward diffusion of these gases makes such second generation USCAs more effective and long lived in the vascular system.

In recent years microbubbles taken up by Kupffer cells, thus possessing a "post-vascular" phase, were registered as a new second-generation USCA in Japan (Sonazoid, GE Healthcare). During the post-vascular Kupffer-phase, the tumour appears as a contrast defect image due to the lack of Kupffer cells and can consequently be characterized.

The usage of some USCAs is not approved in Italy, and authors' experience hare reported is limited to the Sulfur Hexafluoride (SonoVue, Bracco, Milan, Italy).

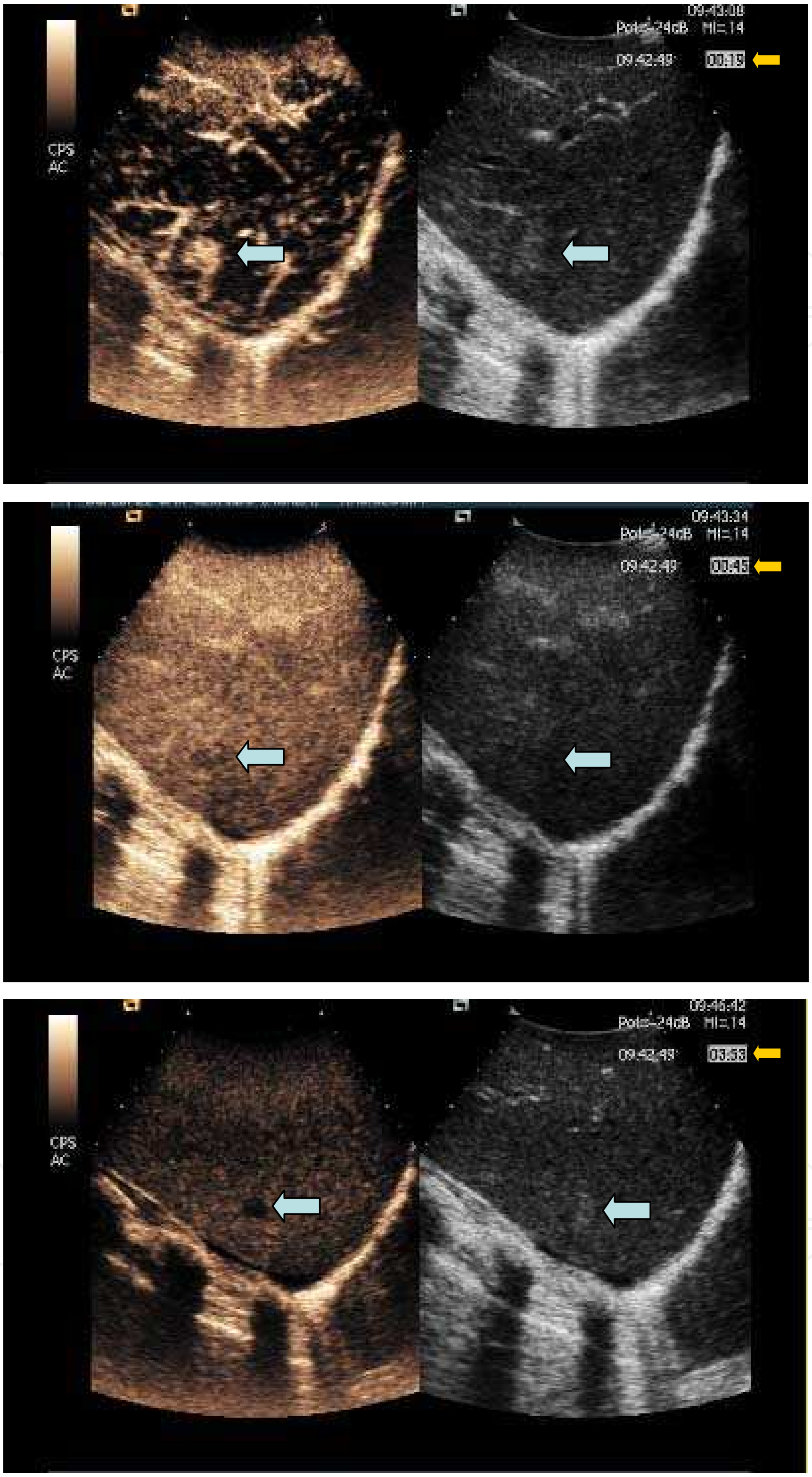

Figure 2. This picture shows a colorectal liver metastases (indicated by azure-blu arrows) in the arterial, portal and tardive phases (time passes form the injection of contrast agents is indicated by yellow arrows) during an contrast-enhanced intra-operative ultrasound study.

