Rezumat

Cu tot progresul tehnologic înregistrat până în prezent, hepatocarcinomul reprezintă încă o provocare diagnostică și terapeutică, managementul optim fiind asigurat doar de o atitudine personalizată, oferită de o abordare multidisciplinară. Ecografia are un rol esențial în ghidurile de conduită pentru această neoplazie, aplicarea intraoperatorie fiind obligatorie pentru creșterea supraviețuirii acestor pacienți, atunci când abordarea chirurgicală este posibilă și indicată. Lucrarea de față subliniază principalele indicații ale ecografiei intraoperatorii pentru diagnosticul și tratamentul hepatocarcinomului, împreună cu domeniile ce au potențial de dezvoltare.

Cuvinte cheie: hepatocarcinom, ecografia intraoperatorie, tehnici ablative, rezecrii hepatice ecoghidate, elastografie

Abstract

With all the technological progress registered so far, hepatocellular...
Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death in the world, with increasing incidence. It is associated with a survival of only 10-15% at 5 years, mainly due to its diagnosis in advanced stages (1). 70-90% of HCC cases occur on a cirrhotic liver (2). The only treatment with curative intent in the case of early-stage HCC, with a survival of up to 50-70% at 5 years is the surgical treatment (liver resections, liver transplantation) and ablative techniques (3).

Current indications for liver resections are tumors developed on a non-cirrhotic liver or small size HCC, developed on a compensated cirrhotic liver (without the presence of portal hypertension). In the case of multicentric HCC, of the presence of major vascular invasion or portal hypertension, the morbidity, prognosis, and possibility of alternative therapies should be taken in account (4).

Ablative techniques, by radio frequency or microwave, are an effective treatment for tumors under 3 cm, with a very good prognosis in patients with altered liver function and/or clinical status that contraindicates surgical treatment (5). However, beyond the standard indications, survival has been improved by using these techniques even in more advanced cases, as ablation can control the progression of the disease or increase patients' eligibility for curative treatment (liver transplant) (6).

Intraoperative ultrasound (IOUS) is an essential tool in hepatobiliary oncological surgery, being a valuable and indispensable imaging technique that offers excellent spatial and contrast resolution, with the possibility of visualizing images in real time, being useful in verifying and confirming preoperative imaging diagnosis and especially in guiding the therapeutic conduit, both in classical and laparoscopic surgery, even allowing changes in the process of therapeutic decision during surgery. Hepatic IOUS plays an essential role in the correct description of liver lesions, topography and loco-regional extension, relationships with neighboring anatomical structures and in the staging of the disease, being used in patients with HCC since early ’70s (7).

In the current article we want to illustrate in a narrative way the main up-to-date applications of IOUS in the surgical treatment of HCC, together with perspective techniques in the field: minimally invasive approach, contrast enhanced intraoperative ultrasound (CE-IOUS) and elastography.

**Elements of Technique and Approach Methods**

**Necessary equipment**

Ideally, ultrasound machines used in the operating room should be compact, mobile, easy to handle and to provide high-quality images (8). Now a days there is a wide selection of accessories used in IOUS: probes of different types, with appropriate shape and with a specific purpose, depending on each case, taking in account the type and location of the lesions. Standard transducers for transabdominal ultrasound can also be used, but there are...
some limitations in terms of image resolution and the large size of the transducer who does not provide optimal handling space (9). However, these conventional transducers can be used at the beginning of the liver examination, to obtain an overview of the anatomy of the organ (9,10). The transducers used in IOUS operate at a high frequency (between 7.5-10 MHz), thus allowing a very good spatial and detailed resolution (8). Transducers of different shapes are available for intraoperative use: linear T-shaped probes, interdigital probes, micro convex probes, T-shaped probes with trapezoid scanning window (11). In the case of liver surgery, the ideal transducer is a small one, which can be easily manipulated in narrow spaces (inter-hepato-phrenic space) and due to the ergonomic design, will allow the operator to have permanent contact with the liver surface, without the possibility to miss some areas (10,12) (Fig. 1).

IOUS can also be used in laparoscopic surgery, dedicated transducers being available for this type of approach, with a typical frequency between 5-10 MHz, linear or convex “side-wire” models, mounted at the end of a long and thin articulated arm, of whose design allows insertion and manipulation through trocars. In the best scenario, the IOUS equipment used in liver surgery should ensure the possibility of using contrast enhanced ultrasound, elastography, pulsed Doppler ultrasound and color/power Doppler.

