Intraoperative ultrasound in surgery for hepatocellular carcinoma

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Imaging-guided therapeutic procedures have modified the approach to HCC both introducing new treatment modalities and also changing the policy of hepatectomies. Indeed, with intraoperative ultrasonography (IOUS) it is possible to achieve better knowledge about tumor location and staging, also with the aid of contrast-enhanced IOUS. However, IOUS also allows to minimise the rate of major hepatectomies maintaining treatment radicality and widening the indication at surgery. Indeed, precise definition of tumor-vessel relationship, intrahepatic vessel distribution and color-Doppler analysis allows performing hepatectomies otherwise not possible. This so-called "radical but conservative" policy has allowed us a safe surgical approach with minimal mortality and major morbidity and effective local treatment with no tumor relapses at the site of the resection. Techniques for safe and radical IOUS-guided liver resections for HCC are here discussed.

KEY WORDS: Hepatocellular carcinoma, Intraoperative ultrasonography, Liver cirrhosis; Liver tumors.

Introduction

Hepatic surgery performed without a parenchyma sparing policy, carries relevant risks for patients' survivals due to the not negligible occurrence of postoperative liver failure. In particular, the coexistence of liver cirrhosis in most cases with hepatocellular carcinoma (HCC) has a considerable adverse effect on the surgical results: as a matter of fact, recent series are still associated with mortality rates above 5%, which is not negligible [1]. For this reason and for the broadening of ultrasound-guided percutaneous therapies [2], the surgical treatment of HCC has loosen its role of first choice treatment. However, the imaging techniques have been introduced also as aids for surgeons in performing liver resection. In fact, since early 80s, intraoperative ultrasonography (IOUS) in hepatic surgery in the case of liver cirrhosis started [3,4]. Now, liver resections can be carried out with no mortality even if cirrhosis is associated [5], combining the needs for oncological radicality and liver parenchyma sparing and this goal is mainly achievable because of IOUS [6,7]. Recently, the demonstration of feasibility and efficacy of contrast-enhanced ultrasonography performed intraoperatively (CE-IOUS) has furthermore stressed the relevance of IOUS guidance during liver surgery [8-11]. In this chapter, the impact of IOUS during surgery for HCC both for staging and resection guidance are discussed; for surgical anatomy, the Brisbane Terminology is here considered [12].

Liver exploration

Nodule Detection and Differentiation

Hard and irregular surface of cirrhotic liver makes difficult the detection of small nodules by palpation; IOUS allows the detection of new lesions in around 30% of

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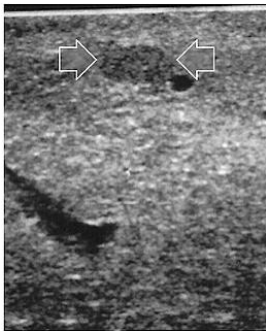
cases [13]. As a consequence of that IOUS exploration of the liver could have a great impact on the surgical strategy; however, more recently impact of IOUS on the operative decision making, when compared with those of preoperative imaging techniques, is reported to be just around 4-7% [14,15]. The problem of the impact of IOUS on the operative decision making depends on two main factors: the surgical policy of each specific team, and the type of tumor. Indeed, the relatively low rates reported [14,15] are also partially motivated by the surgeon's surgical policy: in fact, since a considerable number of patients undergo major hepatectomies, new nodules detected by IOUS in the same hemiliver would have not modified the surgical strategy. Recently, it is shown how major hepatectomies are carried out in the minority of patients [6,7] just because of the extensive use of the IOUS-guidance for achieving parenchymal sparing resections, so that detection of new nodules is more suitable for changing the surgical strategy. Furthermore, most of the patients of the series in which IOUS impact on surgical strategy is less relevant [14,15], were patients who underwent surgery for metastatic disease: in these conditions, historically, IOUS has always had a fundamental role in detecting undiscovered fore-sites [16], and objectively this role may have been influenced by the progresses obtained with the preoperative imaging, although experiences with contrast enhanced IOUS (CEIOUS) in surgery for colorectal cancer (CRC) liver metastases is suggesting a still important role of IOUS also in this sense [10]. Inversely, during surgery for HCC, IOUS allows detection on many nodules in the cirrhotic liver but the minority of them is really a tumor adding the risk to overestimate the tumor stage and making prevalent in these patients the problem of the differentiation of the lesions depicted at IOUS exploration. Indeed, except for those nodules with mosaic ultrasonographic pattern which are malignant in 84% of cases, only 24-30% of hypoechoic nodules, and 0-18% of those hyperechoic are neoplasm [13,17] (Fig. 1 a-c). To overcome this problem even biopsy seems to be not adequate. The only nodule which can be easily differentiated intraoperatively from a HCC or a liver metastases is the small hemangioma which is often discovered primarily at IOUS: it has a typical ultrasonographic pattern and moreover when compressed changes its size and appearance. Further improvement in differential diagnosis of liver nodules with IOUS may be expected by the introduction and diffusion of the intraoperative use of the last generation contrast agents.