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4. IOUS and CEIOUS: The intra-operative re-staging

Nowadays, IOUS is still considered the most accurate diagnostic technique for detecting focal liver lesions [7,8]. Nevertheless, it's remarkable that recent technical ameliorations in radiology allowed better outcomes in terms of sensitivity and specificity regarding the detection of primitive and metastatic liver lesions. In particular, the recent availability of multidetector-row Computerized Tomography (CT) with more than 64 channels and of liver specific contrast agents in Magnetic Resonance (MR) represent a great improvement in the diagnostic accuracy of liver tumours.

Hepatocellular carcinoma (HCC) and colo-rectal liver metastases (CRLM) represent the most common malignant liver lesions and the most common indication to liver resection worldwide, and consequently in this chapter the attention will be focused to the staging of these tumours.

4.1. Colorectal liver metastases

Concerning the detection of synchronous liver metastases, the contrast enhanced CT is reported to have a sensitivity and the specificity of respectively 64-72% and 64-72% [9,10], although some recent studies conducted on smaller populations showed values of sensibility of 71.7–92% [11-14]. On the other hand, concerning the detection of metachronous liver metastases, the efficacy of contrast enhanced CT revealed to be unimpressive in term of sensibility [15].

MR showed sensibility ranging from 42 and 100%; the sensibility of MR with liver-specific non-superparamagnetic contrast agents ranges between 64 and 98%, resulting generally superior when compared to the sensibility of CT scan, and a specificity of 75-79% [16-20].

In literature the data regarding the sensibility of the Positron Emission Tomography (PET) – CT appear contrasting, meanwhile the specificity is considered higher than the ones obtained by contrast enhanced CT and MR [21-23].

The trans abdominal CEUS showed high values of sensibility (80-98%) and specificity (66%-98%) for the detection of CRLM; for lesions larger than 20 mm, when sulphur-hexafluoride microbubbles (SonoVue®, Bracco, Milan, Italy) SonoVue is employed as contrast agent, the sensibility is 100% and consequently superior to conventional ultrasound and comparable to contrast enhanced CT [24-29]. It's remarkable that the studies included in these reviews regard mostly comparisons between different radiologic techniques without the anatomo-pathologic or follow up data.

Several studies demonstrated that IOUS of the liver is useful for the intra-operative re-staging of patients undergoing to liver resection for CRLM [7,8] and of patients undergoing to colorectal resection of the primitive neoplasm even in absence of liver lesions detected during pre-operative work-up [30-31]. The superiority of the IOUS compared to pre-operative studies in terms of sensibility leads to a modification of the surgical strategy [32]. The main limitation of the IOUS is the difficult characterization of the nodules; it has been ridden out after the introduction of the USCAs.

Several studies demonstrated that the CEIOUS is the most accurate diagnostic technique for detection and characterization of liver nodules; both the sensibility and specificity of CEIOUS in studies based on the comparison with other diagnostic techniques like CT and MR rises up to 100% and downsize the diagnostic accuracy of the pre-operative staging and even of the IOUS [33-37].

Preliminary results of a prospective study [59] based on the comparison among CEIOUS, CEUS, CT and RM with liver-specific contrast agent for the detection of liver metastases in patients submitted to colorectal resection for cancer, showed that CEIOUS has higher sensibility and specificity when singularly compared to any other pre-operative technique [Table 2]. These results are consistent with the ones previously published in similar setting of patients. In this survey, when the pre-operative work up is analysed on the whole (CT + RM + CEUS), CEIOUS did not offer an amelioration in terms of sensibility but showed an increased value of specificity for better characterization of liver lesions. Moreover, the CEIOUS modified the surgical strategy in 44.4% of patients even when the pre-operative work up is analysed on the whole (CT + RM + CEUS).

