

EFSUMB History of Ultrasound

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Italy (Internal Medicine)

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THE ORIGIN AND THE FOUNDATION OF THE ITALIAN SOCIETY OF US

The existence of mechanical waves called ultrasounds was first hypothesised in Italy by Lazzaro Spallanzani (Reggio Emilia, Italy, 1729-1799) in 1794, when he observed that bats were able to fly in the dark avoiding non visible obstacles and that this capacity was lost if the bats' ears were plugged. Then, Pierre and Jacques Curie discovered in 1880 the potential of quartz crystals to generate ultrasounds when stimulated by electricity (the piezoelectric effect), which is currently utilised in modern US equipment's. The first practical applications of Ultrasound (US) began after the sinking of the Titanic (1912) when the German Alexander Behm, the Englishman Lewis Richardson and the Canadian Reginald Fessender developed approximately simultaneously and independently from each other, an echo sounder.

In Italy, the first attempts to use US in medicine were done in the '60s using A-Mode instruments in Neurology, Obstetrics and Gastroenterology, but the current clinical application of US for diagnosis started at the beginning of the'70s, practically at the same time in different disciplines: Neurology, Obstetrics and Gynecology, Cardiology and Internal Medicine/Radiology. The availability in clinical practice of some prototypes of bistable instruments (i.e. Sonolayergraph, Toshiba) and of the Vidoson (Siemens) stimulated the interest of some clinicians and radiologists, who started to test the performance of this new technique in their own field and published the first results of their experiments.

The first informal interdisciplinary national meeting collecting together the few experts in the clinical application of US in different disciplines was held in La Spezia in 1974 and was organised by an Obstetrician, Prof. Alberto Zacutti. In that meeting Dr. Bolondi from Bologna, Dr. Durante from Ferrara, Prof. Colagrande from Rome, and Dr. Biggi from Genova presented their preliminary results in Internal Medicine and Radiology using bistable instruments (compound scanners) and real time (Vidoson). In the same year 1974, at an international meeting on pancreatic disease in Salerno (Italy, may 1974), Luigi Bolondi presented the first images of normal pancreas and pancreatic cysts. The first national Congress in Ultrasound was organised in 1975 in Ferrara by the new-born SISUM (Società Italiana per lo Studio degli Ultrasuoni In Medicina). SISUM was a federation of different societies founded at the beginning of the '70s for the study of US in Cardiology, Neurology, Obstetrics and Gynecology. In 1975 in Ferrara the "Section" of Internal Medicine was officially founded within the SISUM. In 1982 the Section of Internal Medicine of the SISUM, following the proposal of Luigi Bolondi, became an independent society, which was named SIUI (Società Italiana di Ultrasonografia Internistica) and in 1983 the SISUM terminated its life.

In 1987 the SIUI, which progressively enlarged the fields of interest and enrolled within its members different specialists, including internists, surgeons, radiologists, gastroenterologists, nephrologists, urologists, vascular surgeons and angiologists, gynaecologists, endocrinologists, specialists in Infectious diseases, changed its constitution and its name and became the SIUMB (Società Italiana di Ultrasonologia in Medicina e Biologia) which was founded in Bologna in 1987 [Figure 1].

Figure 1 Luigi Bolondi (SIUI Secretary) showed to the SIUI President Professor Dalla Palma and the notary of the Society the advantages of the changes to the constitution and of the name of the Society into SIUMB.



In the same year 1987 Luigi Bolondi, on behalf of SIUMB, presented at the EUROSON Congress in Helsinki the official request to become official member of EFSUMB, representing Italian US. The request was accepted.

The official journal of the SIUMB started publication in 1990 and was named "Giornale Italiano di Ultrasonologia". In 1992 the SIUMB was recognised by the President of the Italian Republic as an "Institution of relevant ethical utility". In 1997 the Website of SIUMB was created.

This is the list of the Presidents of the SISUM/SIUI/SIUMB from the foundation until 2021

PIETRO DE ALBERTIS	Presidente S.I.S.U.M.	1979-1981
GIUSEPPE LABÒ	Presidente S.I.S.U.M.	1981-1983
CORRADO COLAGRANDE	Presidente S.I.U.I.	1983-1985
GIANFRANCO FEGIZ	Presidente S.I.U.I.	1985-1987
LUDOVICO DALLA PALMA	Presidente S.I.U.M.B.	1987-1989
LUIGI BARBARA	Presidente S.I.U.M.B.	1989-1991
GIORGIO RIZZATTO	Presidente S.I.U.M.B.	1991-1993
LUIGI BOLONDI	Presidente S.I.U.M.B.	1993-1995
LORENZO DERCHI	Presidente S.I.U.M.B.	1995-1997
LUIGI BUSCARINI	Presidente S.I.U.M.B.	1997-1999
PIETRO PAVLICA	Presidente S.I.U.M.B.	1999-2001
GIAN LUDOVICO RAPACCINI	Presidente S.I.U.M.B.	2001-2003
PAOLO BUSILACCHI	Presidente S.I.U.M.B.	2003-2005
CARLO FILICE	Presidente S.I.U.M.B.	2005-2007
LEOPOLDO RUBALTELLI	Presidente S.I.U.M.B.	2007-2009
GIULIO DI CANDIO	Presidente S.I.U.M.B.	2009-2011
FRANCESCO MARIA DRUDI	Presidente S.I.U.M.B.	2011-2013

MARCELLO ROMANO	Presidente S.I.U.M.B.	2013-2015
STEFANIA SPECA	Presidente S.I.U.M.B	2015-2017
COSIMA SCHIAVONE	Presidente S.I.U.M.B.	2017-2019
VITO CANTISANI	Presidente S.I.U.M.B	2019-2021

During the National SIUMB congress in Catania in 2015 a meeting with former SIUMB President was organised [Figure 2].