Contrast Enhanced Intraoperative Ultrasonography

More recently the introduction of CE-IOUS has set the rate of modified operative decision-making on 30-42% of cases (8-11). Tumor vascularity as a criterion for differentiating the regenerative or dysplastic nodules from the HCC well correlate with the histological evidence of a progressive increase in unpaired arteries from dysplastic to neoplastic nodules in a cirrhotic liver [18]. Certainly, the pattern of vascular enhancement is not sufficient for differentiating malignant from non malignant nodules in a cirrhotic liver with 100% specificity. However, CE-US provides differential diagnosis of FLL with a 95% specificity [19]; of course, must be considered that this last rate was referred to another type of lesion if compared to the target of CEIOUS. Indeed, the intraoperative exploration takes profit of the higher resolution of the ultrasonography done in direct contact with the liver. Therefore, the need of differentiating nodules detected at IOUS is mostly focused on lesions smaller than 1 cm: for these nodules the vascularity as criterion for differential diagnosis is less specific. However, some improvements compared with conventional IOUS could be expected. For this reason, in early 1990s attempts were made to use CE-IOUS using carbon dioxide as contrast material for IOUS, however, the need for arterial catheterization made this technique too invasive [20]. In our preliminary experience CE-IOUS provided remarkable findings, either by adding information on nodular vascularity in patients with HCC, or by detecting nodules that were not visible at IOUS, in patients with CRC liver metastases [9,10]. Focusing the attention on patients operated for HCC our preliminary experience showed results really encouraging [8]: however, they were related to a very limited number of patients, and data did not really meet with the expectancies showing too optimistic findings with 100% specificity. Therefore, we classified the CEIOUS pattern based on our preliminary experience and on what was reported in literature about the CE-US [11,19].


a)


b)

c)

Fig. 1: a) - a mosaic pattern lesion at IOUS (arrows);
b) a hypoechoic lesion at IOUS (arrows);
c) two hyperechoic lesions at IOUS (arrows).


a)

b)

Fig. 2: a) at IOUS a little hypoechoic nodule is found (arrows); b) at CEIOUS, the nodules is not anymore visible and than is classified as type B.

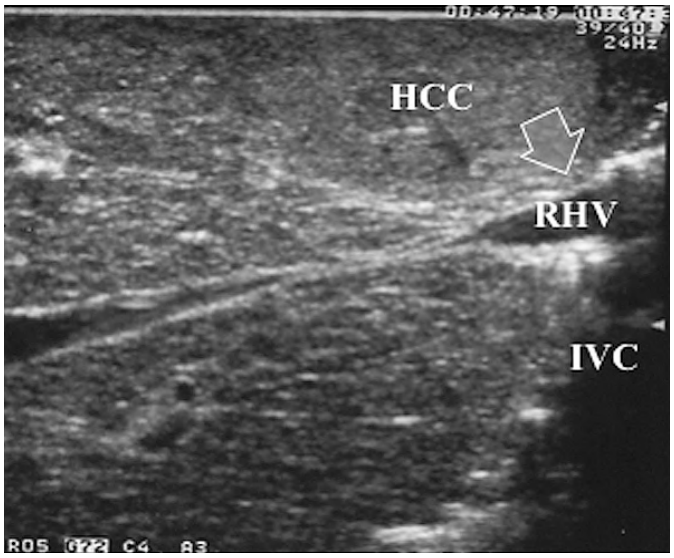


Fig. 3: this patient was carrier of a HCC in contact with the right hepatic vein (RHV) without sign of infiltration; the arrows are indicating site of tumor-vessel contact without RHV wall interruption. Operation consisted in a limited resection of segments 7 and 8 sparing the RHV.