	TC	RM	CEUS	CEIOUS
Sensibility	80%	90%	80%	100%
Specificity	93%	79%	100%	100%

Table 2. Sensibility and specificity of CT, RM, CEUS and CEIOUS

Consequently, all patients undergoing liver resection for CRLM and all patients undergoing colorectal resection for cancer should be submitted to IOUS of the liver; moreover, among these patients, all the ones studied during the pre-operative staging with only one radiologic technique, all the ones studied with more than one technique reporting contrasting results and all the ones with new hepatic nodules during IOUS should be submitted to CEIOUS.

4.2. Hepatocellular carcinoma

Studies regarding the accuracy of pre-operative radiologic examinations for HCC assessed values of sensitivity and specificity of 60-93% and 50-95% for CT and of 52-100% and 42-97% for MR respectively; regarding the RM the best results have been obtained employing liver-specific contrast agents [39-40]. On the other side, it's remarkable that the studies included in these reviews regard mostly comparisons between different radiologic techniques without the anatomo-pathologic or follow up data.

Several studies reported that IOUS detects additional nodules in 33-41% of patients undergoing liver resection for HCC [41-43]. In cirrhotic patients with HCC, IOUS is a useful tool to detect new nodules but cannot differentiate malignant lesions from other liver nodules which account for 70–80% [44]. In fact, the risk nowadays is to overestimate the tumour stage with IOUS or laparoscopic ultrasonography considering that, except for those nodules with mosaic ultrasonographic pattern which are malignant in 84% of cases, only 24–30% of

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hypoechoic nodules, and 0–18% of those hyperechoic are malignant [45]. To overcome this problem even biopsy seems not to be adequate. When sulphur-hexafluoride microbubbles (SonoVue®, Bracco, Milan, Italy), the CEIOUS analysis of nodules vascularization may provide crucial information for their differentiation.

In this sense, Torzilli et al proposed in 2007 [41] a classification for the patterns of enhancement during CEIOUS in 4 categories: A1 (full enhancement in the arterial phase and washout in the delayed phases), A2 (intralesional signs of neovascularization during all phases), A3 (no nodular enhancement but detectability during the liver enhancement), and B (undetectability during the liver enhancement). Following this classification, resection is recommended for A1-3 nodules for high risk of malignancy and no treatment is recommended for B nodules.

With its intra-operative re-staging, CEIOUS shows sensibility of 100%, specificity of 69-100% and can modify the surgical strategy up to 79% of patients [41-43]. All patients undergoing liver resection for HCC should be submitted to IOUS; moreover, all the patients carriers of liver tumours of uncertain differentiation at pre-operative work up and all patients with new nodules at IOUS should be submitted to CEIOUS.

5. Echo-guided liver resection

The modern liver surgery is based on two concepts: a liver resection has to be radical following the oncologic principles and has to be conservative in a parenchyma sparing policy [46]. Consequently the exact resection plane should be carefully planned before the resection using the invaluable ultrasound guidance.

An ultrasound probe is placed on the liver surface and the target lesion to be removed has to be visualized. The surgeon draws on the liver surface the resection plane that includes the tumour; this procedure is simplified by the usage of a linear probe, because if the acoustic waves are parallel, to define the projection of the lesion or of the resection's area on the liver surface is easier (Fig). After that, the parenchymal transection can start, but during the resection the echo-guidance should be used to check if the resection plane is correct or has to be modified.

It's remarkable that the oncologic principles those have to be respected can vary depending on the type of liver tumour.

In presence of CRLM, the most important aspect regards the tumour margin. Positive hepatectomy margin has been indicated as an independent negative prognostic factor for carriers of CRLM [47], but the minimum safe width of free margin has to be established yet. Data regarding the presence of micro-metastases around CRLM are contrasting, reporting rates of micro-metastases ranging from 2% to 58% of patients; consequently, these authors suggested different widths of free margin ranging from 2 to 10 mm [48,49]. If the presence of micrometastases around a CRLM could be related to the cytoreduction after some type chemotherapy has to be clarified yet. The rate of cut edge recurrence is reported to be up to