Figure 2 Meeting of the SIUMB Past Presidents at the National Congress in Catania (2015): From the top left: Carlo Filice, Francesco Drudi, Giulio Di Candio, Gian Ludovico Rapaccini, Paolo Busillacchi, Piero Pavlica; in the bottom lane: Marcello Romano, Leopoldo Rubaltelli, Stefania Speca, Giorgio Rizzatto, Luigi Bolondi, Lorenzo Derchi.



INTERNATIONAL ACTIVITY OF THE ITALIAN SOCIETY OF US

The SISUM, under the chairmanship of the neurosurgeon Professor Carlo Alvisi, organised in Bologna the **3rd EFSUMB congress (Bologna, 1-5 October 1978)** [Figure 3] where Luigi Bolondi had the role of general secretary and Prof Alvisi was nominated EFSUMB President.

Figure 3 Announcement of the 3rd European Congress on Ultrasonics in Medicine in Bologna (1978)



In 1980 the SISUM organised an International School of Ultrasonology in Erice (Sicily). The program included two courses: in Internal Medicine [Figure 4) and in Vascular Diseases. Luigi Bolondi was the Director of the Course in Internal Medicine, where the Faculty was made up of the most famous US experts at that time (Francis Weill, Kenneth Taylor, Barry Goldberg, Hans Henrik Holm, Peter Wells, and others). In that meeting, after a long discussion between

American and European experts it the superiority of real time imaging with multiple array transducers [Figure 5] over the compound scanners was definitely established.



Figure 4 International School of Ultrasonology, organised by SISUM in 1980.

Figure 5 The first model of Real Time multiple linear array transducer (Aloka 202): a true revolution.



After the admission as an EFSUMB member in 1987 the SIUMB started to promote educational and scientific activities. In particular, following the proposal of Luigi Bolondi, the **Euroson School** was established with the aim of giving all European members the possibility

to receive advanced teaching in different fields of US practice with an European standard. The first course of the Euroson School (US in Gastroenterology) was held in Meran (Italy) in 1992. Subsequently Luigi Bolondi was elected EFSUMB President for the period 1996-1999 and under his Chairmanship EFSUMB had the privilege to be asked to organise the **Congress of WFUMB (World Federation for Ultrasound in Medicine and Biology)**, which was held in Florence (Italy) in 2000 [Figure 6]. The Presidents of the local organising committee were Luigi Bolondi and Giorgio Rizzatto (former SIUMB Presidents) [Figure 7] and the general secretary was Fabio Piscaglia. Over 3500 participants attended this Congress, the University of Bologna gave the "Laurea ad Honorem" to one of the pioneers of clinical ultrasonography, Professor Barry Goldberg [Figure 10].

Figure 6 Announcement of the World Congress in Ultrasound, Florence 6-10 May 2000, Organised by the SIUMB in conjunction with EFSUMB and SIUMB.



Figure 7 Luigi Bolondi and Giorgio Rizzatto, Chairmen of the Local Organising Committee of the World Congress in Ultrasound.



Figure 8 Opening Ceremony of the 2000 World Congress. From the left: Piero Pavlica (SIUMB President), Michel Claudon (EFSUMB President), Luigi Bolondi and Giorgio Rizzatto (Chairmen of the Local Organising Committee, Harald Lutz (WFUMB President).



Figure 9 A picture of the social event of the 2000 World Congress: the Concert in the Church of Santa Croce.



Figure 10 "Laurea ad Honorem" of the University of Bologna to Barry Goldberg during the 2000 World Congress.



As EFSUMB President, in order to encourage greater participation by members, he established the rule that the EUROSON Congress should be organised in conjunction with a national US Congress. This rule started with the EUROSON Congress in Tours (France) in conjunction with the French Society of Ultrasound. Over the following years the Italian Society SIUMB had the privilege of organising the **EUROSON Congress of 2006 in Bologna** [Figure 11]. Following this Congress, the University of Bologna gave the "Laurea ad Honorem" to the pioneer of interventional Ultrasonography, Professor Hans Henrik Holm [Figure 12]. In the Centre directed by Prof. Holm many Italian physicians trained in interventional US.

Figure 11 Announcement of the 10th European Congress on Ultrasound (EUROSON) in conjunction with the National SIUMB Congress (Bologna 15-19 September 2006).



Figure 12 Laurea ad Honorem to Hans Henrik Holm during the Euroson in Bologna in 2006.



After Carlo Alvisi and Luigi Bolondi, Fabio Piscaglia was the third Italian EFSUMB President in the years 2011-2013. Under his chairmanship international cooperation continued very actively [Figure 13) It is remarkable that Bologna has been the only town in Europe to have given three Presidents to EFSUMB and to have organised two Euroson Congresses. Figure 13 Dinner at Bolondi's house after a meeting in Bologna for EFSUMB guidelines (September 2012). From the left: Bolondi, Gilja, Sporea, Mrs Sporea, Dietrich, Mrs Dietrich, Piscaglia.



SCIENTIFIC CONTRIBUTION OF ITALY TO THE DEVELOPMENT OF US

The SIUMB has been very active in promoting education and research. It is worth mentioning the big effort made collectively by the whole Italian US community at the beginning of the '90s, when, under the endorsement of SIUMB, a comprehensive and exhaustive textbook and atlas of Ultrasonography (4 volumes of over 1600 pages) was published: "Trattato Italiano di Ultrasonologia" [Figure 14].

Figure 14 Cover of the Italian Textbook and atlas of Echography (1993).



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Italian scientists who made important contributions to the development of the clinical application of US in its early years have been numerous and it is impossible to report the hundreds of articles in the international literature.

We would like just to recall some clinicians who gave international contributions to the development of US **in the years 1975-2000**, recalling few articles demonstrating their activity as pioneers in US and we apologise for not mentioning many others.