Hypoechoic or hyperechoic nodules were considered malignant at CEIOUS if they:
1. showed a full enhancement (hyperechoic) in the arterial phase and became hypoechoic in the delayed portal and late phases (A1);
2. remained hypoechoic with thin vessels detectable into the nodule in the arterial and delayed phases (A2);
3. did not show any early enhancement but remained hypoechoic in the delayed phases without peripheral and/or intralesional neovascularization (A3), it was considered malignant and then removed.

If an hypoechoic or hyperechoic nodule had no early enhancement at CEIOUS and showed a hysoechoic pattern in all the phases in comparison with the surrounding liver parenchyma it was considered a non neoplastic lesion (Fig. 2 a,b). These last were not removed, and their benignity was confirmed after at least 6 months of follow-up if they were still not detectable at spiral CT.

Specificity of this classification criteria is in our experience 69% [11], which is certainly closer to the true performance of CEIOUS, rather than the results obtained at the initial experience [8]. This value is probably not that high especially when compared with that reported for CE-US [19]. However, as we aforementioned the small size of the lesions targeted for CEIOUS study could explain this discrepancy: for these tiny nodules the neovascularity as criterion for differentiation beween malignant and benign lesions has limits which are independent from the method we use for studying them. Therefore, CEIOUS can be helpful in a certain percentage of nodules but not in all: in this perspective the rate of 69% of specificity is encouraging as it means that we can provide proper information with this new technique in 7 out of 10 lesions we detect at the time of laparotomy. For the remnant 3 even histology may be lacking as we know that there is not a common agreement between Western and Eastern pathologists on the definition of early HCC and dysplastic lesions [18,21].

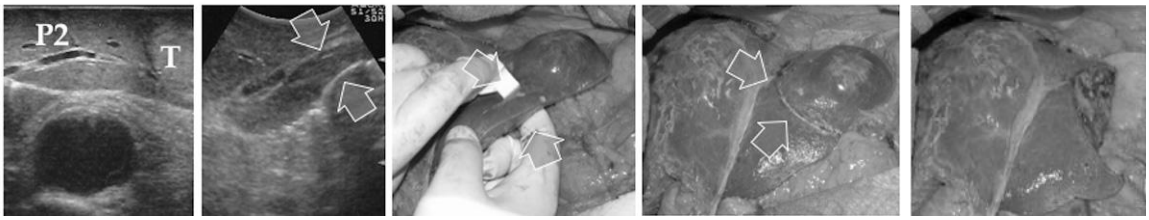
Tumor Location

IOUS allows an accurate three-dimensional reconstruction of the relationship between the tumor and the portal branches, and hepatic veins: this is a fundamental step in the definition of the proper surgical strategy. Indeed, surgical decision making should be obtained having portal branches and hepatic veins as landmarks to reduce the risk of major morbidity and mortality.

Definition of tumor-vessels relationship is relevant for planning the type of resection and for this purpose we classified its appearance at IOUS, and based on this classification each category corresponds to a specific operation.