Examination technique / approaches

 Ideally, in the operating room, the ultrasound machine should be positioned in front of the main operator, in order to simultaneously view both the ultrasound monitor and the operating field, respecting a principle of collinearity between surgeon, liver and monitor. Liver exploration should always begin with the inspection and palpation of it and of the entire peritoneal cavity, steps that should not be omitted in favor of IOUS, as they continue to play a very important role in liver cancer surgery (13). In order to have enough space to handle the transducer and to be able to scan the entire surface of the liver, it is necessary to mobilize the liver by initially cutting the round and falciform ligament and later on the triangular and coronary ligaments. By pulling the round ligament, the surface of the liver is exposed and the liver can be scanned systematically and completely by following portal pedicles and suprahepatic veins (11).

The cirrhotic liver represents a challenge when put in front of a differential diagnosis between regeneration nodules and a real neoplasm (HCC). In these situations, CE-IOUS plays an essential role by characterizing the vascular pattern of cirrhotic nodules, thus making it possible to differentiate between regenerating nodules and malignant tumors (14). Typical for HCC, CE-IOUS indicates a hyperenhancement in the arterial phase and a specific “wash out” of the contrast substance during the venous and late phase, when the tumor appears hypoechoic (15,16). Another vascular pattern corresponding to poorly differentiated HCC is characterized by a hypoechoic pattern with a basket-like peripheral arterial neovascularization (17).

Applications of IOUS in HCC surgery

Intraoperative diagnosis/staging

IOUS has a role in the detection and differential diagnosis of liver lesions (benign versus malignant), in the characterization of lesions, their topography and loco-regional extension, in establishing relationships with neighboring
Iancu et al

anatomical structures and in staging the disease.

In addition to intraoperative confirmation of the lesion, the literature shows that IOUS reveals new lesions in 30% of patients with cirrhotic liver (18). However, most nodules detected by IOUS in cirrhotic patients are not tumoral lesions, conventional IOUS (gray scale) having a risk of overestimation in these situations. In these patients, an essential role is played by CE-IOUS and elastography, methods that allow the characterization of lesions according to the vascular pattern and tissue elasticity (19).

The advantage brought by the option of intraoperative restaging of the lesions consists in the possibility to modify in real time the surgical therapeutic approach by performing a more extensive resection or on the contrary by taking a more conservative attitude (e.g. ablative techniques).

IOUS guided liver resections

During liver resection, the standard radical treatment for HCC, in addition to obtain oncological and functional optimal results, special care should be paid to liver parenchyma preservation, the liver function of cirrhotic patients being usually altered and therefore, the remaining liver volume being an important prognostic factor after resection (20–22).

In modern liver surgery, both for the treatment of HCC and for colorectal liver metastases, the use of IOUS allows the surgeon to perform the so-called "radical but conservative surgery". (23) Practically, by obtaining information about the relationships that the liver lesions have with intrahepatic bilio-vascular structures in real time (by IOUS), the surgeon can guide his resection line, respecting the Glissonian pedicles and suprahepatic veins and by that, preserving as much functional liver parenchyma as possible (10,24,25). This is not possible in classical liver surgery, when resections are based on conventional, descriptive, surface landmarks.

Another major advantage of IOUS is related to the possibility of performing anatomical resections. This principle is based on the anatomy of the liver, in relation to the afferent and efferent vascularization, the exact segmental limits being different from individual to individual, with a contour "in geographic map shape". The benefits of an ideal, anatomical resection are translated into reduced blood loss (because the afferent pedicle is primarily intercepted), a reduced risk of necrosis on the resection parenchyma (because all tissue vascularized by that pedicle is removed) and a reduced risk of micro-satellite metastases recurrence. This technique involves compression to the segmental portal branches corresponding to the targeted area (usually between the transducer and the operator's fingers), thus resulting in a transient ischemia of the parenchyma: the limits can be marked with electrocautery and subsequently, the resection is performed along the previously marked line (24,26–29) (Fig. 2).

IOUS is currently considered as the standard method for guided liver resections. The introduction of CE-IOUS brought major advantages in the evolution of liver surgery, but the technique has the disadvantage of short period of time visualization of the lesion and cannot be used as a navigation tool or to guide the liver resections, this being time consuming (30).