In particular I would like to mention the names of **Carlo Colagrande** (Rome) [(1)] who first in Italy, presented a communication on the use of US in Gastroenterology at the National Congress of Gastroenterology in L'Aquila in 1973; Lionello Gandolfi (Bologna) who collaborated with Luigi Bolondi on the production of the first Italian Text/atlas of Ultrasound in Gastroenterology [Figure 15) published in 1978; Licinio Angelini (Rome) [(2)] who, after a period of study at Thomas Jefferson University in Philadelphia developed the use of US in surgery; **Tito Livraghi** (Vimercate, Milan) [(3-5)][Figures 16 and 17), who was one of the most important pioneers in Interventional US, introducing, first in the world, the technique of Percutaneous Ethanol Injection; Giorgio Rizzatto (Gorizia) [(6)] [Figure 7) a pioneer in breast US; Luigi Solbiati (Busto Arsizio, Milan) [(7, 8)], a pioneer in thyroid US, interventional techniques in Oncology and US contrast agents; Lorenzo Derchi (Genoa) [(9)] for US in abdominal diseases; the group from Piacenza: Luigi Buscarini [(10)], Fabio Fornari [(10)], Elisabetta Buscarini [(11)] and Sandro Rossi [(12)] [Figure 16) (the latter was the first to experiment in the US guided RF thermal ablation of liver tumours; Piero Pavlica (Bologna) [(13)] [Figure 8) for prostate and kidney US; Carlo Filice (Pavia) [(14)] for US in infectious disease; Marcello Caremani and Fabrizio Magnolfi (Arezzo) [(15)] [Figure 17), for US in Gastroenterology and Oncology, Paolo Busilacchi (Ancona) [(16)] for breast US, GianLudovico Rapaccini (Roma)[(17)] for US in Gastroenterology, Giulio Di Candio (Pisa) [(18)] for US in prostate and pancreatic diseases, Antonio Giorgio (Naples) [(19, 20)] [Figure 17) for interventional US in liver diseases. We apologise for many others not reported in this list.

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Figure 15 Textbook and atlas published in 1978 in Italy and in1983 in UK

Figure 16 Tito Livraghi (on the right) attending a meeting in Craiova (Romania) in 2008.



Figure 17 Some of the Italian pioneers in US at a meeting in Gargonza (Arezzo) in 2002. From the second left: Rossi, Bolondi, Magnolfi, Giorgio, Livraghi.



The following is a summary of the history of the scientific contributions by Luigi Bolondi, written by Christoph F Dietrich and Yi Dong, which were published In the *Festschrift* "Luigi Bolondi Felicitations Volume-Studies in Medicine and its history" C Borghi, P Ognibene, A Panaino Eds. Mimesis Publ 2021. It is representative of the evolution of research on US in Gastroenterology in Italy.

The first publications

In 1976, Prof. Luigi Bolondi focused as a very early pioneer of ultrasound of pancreatic disease. He first published a paper in Gut [(21)]. The authors proved that there was good agreement between the echographic picture and surgical findings of pancreatic diseases. It concluded that echography is a simple, safe, and valuable method in addition to existing imaging techniques available for studying the pancreas [Figure 18].



Figure 18 Pseudocyst of the tail of the pancreas (arrow) in chronic calcifying pancreatitis.

In 1978 Luigi Bolondi pioneered the study of the portal venous system and portal hypertension using ultrasonography. In his Lancet publication [(22)] he showed that, on the oblique scans, the right portal vein is always clearly recognisable near the porta hepatis [Figure 19], and Ultrasound (US) can therefore be considered a simple, safe, rapid and important technique in the diagnosis of extrahepatic portal venous obstruction.

Figure 19 The portal vein (PV) on oblique section of abdominal ultrasound with a compound scanner (1978).



After addressing the pancreas and the portal venous system, in 1978, Prof. Bolondi published a paper in the American Journal of Gastroenterology [(23)] on the use of US as a first step in the diagnostic approach to cholestasis. Since then, information gained from this non-invasive technique makes it possible to correctly plan the more complex investigations such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTCD).

Masterpieces in Gastroenterology

In 1985, Prof. Bolondi published a paper in Gastroenterology, which described a new ultrasound method of assessing gastric emptying time based on measurements of the gastric antrum, which is visible in almost all subjects before and after meals. Bolondi et al. concluded that this kind of ultrasound study of the antropyloric region allowed accurate determination of total gastric emptying time [(24)].

In the '80s, Prof. Bolondi was a pioneer of Endoscopic Ultrasonography (EUS) [Figure 20) and an International Meeting was organised in Bologna in 1983 [Figure 21) to present the first experimental results of this technique. By means of EUS the number and anatomical correspondence of the sonographically recognisable layers within the gastric wall in vivo were identified. For the first time in ultrasound history, the authors took into account the physical laws of ultrasound interactions with tissues and concluded that the 1st and the 5th hyperechoic layers were partially generated by ultrasound reflection at the interface liquid/wall; the 2nd hypoechoic layer correspond to the deepest part of the mucosa; the 3rd hyperechoic layer to the muscularis propria. These findings opened a new era for the clinical ultrasound applications in the diagnosis of gastric wall diseases [(25-27)] [Figures 22 and 23]. He also undertook pioneering research on the ultrasound application in the diagnosis of the pseudomembranous colitis [(28)]. Figure 20 Luigi Bolondi, Giancarlo Caletti and Giuseppe Labò (former SISUM President) with prototype equipment for Endoscopic Ultrasonography (Olympus) in 1983.

Figure 21 Announcement of the International Symposium on Endoscopic Ultrasonography (1983).

Figure 22 Normal appearance of five layers within the stomach wall (arrows), well visualised by endoscopic ultrasound in vivo after water filling of the stomach.

Figure 23 Normal appearance of five layers within the stomach wall (arrow) easily recognised by conventional transabdominal ultrasound.