Based on IOUS findings, relationship with intrahepatic vascular structures and its linked surgical behaviour were categorized as follows [6,7]:

1. branch (type 1) or hepatic vein (type A) in contact with a capsulated HCC without vessel wall discontinuation at IOUS: vascular resection is not associated, and just enucleation at the level of the vascular contact is performed (Fig. 3);
2. branch (type 2) or hepatic vein (type B) separated by a thin layer of liver parenchyma (at least 1 mm) from a CRC liver metastases: vascular resection is not associated;
3. branch (type 3) or hepatic vein (type C) in contact with a HCC with undefined margins without vessel wall discontinuation at IOUS: vascular resection is associated;
4. branch (type 4) or hepatic vein (type D) in contact with a CRC liver metastases without vessel wall discontinuation at IOUS: vascular resection is associated;
5. branch (type 5) or hepatic vein (type E) in contact with a HCC or CRC liver metastases with vessel wall discontinuation at IOUS: vascular resection is associated;



a) b) c) d) e)

Fig. 4: a – at IOUS on the right the portal branch to segment 2 (P2) is visualized; b - the surgeon's finger is positioned, and P2 is compressed (arrows); c – the combined compression carried out with the probe and the finger (arrows) induces a transient hepatic ischemia; d –this area to be removed is marked with the electrocautery (arrows); e - the liver cut surface after subsegmental resection of segment 2.

6. branch (type 6) in contact with a HCC without vessel wall discontinuation but with proximal bile duct dilation at IOUS: vascular resection is associated.
Extension of the hepatectomy is always considered for the parenchyma fed by an infiltrated portal branch (types 3-6) [6]. Inversely, in case of infiltration of an hepatic vein an extension of the resection to the whole liver parenchyma theoretically drained by this vein is considered only if there are no accessory hepatic veins at IOUS, and color-Doppler IOUS shows hepatofugal blood flow in the feeding portal branch once the hepatic vein is clamped [7].

Resection guidance

TYPE OF SURGICAL APPROACH

Systematic Segmentectomy
In a cirrhotic patient, the liver volume to be resected must be determined with particular care with the purpose to associate surgical radicality and non-cancerous liver parenchyma sparing. Liver function tests and liver volumetry on CT scans help in this decision. Tumor dissemination from the main lesion through the portal branches cannot be detected with certainty by the pre- and intraoperative imaging modalities [22]. As consequence of that, some authors consider that the resected specimen should comprehend at least the portal area, which includes the lesion [22]. This last is impossible to be correctly identified without the aid of IOUS, especially in a cirrhotic liver where there are generally wide variations and abnormalities in the distributions of the portal branches: for this purpose the systematic segmentectomy has been devised in early 1980s [23,24]. We have recently established alternatives to this approach for tumors located in the left hemiliver which will be also described.

Hooking of the Portal Branch
The segmental portal branches to segment 4 are generally divided in two groups: those for the superior and those for the inferior portion but the commonest branching pattern can be recognized in just half cases [25]. These branches rather than punctured under IOUS guidance, can be approached dissecting the umbilical portion: once exposed the vessel can be encircled with a suture and pulled under IOUS control to verify if it is the branch to S4 inferior or not. Than the proper portal branch can be ligated and divided and the discoloured area which will appear on the liver surface should correspond to the S4 inferior which can be marked with the electrocautery to proceed with the liver dissection: this is a peculiar application of the so-called hooking technique [26]. Furthermore, the subsegment 4 superior could be resected just clamping the portal branch to subsegment 4 inferior, as it is identified with the just described hooking technique; the discoloured subsegment 4 inferior caudally, the plan at IOUS which includes the middle hepatic vein laterally, and that marked by the falciform ligament medially delimitates the area to be resected.

Compression of the Portal Branch
In addition to the hooking technique we have recently proposed a new technique to perform subsegmental resections of segments 2 and 3 without clamping the hepatic artery and puncturing the feeding portal branches [27]: furthermore, we recently applied this technique successfully also for subsegments 4 superior and inferior, and for segment 6. Once the feeding portal branch has been identified at IOUS, it is compressed using the IOUS probe by one side of the liver and the finger by the opposite side: in this way it is possible to induce a transient ischemia of the subsegmental portion of the liver distally to the compression site. This portion can be marked with the electrocautery, the compression is released, and the subsegmentectomy is carried out (Fig. 4 a-e). For subsegment 4 inferior the technique is similar; inversely, to delimitate the subsegment 4 superior the compression is always applied to segment 4 inferior portal branch to obtain the inferior margin of the subsegment 4 superior.
This technique is simple, fast, not invasive and reversible: the possibility to modify the site of compression and then the resection volume allow to size the resection in function of the tumor features and the status of the background liver.