In this idea, the technological contribution facilitated another useful technique for the operator to guide his liver resection: indocyanine green fluorescence imaging technique (ICG-FI). Extrahepatic bile ducts, liver tumors and liver segments can be highlighted based on the fluorescence property of ICG (water-soluble molecule) and its rapid excretion by bile. In practice, ICG is administered intravenously before or during the surgery, at variable intervals, and "illuminates" the surface of the liver when it comes in contact with the infrared light source (31). One of the advantages of using ICG-FI is that it also provides accurate information in the case of liver cirrhosis, in contrast to other substances used for ultrasound guidance: portal hypertension can obstruct ultrasound-guided liver mapping (32). However, the visualization of tumors using ICG-FI is limited by the depth
of penetration of infrared light and the thickness of liver tissue: infrared light can penetrate the tissue only up to 5-10 mm and the tumors located deep inside the parenchyma cannot be visualized (33).

Despite the potential benefits that ICG-FI can bring in hepato-biliary surgery, CE-IOUS remains the gold standard for liver mapping, and more studies are needed to assess the sensitivity and specificity of this method, currently used as a complementary technique (31).

**Guiding ablative techniques**

Interventional therapies are an alternative method of treatment used to control the progression of the disease or to increase patients' eligibility for curative treatment. In the last decades, technological innovations have yielded important results in prolonging survival through the use of local ablative techniques (6).

Using advanced percutaneous techniques or combining ablative techniques with other therapies (intraarterial chemotherapy) has increased the number of cases with treatable HCC, cases initially considered borderline or feasible only for palliative treatment (34).

Radiofrequency (RF) or microwave (MWA) ablations are indicated in patients who are not suitable for surgical resection due to impaired liver function, for unresectable HCC or in patients who are on the waiting list for liver transplantation. There are several ways through which these techniques can be used: percutaneous, by laparotomy or by laparoscopy (35).

There are studies that have shown that short- and long-term outcomes in patients treated by percutaneous ablation are similar to those treated through surgery (36). It emphasizes that ablative surgical techniques are a feasible treatment alternative for tumors whose percutaneous approach is difficult or not possible (37). These ablative techniques can be combined with liver resections or can be staged performed after surgical resections, contributing to the completion of oncological requirements (38).

Laparoscopic ablation is a minimally invasive treatment alternative, indicated when percutaneous ablation is not feasible and when laparotomy is contraindicated or too invasive (39). Of course, laparoscopic surgery comes with several disadvantages related to the evaluation of the liver, the surgeon losing the ability to palpate structures and lesions. IOUS manages to compensate these disadvantages, providing highly useful intraoperative imaging and greater sensitivity in detecting liver lesions than most preoperative imaging techniques cannot see. Laparoscopic intraoperative ultrasound has a sensitivity and
specificity similar to that of open surgery (40).

Regardless of the approach chosen for performing these ablative techniques, IOUS is used to locate the tumors, as a tool to guide the intervention, to avoid damage to vascular or biliary structures and adjacent organs, allowing the insertion of the ablation needle under direct view. Last but not least, IOUS is essential to assess the effectiveness of treatment: the area of necrosis after ablation and possible complications (41). Performed under these conditions, guided ablations with the help of IOUS are safe, well tolerated, being an effective treatment option which provides excellent local control of primary liver tumors (41). Moreover, in the case of small HCC, studies show that intraoperative RFA has a local recurrence rate equivalent to that following surgical resections (42).

Intraoperative contrast enhanced ultrasound

The possibility of performing CE-IOUS has an important role in the treatment of HCC. Currently, the contrast agents used are SonoVue (gaseous sulfur hexafluoride: Bracco, Milan Italy) and Sonazoid (gaseous perfluorotane: GE Healthcare, Norway/DaiichiSankyo, Japan), both effective for characterizing liver lesions and for differentiating benign from malignant lesions (10,43,44). These intra-vascular contrast agents offer the possibility of continuous, real-time monitoring of intra-vascular uptake, which has led to their widespread use. The gas-filled microbubbles of these agents tolerate low acoustic pressures, enabling continuous observation during the arterial phase and repeated scanning during the late phase (24).

CE-IOUS is additional for surgical navigation and provides the surgeon essential information for the diagnosis and staging of the disease (45,46), being considered the most useful imaging technique in the surgical treatment of HCC (47).