EUS enables high-resolution imaging of the stomach and can demonstrate the different layers of the gastric wall. Therefore, Prof. Bolondi proposed EUS in 1987 for use in evaluating the extension of gastric neoplasms. Three different ultrasound patterns were found in gastric lymphomas [Figure 24]. However, gastric carcinomas had a more echogenic pattern and a different trend of diffusion, with no extended longitudinal hypoechoic infiltration of the superficial layers or extended hypoechoic transmural infiltration [(29)]. Ever since then,

endoscopic ultrasound has become increasingly useful for the detection of the early stages of infiltration of gastric malignant tumours when the overlying mucosa is still intact [(30)].

Figure 24 Diffuse gastric lymphoma with extended longitudinal thickening (arrows) of the gastric wall (2 cm thick) and complete disappearance of normal layers [(14)].

EUS also contributed to the correct diagnosis in gastric submucosal tumours. Leiomyoma and lipoma are easily recognised by their location and echogenicity [Figure 25]. In gastric submucosal tumours, endoscopic ultrasound can reduce the need for aggressive and risky biopsy or exploratory laparotomy.

Figure 25 A leiomyoma (arrow) mimicking a large polypoid lesion was detected within the water-filled stomach.

Portal Hypertension (with and without Budd Chiari Syndrome, BCS)

The first application of ultrasound in the assessment of the portal venous system was reported in the Lancet in the year 1978 [(22)]. In 1982, Prof. Bolondi assessed the usefulness of ultrasound for the diagnosis of portal hypertension due to liver cirrhosis [Figure 26]. For the first time, a lack of normal caliber variation (an increase during inspiration and a decrease during expiration) in the vessels of the portal venous system was proposed as an ultrasound sign of portal hypertension. The pathophysiological and clinical significance of these findings are discussed in detail [(30-32)]. The sonographic findings in portal hypertension and its correlation with the presence and size of oesophageal varices were also evaluated and reported [(33)].

Figure 26 Portal hypertension due to liver cirrhosis. Patent and dilated umbilical vein both in transverse (a) and sagittal scan (b) [(18)].

In 1991, Prof. Bolondi showed that Doppler ultrasonography provided qualitative data on flow direction and pattern in the hepatic venous system [(34)], thereby contributing significantly to the diagnosis of Budd-Chiari syndrome (BCS) [(35)]. Bolondi et al. findings demonstrated that absent or reversed flow in the hepatic veins and/or flat flow in the hepatic veins are associated with reversed flow in the inferior vena cava and may be considered diagnostic for BCS [(35)]. They further assessed the influence of oesophageal varices and spontaneous portal-systemic shunts on postprandial splanchnic haemodynamics [(36)] and the interobserver, interequipment, and time-dependent variability's of echo-

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Doppler measurements of portal blood flow velocity (PBV), portal vein diameters (PVDs) and their derived parameters, portal blood flow (PBF), and congestion index (CI) in patients with cirrhosis [Figure 24]. Their results were published in Hepatology and indicated that (1) a significant systematic variability exists between Doppler measurements with different equipment; (2) there is no significant time-dependent systematic variability of Doppler measurements; and (3) a cooperative training program reduces the interobserver variability for direct measurements, such as PBV [(37)]. In addition they studied changes of Doppler waveform of hepatic veins in liver cirrhosis [(38)] and the effect of propranolol on portosystemic collateral circulation in patients with cirrhosis [(39)].

In the 1980s, a quantitative measurement of the volume of blood flow by Doppler flowmetry was attempted in some of the major abdominal arteries and veins, but the reliability of these measurements was still questioned [(40, 41)]. Systematic variability existed among mesenteric Doppler measurements obtained by different operators using different commercially available equipment [(42)]. Prof. Bolondi suggested that the qualitative information on flow pattern provided by Doppler investigation not only contributed to clarifying doubtful images in real-time ultrasound, but also provide new insights into clinical conditions [(43)].

In another study they evaluated the effect of two different doses of secretin on portal haemodynamics (by pulsed Doppler associated with real time ultrasound) in 24 healthy humans. They suggested that secretin had an appreciable vasoactive effect and induced a significant increase in portal venous flow even at doses much lower than those necessary for a maximal stimulation of exocrine pancreatic secretion [(44)].

The commitment of Prof. Bolondi's group to the understanding of portal hypertension and chronic liver disease by using ultrasound and Doppler-ultrasound is shown by a large number of papers published in the following decade, including US use to detect unusual spontaneous portosystemic shunts associated with uncomplicated portal hypertension, to evaluate the morphological bases of splenic circulation in congestive splenomegaly in cirrhosis of different aetiology [(45)], to assess the hepatic artery resistance in portal vein thrombosis [(46)], diagnosis and monitoring of portohepatic vascular pathology and liver disease [(47)].

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Focal liver lesions

Prof. Bolondi and his team shaped the applications of ultrasound to identify and characterise focal liver lesions from very early times [(48)]. His interest was broad, ranging from the diagnosis of hepatic cysts and haemangiomas [(49)] to that of malignancies in patients with cirrhosis [Figures 27 and 28].

Figure 27 Liver cyst by longitudinal scan. Compound Grey scale (1976)

Figure 28 Hypoechoic liver metastases (m) by longitudinal scan. Compound Grey scale (1976)

Hepatocellular carcinoma

Luigi Bolondi reported the relationship between alpha- fetoprotein serum levels, tumour volume and growth rate of HCC in a western population [(50)]. He assessed between March 1989 and November 1991 the cost effectiveness of a US surveillance programme in a cohort of 313 patients with liver cirrhosis for the early diagnosis and treatment of HCC [(51)]. In a large retrospective study on 2091 biopsies, Prof. Bolondi investigated ultrasound-guided fine-needle biopsy of focal liver lesions [(10)], proving that the diagnostic accuracy of fine-needle biopsies was very high (only one false positive was observed), both for aspiration biopsy (93.4%) and for cutting biopsy (95.1%) [(10, 51)].