13.3% for a margin inferior to 2 mm, but if the surgical margin could represents a prognostic factor for patients survival is still debated [48,49]. Anyway, all the authors agree that micrometastases are confined to a short distance from the tumour (mostly less than 5-10 mm) and that a tumour margin of 10 mm is safe without risk of cut-edge recurrence. The more reasonable approach for carriers of CRLM should be to guarantee a 10 mm margin when possible, so the surgeon during the echo-guided definition of the resection plane should consider this margin. Anyway, because liver resection plus chemotheraphy provides the best chance of cure for carriers of CRLM, complete removal of the tumour with a minimum margin (even less than 2 mm) is justified when technically unavoidable for tumours size, location or number. This aspect is of paramount importance in presence of tumours next to or in contact with major vessels; in these cases, in absence of clear signs of vascular invasion at the IOUS, the vessel resection and consequent major liver resection should be avoided, offering with a parenchyma sparing policy lower post-operative morbidity and mortality. Moreover the avoidance of major hepatectomy allows the possibility of further repeated hepatectomies in patients with disease recurrence, those have shown similar morbidity and mortality compared to first hepatectomy [50].

In presence of HCC, the most important aspect regards the type of surgical resection to be performed, anatomic or non-anatomic. Anatomic resection should be considered the gold standard approach for liver resection in patients with HCC, meanwhile non-anatomic resection should be indicated only in selected patients with HCC set on cirrhosis with poor liver function. Indeed, tumour dissemination from the main lesion through the portal branches demands an anatomic approach with removal of at least the portal area which includes the lesion. The surgical margin per se does not represent a main aspect, because an anatomic resection (segmentectomy or sub-segmentectomy) can be considered adequate even in presence of a narrow margin, while a non-anatomic resection of a nodule with a 10 or even 20 mm margin could be inadequate if the portal branch feeding the nodule has not be removed. HCCs are usually associated with liver cirrhosis, and several series reported that liver resection in cirrhotic patients is related to not negligible postoperative mortality and morbidity [51,52]. The main problem to overcome when planning a surgical approach is to find a balance between the liver volume to be resected, which should be drastically reduced, and the need to perform, if possible, an anatomic resection. The use of IOUS as guidance is indispensable in this sense, but there are several methods up to now available for this procedure. The most diffused technique is the puncture technique proposed by Makuuchi et al in 1981 [53,54]. With this technique, the portal branch feeding the tumour to be resected is punctured under IOUS-guidance, through a free-hand technique or with a proper device, and then dye (usually indigo-carmine) is injected into the vessel while the hepatic artery at the hepatic hilum is clamped. The stained area becomes evident on the liver surface, it is marked with the electrocautery, and hepatic artery clamping is released. The main disadvantage of this technique, other than the quite high skill in puncturing millimetric vessels, is the fact that if the ink regurgitates or is injected into the wrong portal branch, it could be difficult to identify the proper area to be removed. Furthermore, clamping of the hepatic artery is recommended but not always feasible without the need for a hilar dissection to tape the vessel to be clamped. Other methods have been proposed such as a balloon catheter in-

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serted transhepatically to occlude the feeding portal branch [55], or, more recently, through the mesenteric vein [56]. Mazziotti et al. proposed for segment 8 resection the division of the liver along the main portal fissure, and subsequently to approach the segment 8 glissonian pedicle intraparenchymally [57]. Santambrogio et al. have even recently suggested ablation of the feeding portal and arterial branches [58].

More recently Torzilli et al. proposed the ultrasound-guided finger compression technique, consisting in the demarcation of the resection area (segmental either subsegmental) by IOUS-guided finger compression of the vascular pedicle feeding the tumor at the level closest to the tumour but oncologically suitable. This maneuver is constantly monitored in real-time by simply using the same IOUS probe and it is maintained until the surface of the targeted liver area begins to discolor and can be easily marked with the electrocautery [59]. Torzilli's technique offers several advantages, including the non-invasiveness (no intravascular catheter) and rapid reversibility, and consequently can be repeated if necessary.

In general, any other type of primitive or metastatic liver tumours, when a surgical treatment is indicated, can be managed by means of a surgical resection with adequate margins, but in literature data concerning other specific tumours are still lacking.