The literature indicates that there are no statistically significant differences between CE-IOUS and MRI in terms of the ability to make a differential diagnosis of liver tumors (48). CE-IOUS can accurately characterize the vascular pattern of liver nodules, thus contributing to differentiate the regenerative nodule from the neoplastic ones (14) (Fig. 3).

The contrast agent available and used in Europe is made of sulfur hexafluoride microbubbles stabilized by a phospholipid shell (SonoVue, Bracco Imaging, Milan, Italy). As a method of examination, the ultrasound is set on the contrast module, it is preferable the ultrasound to be in the B mode and the CE-IOUS to be displayed simultaneously (side-by-side). The contrast substance is prepared as a solution by adding powder and shaking it, after which it is injected intravenously, being quickly “captured” by the vascular system and giving the operator the opportunity to initiate the examination and record the process of capturing the contrast agent by the examined structures.
Due to the long process of carcinogenesis of HCC, neovascularization in small lesions may not be visible with routine imaging methods. The echogenicity of these lesions can often change, especially post-therapeutic (embolization, RFA), making it difficult to identify typical signs of malignancy: irregular and hypoechoic margin at the periphery of the lesion (49,50).

Hypervascularization of visible HCC in the arterial phase and washout of the specific contrast agent in the portal phase, which continues in the late phase, are visible intraoperatively only with the help of CE-IOUS (16). Torzzili et al classified the vascular pattern of HCC nodules evaluated during surgical procedures into four categories (51) (Fig. 5). Surgical resection is recommended for three of the four patterns the treatment plan being modified in 78% of cases after CE-IOUS. (50) CE-IOUS facilitates outlining the resection area and determining the dissection plane, resulting in easier resection guidance (24).

The technique has the advantage of being reproducible, it is not expensive, but it has the disadvantage that it depends on the experience of the examiner and the equipment used.

In ablative techniques, the CE-IOUS plays a key role for the intraoperative verification of the post-ablation necrosis area, providing the possibility to repeat and complete the ablation when the situation requires it (52).

**Figure 4.** Contrast enhanced intraoperative ultrasound of a hepatocellular carcinoma barely visible in gray scale (left). Characteristic aspect of “wash out” in the delayed phase (right). (from personal files of the authors)

**Figure 5.** Classification of patterns of enhancement in CEIOUS of those lesions detected in IOUS during surgery for HCC. Lesions having a class A pattern, featured by a hyper vascular enhancement in early phase (A1-2), or any hypoechoic pattern in the delayed phases (A1-3), has to be resected; lesions showing a class B pattern of enhancement has no indication to be removed; (from Guido Torzilli. Ultrasound-Guided Liver Surgery. Springer. 2014) (24)
Intraoperative elastography

A newer method, as a practical applicability of IOUS is elastography, a non-invasive and non-irradiating technique that evaluates the elasticity of tissues in organs. It can be strain or shear wave type. Strain elastography is based on compression, being a qualitative method that is based on the deformation of the tissue produced by compression; thus, a color map is obtained and depending on this color code we can assess the probability of malignancy or benignity (Fig. 6). The second method (shear-wave) is a quantitative method that is based on recording the shear waves generated by compression; likewise, a color map is made, evaluated by values quantified in kilopascals (kPa) (53).

Elastography has currently established applications in transparietal ultrasound, especially in liver pathology to quantify the degree of fibrosis and less often for the differential diagnosis of liver tumors.

Intraoperative research shows that hepatic intraoperative elastography may have an additive role in intraoperative palpation (which is subjective, depending on the surgeon's experience) and practically replace it, especially in the case of small tumors, difficult to identify on a pathological liver, such as the cirrhotic one. (54)

The literature indicates that intraoperative elastography may be useful for the differential diagnosis of liver tumors (benign vs. malignant) and may even guide us to a diagnosis of primary tumors (HCC) or secondary tumors (metastases) (19,54). Unfortunately, in terms of the accuracy and sensitivity of elastography, reports show that currently CE-IOUS is clearly superior, with an accuracy of 94% versus 69% and even better results can be obtained by combining the two methods (55–57). The conclusions are quite clear in the literature, CE-IUOS being currently more sensitive than elastography and having an indication of first intention (58).