To define indications for percutaneous ethanol injection (PEI) in patients with HCC and cirrhosis, Prof. Bolondi and his team collaborated to a long-term follow- up of 746 patients between 1985 to 1993 [(52)]. They indicated that PEI is safe, effective, and repeatable and had low cost. Survival after PEI was comparable to that after surgery [(3-5)]. These findings strengthened the use of US-guided loco regional therapies for HCC.

Prof. Bolondi and his team made some breakthrough discoveries in the liver transplantation area. They investigated the long-term changes induced by orthotopic liver transplantation (OLT) on several hemodynamic parameters and first reported in Hepatology in 1999 that systemic, renal, and splanchnic circulatory alterations of cirrhosis are restored to normal after OLT [(53)].

Contrast enhanced ultrasound was a new imaging method at that time. Prof. Bolondi first evaluated the use of Levovist to assess splanchnic haemodynamics in cirrhotic patients [(54)] and in liver transplantation, and to assess the conservative management of post-transplant intra-hepatic pseudo-aneurysm. Diagnosis of HCC relies strongly on the detection of hypervascularity in the arterial phase. Luigi Bolondi first investigated the usefulness of low mechanical index harmonic ultrasound, using a second generation contrast enhanced technique in the assessment of vascular pattern of HCC shown to be hypervascular at spiral CT [Figure 29]. Contrast enhanced ultrasound showed good diagnostic agreement with spiral CT in hypervascular HCC and might be proposed for the immediate vascular characterisation of nodules detected on US and used as second imaging technique to confirm hypervascularity in cirrhotic nodules [(55)].

Figure 29 Vascular enhancement pattern of hepatocellular carcinoma using contrast enhanced ultrasound (picture taken in 2002).

Prof. Bolondi and his group indicated the value and limitation of the different Doppler ultrasound modalities for the assessment of vascular patterns of small liver mass lesions. In a prospective study [(56)], Prof. Bolondi examined the impact of arterial hypervascularity, as established by the European Association for the Study of the Liver (EASL) recommendations, as a criterion for characterising small (1 - 3 cm) nodules in liver cirrhosis. They suggested in their paper published in Hepatology that the non-invasive EASL criteria for diagnosis of HCC are satisfied in only 61% of small nodules in liver cirrhosis. Any nodule larger than 2 cm should be regarded as highly suspicious for HCC [(57)]. They also made cost analysis of recall strategies for non-invasive diagnosis of small hepatocellular carcinoma [(58)].

Prof. Bolondi and his team also used real-time contrast enhanced harmonic sonography at low acoustic energy to evaluate liver metastases from rectal carcinoma [(59)], gastrointestinal cancer and metastatic portal vein thrombosis [(60)]. They also differentiated between various liver tumours [(61-63)] and made quantitative analysis of liver tumour perfusion by contrast enhanced ultrasound [(64)].

Prof. Bolondi and his team evaluated the safety of Sonovue in abdominal applications in a retrospective analysis of 23,188 investigations [(65)]. He published the first guideline for the use of contrast agents in ultrasound in January 2004 [(66)] and a position paper of the Italian Association for the Study of the Liver (AISF) for the multidisciplinary clinical approach to hepatocellular carcinoma [(67)]. Luigi Bolondi's team also compared international guidelines for non-invasive diagnosis of hepatocellular carcinoma and updated the contrast enhanced ultrasound guideline in 2008 [(68)]. Luigi Bolondi's contribution to hepatology and medicine goes far beyond ultrasound. In the field of advanced HCC, he was one of the authors of two

large randomised controlled trials proving that systemic therapy using a multikinase inhibitor (Sorafenib) and Cabozantinib can improve survival. The results were published in two articles in the New England Journal of Medicine [(69, 70)]. The intermediate stage of HCC comprises a highly heterogeneous patient population and, therefore, poses unique challenges for therapeutic management, different from the early and advanced stages [(71)]. In April 2012, Prof. Bolondi joined a panel of experts and discussed unresolved issues surrounding the application of guidelines when managing patients with intermediate HCC. The meeting explored the applicability of a subclassification system for intermediate HCC patients to tailor therapeutic interventions based on the evidence available to date and expert opinion [(71)].

Pancreatic disease

Prof. Bolondi and his team first made an evaluation of echography for the diagnosis of pancreatic disease in 1975 [(1)] [Figures 30 and 31], comparing morphological changes with functional impairment [(72, 73)]. They also evaluated the effect of secretin stimulation on the US appearance of the normal pancreas and in case of chronic pancreatitis [(74)].

Figure 30 Enlarged head of the Pancreas – Longitudinal scan – Compound bistable scanner (1974)

Figure 31 Enlarged head of the pancreas – Transverse scan – Compound bistable scanner (1974).

For ultrasound imaging of the pancreas, the body is the best visualised part of the pancreas, however, the head and the tail are always obscured by gas in the stomach or duodenum. In order to improve the pancreatic ultrasound imaging, Prof. Bolondi stimulated pancreatic juice secretion by a standard dose of intravenous secretin in 24 normal subjects. They observed that 4 to 5 minutes after hormone administration pancreatic juice outflow into the duodenum generated a fluid-filled echo free area around the head of the pancreas, allowing excellent visualisation of its boundaries and other channel structures [Figure 32]. They also observed that secretin injection induces a dilatation of the Wirsung duct, which can be easily visualised [Figure 33]. The dilatation is absent or irregular in case of chronic pancreatitis [(75, 76)]. This method was also suggested to be utilised in selected patients whenever a pathological condition of the pancreatic head region is suspected.

Figure 32 A figure in Prof. Bolondi's paper showed Improvement of pancreatic head visualisation after secretin-induced pancreatic secretion.