Limited Resection
Anatomical and non-anatomical surgical approach for HCC is still a controversial issue [22,28], since there are no studies comparing in a really randomized study the two

different operations. However, recent reports seems to confirm adequacy in terms of oncological radicality of limited resections for HCC once IOUS is extensively used [6,7]. The IOUS-guided limited resection is simpler than the systematic segmentectomy because there is no need for identifying the area of the liver fed by the portal branch to be ligated. After the identification of the tumor, the surgeon under IOUS control can mark with the electrocautery the border of the lesion on the surface of the liver just above the nodule. To carry out this manoeuvre the flat and thin tip of the electrocautery is positioned between the probe and the liver surface: this manoeuvre results in a shadow at the IOUS image which runs deeply just below the electrocautery. In this way it is possible to define the position of the electrocautery with the tumor edge and consequently to mark with the electrocautery itself the nodule profile on the liver surface and to select the safer edge for the incision. The adequacy of the marked edge can be furthermore checked with IOUS as the air trapped between the probe and the irregular surface of the demarcation line draw with the electrocautery on the liver surface can be visualized at IOUS.

Another way to draw precisely on the liver surface with the aid of IOUS the tumor edge is carried out using the finger tips. With the probe positioned on the liver surface the surgeon's finger-tip pushes on the opposite side and its profile is visualized at IOUS: as consequence relations between the finger-tip and the tumor edge can be precisely estimated and the resection area can be marked on the liver surface.

Liver parenchyma dissection

The main advantage provided by the resection guidance accomplished with the aid of IOUS is the modification of the traditional way to dissect the liver tissue which was done on vertical planes to avoid the tumor exposure on the cut surface. IOUS allows to follow in real-time the dissection plane, to put it constantly in relations with the tumor edge, and than to modify its direction when needed: this is because it is possible to visualize on the IOUS image the dissection plane which appears as an echoic line due to the entrapment of air bubbles and clots between the faced cut surfaces (Fig. 5). If the dissection plane is not clearly visible, it can be better visualized inserting a gauze or a specifically devised silicon gauze between the faced cut surfaces. These techniques allow the surgeon to keep the proper dissection plane: an early recognition of a wrong dissection plane permits to modify it properly and to avoid a possible tumor exposure. In this way it is possible to carry out a rounded trajectory of the dissection plane around the tumor avoiding its exposure, and allowing to spare important vascular structures: this results in more conservative but radical treatments and in a lower rate of major hepatectomies. Furthermore, in those patients in which major resections are needed IOUS allows to better achieve the proper dissection plane, which should run along the hepatic vein to be fully anatomic.

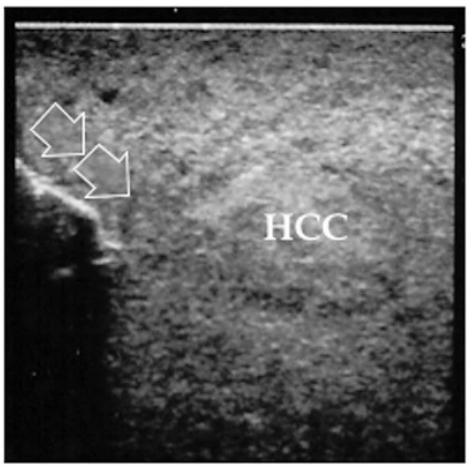


Fig. 5: at IOUS the dissection line can be well visualized (arrows), and it runs towards the small HCC.