The role of elastography was also investigated in the evaluation of the necrotic area after ablation (59,60). The first studies appeared in 2014 and showed that elastography cannot accurately describe the area after ablation (61). There are, however, more recent in vivo experimental models that suggest that elastography has potential in this field, which underscores the need for further research (62).

Perspectives

The continuous development of technology will of course lead to an increased use of IOUS by surgeons, offering the possibility of extending the indications for liver resections, with the ultimate goal that more patients will benefit from radical surgery, preserving as much functional parenchyma as possible.

CE-IOUS already has a well-defined role, both for diagnosis and for evaluating the effectiveness of therapies. Progress could be made by improving current contrast agents based on nanoparticles (NP) and nanomedicine. The ideal contrast agent should accumulate selectively in the target tissue to improve image contrast, as NP can facilitate this transport. The introduction of designed microparticles or NP into theranostic biomedicine can substantially improve the imaging contrast/precision and enhance the therapeutic efficiency (63).

Elastography remains an easy and quick technique to be performed intraoperatively that could replace/improve the subjective palpation of the surgeon, especially in the case of intraparenchymal tumors. The potential benefits that it could bring intraoperatively are still subject of research.
Intraoperative fluorescence and advanced navigation techniques in which preoperative imaging is projected directly into the surgical site (virtual reality) are techniques already used in centers of excellence in the world. Even if the feasibility of these techniques is proven, the need for equipment and the currently high costs limits their large-scale implementation. The combination of these techniques with IOUS brings clear benefits through real-time 3D characterization of already identified lesions.

Conclusions

HCC represents a therapeutic challenge, often requiring personalized treatment due to the presence of liver cirrhosis that can limit radical treatments. Regardless of the chosen management, IOUS can play an extremely important role in the diagnosis and staging of the disease, with benefits and practical applications in the treatment of tumors, especially when contrast administration and elastography are associated. IOUS is indispensable for the surgeon when opting for a radical oncological treatment, through the contribution brought in guiding the surgical procedures (resection and/or ablation) and through the possibility of evaluating the effectiveness of the treatment at the time of surgery.

Conflict of interest

The authors have no conflict of interest.