One more and recent application of IOUS in hepatic surgery concerns the management of liver tumours involving an hepatic vein (HV) next to the caval confluence. These lesions traditionally require a major hepatectomy, with resection of the involved vein and the portion of parenchyma drained by that vein. Nevertheless, as previously reported, morbidity and mortality after major hepatic resections are not negligible, especially in cirrhotic patients [51,52]. A careful intra-operative study of the liver anatomy can offer alternatives to major hepatectomy. In 1987 Makuuchi M et al. introduced a new hepatectomy procedure for resection of the right hepatic vein (when invaded by a tumour) and preservation of the inferior right hepatic vein, an accessory hepatic vein draining segment VI present in 20-25% of patients [60]. Then, in 2010 Torzilli et al. suggested a set of criteria to be met for a parenchyma-sparing liver resection in presence of liver tumours invading any HV at its caval confluence [61]. The criteria are based on the direct or indirect signs of presence of venous anastomoses connecting adjacent HV, those had been previously highlighted in 1958 by Couinaud C et al. during studies performed on liver specimens [62] and can now be detected intra-operatively during IOUS [63].

A segment of a HV can be resected while avoiding the removal of the complete portion of the liver drained by that vein when, during HV finger compression at the hepatocaval confluence, at least one of these criteria is satisfied:

1. Reversal flow direction in the peripheral portion of the hepatic vein to be removed, which suggests drainage through collateral circulation in adjacent HV or inferior cava vein (IVC)

2. Hepatopetal flow in the portal branch feeding the areas to be spared

3. Detectable connecting veins with adjacent HV or IVC

It is remarkable how every surgical procedure performed on the liver is strictly dependent from the knowledge of the liver anatomy and from the ultrasounds; definitely in liver surgery the ultrasounds represent the link between the surgical anatomy and the surgical intervention.

6. Laparoscopic ultrasound

Due to improvements in technologies and increasing surgeon's experiences, the number of hepatectomy performed laparoscopically increased exponentially around the world in the recent years, and consequently the usage of laparoscopic ultrasound (LUS) of the liver [64]. Main goals of LUS are the same of ones presented in open liver surgery; anyway LUS has a few theoretical drawbacks if compared to traditional IOUS, including the difficulty in the ultrasound study of the superior and posterior segments and the limited diffusion of laparoscopic probe equipped for the contrast enhanced study.

Other indications to LUS include the re-staging before laparotomic liver surgery or before laparoscopic resection of gastrointestinal cancer (more frequently of colorectal cancer). Diagnostic laparoscopy combined with LUS is considered an adequate staging modality for primary liver malignancies and permits to avoid unnecessary laparotomies [65]. Nevertheless, the LUS seems to play a limited role in staging patients with potentially resectable CRLM candidates for open liver resection; this is owing mainly to the low sensitivity rate of 59% [66]. Consequently there may be a role for laparoscopy for diagnosing suspected peritoneal disease, but LUS should not be used routinely in patients with CRLM candidates for open liver resection.

The LUS of the liver at the time of primary resection of colorectal cancer is reported to yield more lesions than preoperative contrast-enhanced computerized tomography and could be considered for routine use during laparoscopic oncologic colorectal surgery [67].

One further indication for LUS is laparoscopic radiofrequency in patients carriers of HCC and not amenable to liver resection or percutaneous ablation; in these patients, LUS is an invaluable tool, either in the pre-treatment imaging to re-stage the patient, evaluate the relationship of the tumour with the surrounding structures and to guide the insertion of the electrode into the tumour, either for the post-treatment imaging evaluation [68].

7. Conclusions

Ultrasonography is an invaluable tool in hepatic surgery, either for the intra-operative restaging, either for the guidance during the surgical procedure. The only major drawback of this IOUS-guided liver surgery is the need for hepatic surgeons to be trained in the use of ultrasound. Indeed, to be fully profitable, IOUS and CEIOUS should be carried out by the surgeon himself who can then use the information obtained by the ultrasound exploration in a surgical perspective. Organization of a training program for liver surgeons is far from being carried out worldwide, but it should be considered a main goal for hepato-biliary surgeons, because the liver surgeons must be equipped with ultrasound skills as like as with surgical technical skills.

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