Figure 33 Progressive dilatation of the Wirsung duct under secretin stimulation (picture of 1983 with a linear array transducer)

Intraoperative US

Intraoperative ultrasonography was first used in the 1980s patients during surgery for suspected liver tumours. This new imaging technique facilitated the diagnosis of small liver tumours and also aided the surgeon in his choice of technique, especially in cases of cirrhosis of the liver. A resection can be avoided altogether when multiple lesions are involved, or echo-guided subsegmentary resections can be performed in cirrhotic livers when a less extended resection is required. This technique makes it possible to establish the relationship between the tumour and intrahepatic vessels, thus preventing vascular injury and making radical hepatic resection safer [(75, 77)].

References

1. Colagrande C. Introduction to the imaging of biliary obstruction. Rays 1989;14:13-15.

2. Angelini L, Bezzi M, Tucci G, Bezzi M, Ciulli A, Bonifacino A, Fegiz G. Intraoperative highresolution hepatosonography in the detection of occult metastases in colorectal carcinoma. Ital J Surg Sci 1983;13:203-208.

3. Livraghi T, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, Salmi A, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. Cancer 1992;69:925-929.

4. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995;197:101-108.

5. Livraghi T, Salmi A, Bolondi L, Marin G, Arienti V, Monti F, Vettori C. Small hepatocellular carcinoma: percutaneous alcohol injection--results in 23 patients. Radiology 1988;168:313-317.

6. Rizzatto G, Chersevani R, Abbona M, Lombardo VL, Macorig D. High-resolution sonography of breast carcinoma. Eur J Radiol 1997;24:11-19.

7. Schober O, Schwarzrock R. The thyroid gland with low uptake lesions: evaluation by ultrasound. Radiology 1986;158:277-278.

8. Solbiati L, Giangrande A, De Pra L, Bellotti E, Cantu P, Ravetto C. Percutaneous ethanol injection of parathyroid tumors under US guidance: treatment for secondary hyperparathyroidism. Radiology 1985;155:607-610.

9. Derchi LE, Ierace T, De Pra L, Solbiati L, Rizzatto G, Musante F. The sonographic appearance of duodenal lesions. J Ultrasound Med 1986;5:269-273.

10. Buscarini L, Fornari F, Bolondi L, Colombo P, Livraghi T, Magnolfi F, Rapaccini GL, et al. Ultrasound-guided fine-needle biopsy of focal liver lesions: techniques, diagnostic accuracy and complications. A retrospective study on 2091 biopsies. J Hepatol 1990;11:344-348.

11. Buscarini E, Buscarini L. The role of endosonography in the diagnosis of choledocholithiasis. Eur J Ultrasound 1999;10:117-125.

12. Rossi S, Di Stasi M, Buscarini E, Quaretti P, Garbagnati F, Squassante L, Paties CT, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR Am J Roentgenol 1996;167:759-768.

13. Veneziano S, Pavlica P, Viglietta G, Lalanne MG. US-guided prostatic biopsy in 63 cases. Eur J Radiol 1989;9:64-66.

14. Filice C, Pirola F, Brunetti E, Dughetti S, Strosselli M, Foglieni CS. A new therapeutic approach for hydatid liver cysts. Aspiration and alcohol injection under sonographic guidance. Gastroenterology 1990;98:1366-1368.

15. Di Stasi M, Buscarini L, Livraghi T, Giorgio A, Salmi A, De Sio I, Brunello F, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. Scand J Gastroenterol 1997;32:1168-1173.

16. Busilacchi P, Draghi F, Preda L, Ferranti C. Has color Doppler a role in the evaluation of mammary lesions? J Ultrasound 2012;15:93-98.

17. Rapaccini GL, Pompili M, Caturelli E, Anti M, Aliotta A, Cedrone A, Amadei E, et al. Focal ultrasound lesions in liver cirrhosis diagnosed as regenerating nodules by fine-needle biopsy. Follow-up of 12 cases. Dig Dis Sci 1990;35:422-427.

18. DiCandio G, Mosca F, Campatelli A, Bianchini M, D'Elia F, Dellagiovampaola C. Sonographic detection of postsurgical recurrence of Crohn disease. AJR Am J Roentgenol 1986;146:523-526. 19. Giorgio A, Tarantino L, Francica G, Mariniello N, Nuzzo A, del Viscovo L, Rotondo A. One-shot percutaneous ethanol injection of liver tumors under general anesthesia: preliminary data on efficacy and complications. Cardiovasc Intervent Radiol 1996;19:27-31.

20. Giorgio A, Tarantino L, Mariniello N, Francica G, Scala E, Amoroso P, Nuzzo A, et al. Pyogenic liver abscesses: 13 years of experience in percutaneous needle aspiration with US guidance. Radiology 1995;195:122-124.

21. Fontana G, Bolondi L, Conti M, Plicchi G, Gullo L, Caletti GC, Labo G. An evaluation of echography in the diagnosis of pancreatic disease. Gut 1976;17:228-234.

22. Bolondi L, Gandolfi L. Ultrasonography in assessment of portal venous system. Lancet 1978;1:656-657.

23. Bolondi L, Gandolfi L, Rossi A, Caletti GC, Fontana G, Labo G. Ultrasound in the diagnosis of cholestatic jaundice. Am J Gastroenterol 1979;71:168-176.

24. Bolondi L, Bortolotti M, Santi V, Calletti T, Gaiani S, Labo G. Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology 1985;89:752-759.

25. Bolondi L, Caletti G, Casanova P, Villanacci V, Grigioni W, Labo G. Problems and variations in the interpretation of the ultrasound feature of the normal upper and lower GI tract wall. Scand J Gastroenterol Suppl 1986;123:16-26.

26. Bolondi L, Casanova P, Santi V, Caletti G, Barbara L, Labo G. The sonographic appearance of the normal gastric wall: an in vitro study. Ultrasound Med Biol 1986;12:991-998.