References

1. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abeacasis MM, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723–50.
2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391(10127):1301–14.
3. Liver EA for the S of the, Cancer EO for R and T of. EASL&JK2013:EDRC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
4. Allaire M, Gouraud C, Lim C, Le Cleach A, Wagner M, Scallion D. New frontiers in liver resection for hepatocellular carcinoma. JHEP Reports. 2020;2(4):100134.
5. Gao J, Wang S-H, Ding X-M, Sun W-B, Li X-L, Xin Z-H, et al. Radio-frequency ablation for single hepatocellular carcinoma 3 cm or less as first-line treatment. World J Gastroenterol. 2015 May;21(17):5287–94.
6. Renuzzi M, Tovoli F, Clemente A, Ierardi AM, Petta I, Peta G, et al. Ablation for hepatocellular carcinoma: beyond the standard indications. Med Oncol. 2020;37(4):1–10.
7. Makuch M, Torzilli G, Maci J. History of intraoperative ultrasound. Ultrasound Med Biol. 1998 Nov;24(9):1229–42.
8. Jakimowicz JJ. Intraoperative ultrasonography in open and laparoscopic abdominal surgery: an overview. Surg Endosc. 2006;20 Suppl 2:S425–35.
9. Kruikal JB, Kane RA. Intraoperative ultrasonography of the liver. Crit Rev Diag Imaging. 1995;36(3):175–226.
10. Donadon M, Costa G, Torzilli G. State of the art of intraoperative ultrasound in liver surgery: current use for staging and resection guidance. Ultraschall Med. 2014;35(6):500–3.
11. Donadon M, Torzilli G. Intraoperative ultrasound in patients with hepatocellular carcinoma: From daily practice to future trends. Liver Cancer. 2013; 2(1):16–24.
12. Patel NA, Roh MS. Utility of intraoperative liver ultrasound. Surg Clin North Am. 2004;84(2):513–24.
13. Machi J, Oishi AJ, Furumoto NL, Oishi RH. Intraoperative ultrasound. Surg Clin. 2004;84(4):1085–111.
14. Gong NM, Yin HH, Cai WH, Li GW, Wang JX, Gu CY, et al. IOUS and CE-IOUS during hepatic resection for patients with hepatocellular carcinoma in liver cirrhosis. Clin Hemorheol Microcirc. 2019;71(4):483–98.
15. Badea R. Ultrasound Imaging of Liver Tumors – Current Clinical Applications. In: Julianov SIE-A, editor. Rijeka: IntechOpen; 2012. p. Ch. 5.
16. Pace C, Nardone V, Roma S, Chegai F, Toti L, Manzia TM, et al. Evaluation of Contrast-Enhanced Intraoperative Ultrasound in the Detection and Management of Liver Lesions in Patients with Hepatocellular Carcinoma. J Oncol. 2019;2019:680040. eCollection 2019.
17. Torzilli G, Oliviari N, Moroni E, Del Fabbro D, Gambetti A, Leoni P, et al. Contrast-enhanced intraoperative ultrasonography in surgery for hepatocellular carcinoma in cirrhosis. Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc. 2004;10(2 Suppl 1):S34-8.
18. Kokudo N, Bandai Y, Imanishi H, Minagawa M, Uedera Y, Hanhara Y, et al. Management of new hepatic nodules detected by intraoperative ultrasound during hepatic resection for hepatocellular carcinoma. Surgery. 1996;119(6):634–40.
19. Kato K, Sugimoto H, Kanazumi N, Nomoto S, Takeda S, Nakao A. Intraoperative application of real-time tissue elastography for the diagnosis of liver tumours. Liver Int. 2008;28(3):1264–71.
20. Lu Q, Luo Y, Yuan C-X, Zeng Y, Wu H, Lei Z, et al. Value of contrast-enhanced intraoperative ultrasound for cirrhotic patients with hepatocellular carcinoma: a report of 20 cases. World J Gastroenterol. 2008;14(25): 4005–10.
21. Kibori M, Matsu Y, Kitade H, Kwon A-H, Kaniyama Y. Hepatic resection for hepatocellular carcinoma in severely cirrhotic livers. Hepatogastroenterology. 2003;50(50):491–6.
22. Ezaki T, Yamamoto K, Yamaguchi H, Sasaki Y, Ishida T, Mori M, et al. Hepatic resection for hepatocellular carcinoma existing with liver cirrhosis. Hepatogastroenterology. 2002;49(47):1363–8.
23. Torzilli G, Montorsi M, Donadon M, Palmisano A, Del Fabbro D, Gambetti A, et al. “Radical but conservative” is the main goal for ultrasound-guided liver resection: prospective validation of this approach. J Am Coll Surg. 2005;201(4):517–28.
24. Torzilli G. Ultrasound-Guided Liver Surgery. Springer; 2014.
25. Donadon M, Procopio F, Torzilli G. Tailoring the area of hepatic resection using inflow and outflow modulation. World J Gastroenterol. 2013;19(7): 1049–55.
26. Xiang C, Liu Z, Dong J, Sano K, Makuch M. Precise anatomical resection of the ventral part of Segment VIII. Int J Surg Case Rep. 2014;5(12):924–6.
27. Torzilli G, Procopio F, Palmisano A, Donadon M, Del Fabbro D, Marconi M, et al. Total or partial anatomical resection of segment 8 using the ultrasound-guided finger compression technique. HPB (Oxford). 2011;13(8):586–91.
28. Torzilli G, Procopio F, Palmisano A, Cimino M, Del Fabbro D, Donadon M, et al. New technique for defining the right anterior section intraoperatively using ultrasound-guided finger counter-compression. J Am Coll Surg. 2009;209(2):e8-11.
29. Tordzili G, Makuschi M. Ultrasound-guided finger compression in liver subsegmentectomy for hepatocellular carcinoma. Surg Endosc. 2004;18(1):136-9.

30. Polesel A, Franchi E, Canepa MC, Barbieri L, Briani L, Ferrario J, et al. Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer. HPB (Oxford). 2013;15(12):928-34.

31. Rossi G, Tarasconi A, Baiocchi G, De' Angelis GL, Galani F, Di Mario F, et al. Fluorescence guided surgery in liver tumors: applications and advantages. Acta Biomed. 2018;89(3):135-40.

32. Aoki T, Murakami M, Yasuda D, Shinzui Y, Kubo T, Matsuoka K, et al. Intraoperative fluorescent imaging using indocyanine green for liver mapping and cholangiography. J Hepato-Biliary Pancreat Sci. 2010;17(5):590-4.