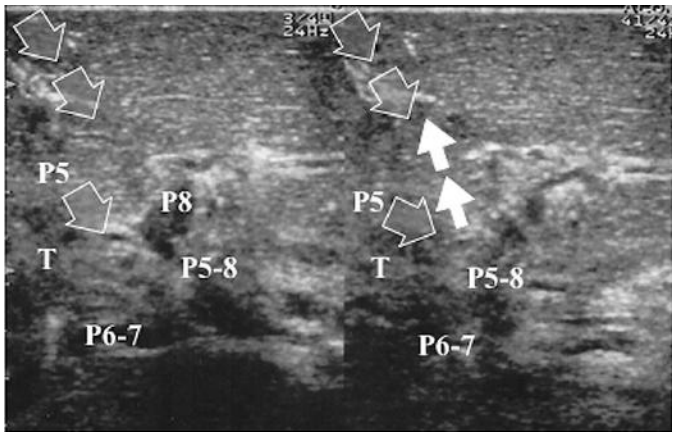


Fig. 6: a) passing between the portal branch to segment 8 (P8) and the tumor (T) is the objective of the dissection plane (transparent arrows), but a portal banch is encountered on the dissection plane and is encircled with a stitch; b) once the traction is applied pulling up the stitch (white arrows) the thin vessel to segment 5 (P5) is modified which indicates that it corresponds to the vessel encircled with the stitch and therefore it can be ligated and divided safely. P5-8 = portal branch to the right anterior section; P6-7 = portal branch to the right posterior section.

The artefacts, which allows to show at IOUS the dissection plan could sometimes mask structures such as portal branches which should be ligated or conversely respected. For this reason to better visualise the targeted point where the portal branch should be divided, the so-called hooking technique has been devised [29]. When the Glissonian sheath is exposed and skeletonized, it is encircled with a stitch, which is visualized by IOUS as an echogenic spot with a posterior shadow. Then under sonographic control, the stitch, hooking the exposed vessel, is gently pulled up, which stretches the portal branch slightly and the traction point is demonstrated clearly by IOUS. If the exposed portal branch is not clearly visi-

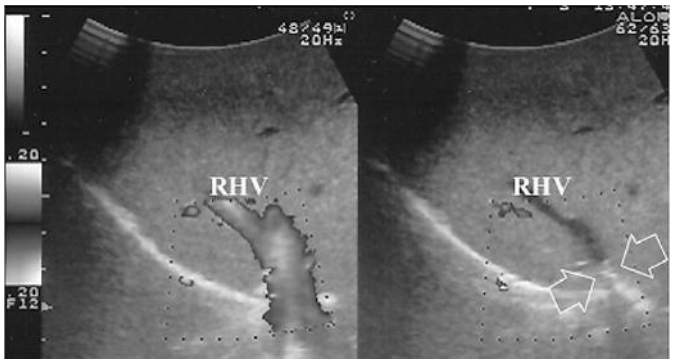


Fig. 7: a) at IOUS the caval confluence of the right hepatic vein (RHV) is visualized and color-Doppler shows a regular flow (blue colour); b) the surgeon position his fingers at the level of RHV caval confluence without for that having had to skeletonize the RHV, and with the fingers themselves bluntly compress the RHV (arrows): the temporary occlusion of the vessel can be well confirmed by the disappearance of any sign of blood flow at color-Doppler IOUS.

ble because it has collapsed, the portal triad is unclamped to enable it to fill with blood and then it is visualised better by IOUS. If the target site is correct, the portal branch is ligated and divided and segmentectomy is completed under IOUS guidance; conversely, if the exposed vessel was not the targeted one, it is spared and useless sacrifice of further liver parenchyma is avoided.

A practical example in which the hooking technique is used is during ventral or dorsal subsegmentectomy of segment eight. The portal trunk to this segment may show bifurcation in its dorsal branch and ventral trunk just close to the origin of the portal vessel to segment five. In this situation, there is the risk of ligating and dividing the portal branch of segment five instead of the planned subsegmental branch of segment eight and then, necrosis of the segment five may occur.

The hooking technique under IOUS control enables the identification of the branch, which was encircled, and then the surgeon can decide with certainty whether to ligate it. This technique is also useful in case of tumor thrombus in major portal branches. In this situation, once the portal branch is skeletonized, it is encircled with a stitch and, under IOUS control, the stitch, is gently pulled up: this traction stretches the portal branch slightly and the traction point is demonstrated clearly by IOUS (Fig. 6 a,b). If the traction point is not at the level of the tumor thrombus it is possible to ligate the portal branch and proceed with the liver resection being sure that thrombus will not migrate because of surgical manipulation [30].