27. Caletti G, Bolondi L, Labo G. Ultrasonic endoscopy--the gastrointestinal wall. Scand J Gastroenterol Suppl 1984;102:5-8.

28. Bolondi L, Ferrentino M, Trevisani F, Bernardi M, Gasbarrini G. Sonographic appearance of pseudomembranous colitis. J Ultrasound Med 1985;4:489-492.

29. Bolondi L, Casanova P, Caletti GC, Grigioni W, Zani L, Barbara L. Primary gastric lymphoma versus gastric carcinoma: endoscopic US evaluation. Radiology 1987;165:821-826.

30. Bolondi L, De Giorgio R, Santi V, Paparo GF, Pileri S, Di Febo G, Caletti GC, et al. Primary non-Hodgkin's T-cell lymphoma of the esophagus. A case with peculiar endoscopic ultrasonographic pattern. Dig Dis Sci 1990;35:1426-1430.

31. Gaiani S, Bolondi L, Li Bassi S, Zironi G, Siringo S, Barbara L. Prevalence of spontaneous hepatofugal portal flow in liver cirrhosis. Clinical and endoscopic correlation in 228 patients. Gastroenterology 1991;100:160-167.

32. Piscaglia F, Donati G, Serra C, Muratori R, Solmi L, Gaiani S, Gramantieri L, et al. Value of splanchnic Doppler ultrasound in the diagnosis of portal hypertension. Ultrasound Med Biol 2001;27:893-899.

33. Bolondi L, Caletti G, Brocchi E, Ferrentino M, Calcamuggi G, Casanova P, Gasbarrini G, et al. Ultrasonographic findings in portal hypertension: correlation with the presence and size of oesophageal varices. Ultrasound Med Biol 1983;Suppl 2:499-503.

34. Bolondi L, Gaiani S, Barbara L. Accuracy and reproducibility of portal flow measurement by Doppler US. J Hepatol 1991;13:269-273.

35. Bolondi L, Gaiani S, Li Bassi S, Zironi G, Bonino F, Brunetto M, Barbara L. Diagnosis of Budd-Chiari syndrome by pulsed Doppler ultrasound. Gastroenterology 1991;100:1324-1331.

36. Siringo S, Piscaglia F, Zironi G, Sofia S, Gaiani S, Zammataro M, Bolondi L. Influence of esophageal varices and spontaneous portal-systemic shunts on postprandial splanchnic hemodynamics. Am J Gastroenterol 2001;96:550-556.

37. Sabba C, Merkel C, Zoli M, Ferraioli G, Gaiani S, Sacerdoti D, Bolondi L. Interobserver and interequipment variability of echo-Doppler examination of the portal vein: effect of a cooperative training program. Hepatology 1995;21:428-433.

38. Bolondi L, Li Bassi S, Gaiani S, Zironi G, Benzi G, Santi V, Barbara L. Liver cirrhosis: changes of Doppler waveform of hepatic veins. Radiology 1991;178:513-516.

39. Gaiani S, Bolondi L, Fenyves D, Zironi G, Rigamonti A, Barbara L. Effect of propranolol on portosystemic collateral circulation in patients with cirrhosis. Hepatology 1991;14:824-829.

40. Piscaglia F, Gaiani S, Bolondi L. Diagnosis of cirrhosis and portal hypertension. Am J Gastroenterol 1998;93:1598-1599.

41. Sacerdoti D, Gaiani S, Buonamico P, Merkel C, Zoli M, Bolondi L, Sabba C. Interobserver and interequipment variability of hepatic, splenic, and renal arterial Doppler resistance indices in normal subjects and patients with cirrhosis. J Hepatol 1997;27:986-992.

42. Piscaglia F, Gaiani S, Siringo S, Gramantieri L, Serra C, Bolondi L. Duplex-Doppler evaluation of the effects of propranolol and isosorbide-5-mononitrate on portal flow and splanchnic arterial circulation in cirrhosis. Aliment Pharmacol Ther 1998;12:475-481.

43. Bolondi L, Li Bassi S, Gaiani S, Barbara L. Doppler flowmetry in portal hypertension. J Gastroenterol Hepatol 1990;5:459-467.

44. Bolondi L, Gaiani S, Li Bassi S, Zironi G, Casanova P, Barbara L. Effect of secretin on portal venous flow. Gut 1990;31:1306-1310.

45. Bolondi L, Zironi G, Gaiani S, Li Bassi S, Benzi G, Barbara L. Caliber of splenic and hepatic arteries and spleen size in cirrhosis of different etiology. Liver 1991;11:198-205.
46. Piscaglia F, Gaiani S, Zironi G, Siringo S, Bolondi L. Hepatic artery resistance in portal

vein thrombosis. Radiology 1996;200:285-286.

47. Bolondi L, Gaiani S, Gebel M. Portohepatic vascular pathology and liver disease: diagnosis and monitoring. Eur J Ultrasound 1998;7 Suppl 3:S41-52.

48. Gandolfi L, Bolondi L, Rossi A, Fontana G. [Role of grey scale echotomography in the diagnosis of liver diseases]. Recenti Prog Med 1977;63:527-538.

49. Gandolfi L, Solmi L, Bolondi L, Rossi A, Casanova P, Leo P. The value of ultrasonography in the diagnosis of hepatic haemangiomas. Eur J Radiol 1983;3:222-226.

50. Bolondi L, Benzi G, Santi V, Gaiani S, Li Bassi SL, Zironi G, Mazziotti A, et al. Relationship between alpha-fetoprotein serum levels, tumour volume and growth rate of hepatocellular carcinoma in a western population. Ital J Gastroenterol 1990;22:190-194.

51. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001;48:251-259.