33. Kudo H, Ishiwa T, Tani K, Harada N, Ichida A, Shinzui A, et al. Visualization of subcapsular hepatic malignancy by indocyanine green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc. 2014;28(9):2504-8.

34. Nault J-C, Sutter O, Nahon P, Ganne-Carrié N, Sèror O. Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations. J Hepatology. 2018;68(4):783-97.

35. Eisele RM. Advances in local ablation of malignant liver lesions. World J Gastroenterol. 2016;22(15):3868-91.

36. Wong J, Lee K-F, Yu SC-H, Lee PS-F, Cheung YS, Chong C-N, et al. Percutaneous radiofrequency ablation versus surgical radiofrequency ablation for malignant liver tumours: the long-term results. HPB (Oxford). 2013;15(5):609-17.

37. Kim HO, Kim SK, Son BH, Yoo CH, Hong HP, Cho YK, et al. Intraoperative radiofrequency ablation with or without tumorectomy for hepatocellular carcinoma in locations difficult for a percutaneous approach. Hepatobiliary Pancreat Dis Int. 2009;8(6):591-6.

38. Cheung TT, Ng KK, Chok KS, Chan SC, Poon RT, Lo CM, et al. Combined resection and radiofrequency ablation for multifocal hepatocellular carcinoma: prognosis and outcomes. World J Gastroenterol. 2010;16(24):3066-62.

39. Bartho A, Bartos D, Sparzex Z, Iancu I, Ciobanu L, Iancu C, et al. Laparoscopic Contrast-Enhanced Ultrasonography for Real Time Monitoring of Laparoscopic Radiofrequency Ablation for Hepatocellular Carcinoma: An Observational Pilot Study. J Gastrointestin Liver Dis. 2019;28(4):457-62.

40. Tandan VR, Asch M, Margolis M, Page A, Gallinger S, et al. Laparoscopic vs. open laparoscopic ultrasound examination of the liver: A controlled study. J Gastrointestinal Surg Off J Soc Surg Aliment Tract. 1997;1(2):141-6.

41. Machi J, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, et al. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. J Gastrointestinal Surg Off J Soc Surg Aliment Tract. 2001;5(5):477-89.

42. El-Gendi A, El-Shafie M, Abdel-Aziz F, Bedewy E. Intraoperative ablation for small HCC not amenable for percutaneous radiofrequency ablation in Child A cirrhotic patients. J Gastrointestinal Surg Off J Soc Surg Aliment Tract. 2013;17(4):712-8.

43. Luo W, Numata K, Kondo M, Morimoto M, Sugimori K, Hiratsuka K, et al. Sonozoid-enhanced ultrasound microscopy for evaluation of the enhancement patterns of focal liver tumors in the late phase by intermittent imaging with a high mechanical index. J ultrasound Med Off J Am J Obst Gynecol. 2009;28(4):439-48.

44. Trillaud H, Brutel J-M, Valette P-J, Vilgrain V, Schmutz G, Oyen R, et al. Characterization of focal liver lesions with Sonovue-enhanced sonography: international multicenter-study in comparison to CT and MRI. World J Gastroenterol. 2000;15(30):3748-56.

45. Sato K, Tanaka S, Mitsunori Y, Mogushi K, Yason M, Aihara A, et al. Contrast-enhanced intraoperative vascular imaging of hepatocellular carcinoma: Clinical and biological significance. Hepatology. 2013;57(4):1436-47.

46. Kruskal JB, Kane RA. Intraoperative US of the Liver: Techniques and Clinical Applications. Radiographics. 2006;26(4):1067-84.

47. Nakamura I, Hatanaka E, Tada M, Kawabata Y, Tamagawa S, Kurimoto A, et al. Enhanced patterns on intraoperative contrast-enhanced ultrasound predict outcomes after curative liver resection in patients with hepatocellular carcinoma. Surg Today. 2021;51(5):764-776. Epub 2020 Sep 22.

48. Hul S, Platz Batista da Silva N, Wiesinger I, Hornung M, Scherer MN, Lang S, et al. Analysis of Liver Tumors Using Preoperative and Intraoperative Contrast-Enhanced Ultrasound (CEUS/OCEUS) by Radiologists in Comparison to Magnetic Resonance Imaging and Histopathology. Rofo. 2017;189(5):431-40.