During liver dissection the back-flow bleeding from the hepatic veins is an important source of blood loss, and it is one of the most important factors in determining the short-term and long-term patient's outcome. Therefore, limiting the backflow bleeding from the hepatic veins is a priority in liver resections. We described a ultrasound-guided technique for backflow bleeding control from the RHV during right-sided liver resection [31]. The technique is very simple: once the right surface of the extrahepatic RHV is exposed to allow its compression by surgeon's finger-tips, the effectiveness of finger compression is checked by IOUS, and color-Doppler (Fig. 7 a, b).

Post-resectional control

Two are the possibilities given by IOUS after nodule removal: one is the "water bath" technique which consists in the real-time control of the proper resection of the targeted nodule verifying its complete inclusion in the specimen just once removed from the liver [32]; the second is done checking the cut surface refilled with saline to avoid the artefacts generated by the residual air bubbles and clots.

Conclusions

IOUS still remains the best method for staging the liver involvement by the tumor, and it has been discussed how new improvements are expected by adding the CEIOUS with the aim of ameliorating the specificity of the ultrasound exploration. The aforementioned methods for performing a IOUS-guided resection guarantee whenever possible both anatomical and limited resection with a radical intent: this has consequences either for the effectiveness of the surgical treatment than for its safety. Indeed, this kind of surgery allows radical surgical treatment of HCC without mortality [5]. Procedures, which are not IOUS-guided, led to dangerous and useless major resection or incomplete operations. Inversely, IOUS tumor-vessel classification and the related surgical policy has proven that in selected patients is possible to get close to the tumor burden without increasing the risk of incomplete removal, and as consequence of local recurrence [6,7]. In practice this evidence means that with IOUS guidance is possible to perform conservative but radical hepatectomies also in complex presentations, and then to enlarge the surgical indications. With this approach the rate of major hepatectomies has been limited to up to 8% in patients with tumors involving one or more hepatic veins close to their caval confluence, without for that performing any vascular reconstruction [7]. These results not only underline how the IOUS guidance allows operation otherwise not feasible, but, just because this approach reduces the rate of major hepatectomies, it could be discussed the real need for interventions such as preoperative portal vein embolization which are adopted to secure from liver failure after major removal of liver parenchyma.

Nowadays it can be affirmed that liver resection is an imaging-guided procedure and as every interventional imaging-guided procedure, its features are the highest therapeutic efficacy combined with the minimal inva-

siveness. With IOUS aid it is nowadays possible to carry out surgical procedures contemporary safe, oncologically radical and conservative for the liver function. Mostly because of that surgery can be still considered the treatment of choice for most of liver tumors. For this purpose, IOUS should be a familiar instrument for hepatic surgeon. The American College of Surgeons has recently recognized the need for surgeons of a specific training in US, and similarly have been started in Europe a School for Surgical Ultrasonography, meanwhile dedicated monographs have been published almost simultaneously in America and in Europe [33-35]. The way for a wider diffusion of ultrasound in surgeons' practice has been definitely and hopefully opened.

Riassunto

Le procedure imaging-guidate hanno modificato l'approccio all'epatocarcinoma sia introducendo nuove metodiche di trattamento, ma anche modificando la strategia chirurgica. Infatti, l'ecografia intraoperatoria, anche con l'aiuto del mezzo di contrasto, consente di definire con precisione la sede del tumore ed il bilancio di estensione della malattia. Inoltre, la guida ecografica premette di minimizzare il tasso di resezioni epatiche maggiori, mantenendo la radicalità oncologica e di fatto allargando le indicazioni al trattamento chirurgico. La precisa definizione dei rapporti tra tumore e vasi intraepatici, la presenza di vasi accessori e l'analisi color-Doppler sono elementi, ottenibili con l'ecografia, ed in grado di rendere fattibili interventi che altrimenti non lo sarebbero. L'approccio definito "radicale ma conservativo" consente di effettuare interventi sicuri, con tassi di mortalità e morbilità maggiore minimi, ed efficaci, non risultando gravati da recidive locali. Gli aspetti tecnici di questo approccio sono stati qui descritti ed analizzati.

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