52. Gozzetti G, Mazziotti A, Bolondi L, Cavallari A, Grigioni W, Casanova P, Bellusci R, et al. Intraoperative ultrasonography in surgery for liver tumors. Surgery 1986;99:523-530.

53. Piscaglia F, Zironi G, Gaiani S, Mazziotti A, Cavallari A, Gramantieri L, Valgimigli M, et al. Systemic and splanchnic hemodynamic changes after liver transplantation for cirrhosis: a long-term prospective study. Hepatology 1999;30:58-64.

54. Gaiani S, Serra C, Piscaglia F, Celli N, Rasciti L, Miglioli M, Bolondi L. Effect of Levovist on splanchnic hemodynamics in cirrhotic patients. Ultrasound Med Biol 2003;29:643-648.
55. Gaiani S, Celli N, Piscaglia F, Cecilioni L, Losinno F, Giangregorio F, Mancini M, et al. Usefulness of contrast-enhanced perfusional sonography in the assessment of hepatocellular carcinoma hypervascular at spiral computed tomography. J Hepatol 2004;41:421-426.

56. Gaiani S, Casali A, Serra C, Piscaglia F, Gramantieri L, Volpe L, Siringo S, et al. Assessment of vascular patterns of small liver mass lesions: value and limitation of the different Doppler ultrasound modalities. Am J Gastroenterol 2000;95:3537-3546.

57. Bolondi L, Gaiani S, Celli N, Golfieri R, Grigioni WF, Leoni S, Venturi AM, et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology 2005;42:27-34.

58. Piscaglia F, Leoni S, Cabibbo G, Borghi A, Imbriaco G, Golfieri R, Bolondi L. Cost analysis of recall strategies for non-invasive diagnosis of small hepatocellular carcinoma. Dig Liver Dis 2010;42:729-734.

59. Piscaglia F, Gaiani S, Tamberi S, Celli N, Cecilioni L, Gramantieri L, Bolondi L. Liver metastases from rectal carcinoma: disease progression during chemotherapy despite loss of arterial-phase hypervascularity on real-time contrast-enhanced harmonic sonography at low acoustic energy. J Clin Ultrasound 2003;31:387-391.

60. Venturi A, Piscaglia F, Silvagni E, Righini R, Fabbrizio B, Cescon M, Bolondi L. Role of real-time contrast-enhanced ultrasound in the assessment of metastatic portal vein thrombosis. Ultraschall Med 2007;28:75-78.

61. Bolondi L. The appropriate allocation of CEUS in the diagnostic algorithm of liver lesions: a debated issue. Ultrasound Med Biol 2013;39:183-185.

62. Bolondi L, Correas JM, Lencioni R, Weskott HP, Piscaglia F. New perspectives for the use of contrast-enhanced liver ultrasound in clinical practice. Dig Liver Dis 2007;39:187-195.

63. Ignee A, Livraghi T, Tranquart F, Bolondi L, Dietrich C, Albrecht T. Ver besserte Detektion von Leberläsionen durch Ultraschall-Kontrastmittel der zweiten Generation im Vergleich zur konventionellen Sonographie. Endoskopie heute 2009; 22:105-109.

64. Salvatore V, Borghi A, Sagrini E, Galassi M, Gianstefani A, Bolondi L, Piscaglia F. Quantification of enhancement of focal liver lesions during contrast-enhanced ultrasound (CEUS). Analysis of ten selected frames is more simple but as reliable as the analysis of the entire loop for most parameters. Eur J Radiol 2012;81:709-713.

65. Piscaglia F, Bolondi L, Italian Society for Ultrasound in M, Biology Study Group on Ultrasound Contrast A. The safety of Sonovue in abdominal applications: retrospective analysis of 23188 investigations. Ultrasound Med Biol 2006;32:1369-1375.

66. Albrecht T, Blomley M, Bolondi L, Claudon M, Correas JM, Cosgrove D, Greiner L, et al. Guidelines for the use of contrast agents in ultrasound. January 2004. Ultraschall Med 2004;25:249-256.

67. Italian Association for the Study of the L, Panel AE, Committee AC, Bolondi L, Cillo U, Colombo M, Craxi A, et al. Position paper of the Italian Association for the Study of the Liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. Dig Liver Dis 2013;45:712-723.

68. Claudon M, Cosgrove D, Albrecht T, Bolondi L, Bosio M, Calliada F, Correas JM, et al. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) - update 2008. Ultraschall Med 2008;29:28-44.

69. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, Cicin I, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. N Engl J Med 2018;379:54-63.

70. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.

71. Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348-359.

72. Bolondi L, Li Bassi S, Gaiani S, Barbara L. Sonography of chronic pancreatitis. Radiol Clin North Am 1989;27:815-833.

73. Bolondi L, Priori P, Gullo L, Santi V, Li Bassi S, Barbara L, Labo G. Relationship between morphological changes detected by ultrasonography and pancreatic exocrine function in chronic pancreatitis. Pancreas 1987;2:222-229.

74. Bolondi L, Gaiani S, Gullo L, Labo G. Secretin administration induces a dilatation of main pancreatic duct. Dig Dis Sci 1984;29:802-808.

75. Bolondi L, Gaiani S, Casanova P, Testa S, Priori P, Labo G. Improvement of pancreatic ultrasound imaging after secretin administration. Ultrasound Med Biol 1983;9:497-501.

76. Bolondi L, Li Bassi S, Gaiani S, Santi V, Gullo L, Barbara L. Impaired response of main pancreatic duct to secretin stimulation in early chronic pancreatitis. Dig Dis Sci 1989;34:834-840.

77. Gozzetti G, Mazziotti A, Cavallari A, Bellusci R, Bolondi L, Grigioni W, Bragaglia R, et al. Clinical experience with hepatic resections for hepatocellular carcinoma in patients with cirrhosis. Surg Gynecol Obstet 1988;166:503-510.