49. Gaianni S, Dellí N, Piscaglia F, Cecilloni L, Losinno F, Giangregorio F, et al. Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. J Hepato. 2004;41(3):421-6.

50. Dietrich CF, Kratzer W, Strobe D, Danse E, Fessl R, Bunk A, et al. Assessment of metastatic liver disease in patients with primary extrathoracic tumors by contrast-enhanced sonography versus CT and MRI. World J Gastroenterol. 2006;12(11):1699–705.

51. Tordzili G, Palmisano A, Del Fabbro D, Marconi M, Donadon M, Spirelli E, et al. Contrast-enhanced intraoperative ultrasonography during surgery for hepatocellular carcinoma in liver cirrhosis: is it useful or useless? A prospective cohort study of our experience. Ann Surg Oncol. 2007;14(4):1347–55.

52. Bartos A, Iancu I, Ciobanu L, Badescu R, Spârchez Z, Bartos D. Intraoperative ultrasound in liver and pancreatic surgery. Med Ultrasound. 2020;40:1–10.

53. Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, et al. EFSUMB Guidelines and Recommendations on the clinical use of ultrasound elastography part 2: Clinical applications. Ultraschall der Medizin. 2013;34(3):238-53.

54. Onishi K, Inoue Y, Hasegawa K, Sakamoto Y, Oikawa H, Aoki T, et al. Differential diagnosis of liver tumours using intraoperative real-time tissue elastography. BJU International. 2015;102(3):246-53.

55. Wege AK, Schardt K, Schaefer S, Kroemer A, Brockhoff G, Jung EM. High resolution ultrasound including elastography and contrast-enhanced ultrasound (CEUS) for early detection and characterization of liver lesions in the human tumor mouse model.Clin Hemorheol Micorocirc. 2012;52(2-4):93–106.

56. Platz Batista Da Silva N, Schauer M, Hornung M, Lang S, Beyer LP, Wiesinger I, et al. Intraoperative dignity assessment of hepatocellular tumors using semi-quantitative strain elastography and contrast-enhanced ultrasound for optimisation of liver tumor surgery. Clin Hemorheol Microcirc. 2016;64(4):735-45.

57. Jung EM, Platz Batista da Silva N, Jung W, Farkas S, Stroscio-Szczesny C, Renzert J. Is Strain Elastography (10-SE) Sufficient for Characterization of Liver Lesions before Surgical Resection–Or Is Contrast Enhanced Ultrasound (CEUS) Necessary? PLoS One. 2015;10(6):e0123737.

58. da Silva NPB, Hornung M, Beyer LP, Hackl C, Brunner S, Schiltz HJ, et al. Intraoperative Shear Wave Elastography vs. Contrast-Enhanced Ultrasound for the Characterization and Differentiation of Focal Liver Lesions to Optimize Liver Tumor Surgery. Ultraschall Med. 2019;40(2):205–11.

59. Wiggermann P, Brünn R, Renzert J, Loss M, Wösner H, Schreyer AG, et al. Monitoring during hepatic radiofrequency ablation (RFA): Comparison of real-time ultrasound elastography (RTE) and contrast-enhanced ultrasound (CEUS): First clinical results of 25 patients. Ultraschall der Medizin. 2013;34(6):590–4.

60. Boctor E, DeolIVEIRA M, Chotli M, Ghanem R, Taylor R, Hager G, et al. Ultrasound monitoring of tissue ablation via deformation model and shape priors. Lect Notes Comput Sci (including Subser Lect Notes Artif Intell Lect Notes Bioinformatics). 2006;4191 LNCs:405–12.

61. Correa-Gallego C, Karkar AM, Monette S, Ezell PC, Jamagain WR, Kingham TP. Intraoperative Ultrasound and Tissue Elastography Measurements Do Not Predict the Size of Hepatic Microwave Ablations. Acad Radiol. 2014;21(1):72–8.

62. Giménez M, Davileux CF, Sassamondi P, Serra E, Quero G, Palermo M, et al. Applications of Elastography in Ablation Therapies: An Animal Model in Vivo Study. J Laparoendosc Adv Surg Tech. 2020;30(9):980–6.

63. Qian X, Han X, Chen Y. Insights into the unique functionality of inorganic micro/nanoparticles for versatile ultrasound theranostics. Biomaterials. 2017;142:13-30.