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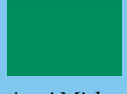

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EDITORIAL

Real-time dosimetry in external beam radiation therapy

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Abstract

With growing complexity in radiotherapy treatment delivery, it has become mandatory to check each and every treatment plan before implementing clinically. This process is currently administered by an independent secondary check of all treatment parameters and as a pre-treatment quality assurance (QA) check for intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy treatment plans. Although pre-treatment IMRT QA is aimed to ensure the correct dose is delivered to the patient, it does not necessarily predict the clinically relevant patient dose errors. During radiotherapy, treatment uncertainties can affect tumor control and may increase complications to surrounding normal tissues. To combat this, image guided radiotherapy is employed to help ensure the plan conditions are mimicked on the treatment machine. However, it does not provide information on actual delivered dose to the tumor volume. Knowledge of actual dose delivered during treatment aid in confirming the prescribed dose and also to replan/reassess the treatment in situations where the planned dose is not delivered as expected by the treating physician. Major accidents in radiotherapy would have been averted if real time dosimetry is incorporated as part of the routine radiotherapy procedure. Of late real-time dosimetry is becoming popular with complex treatments in radiotherapy. Real-time dosimetry can be either in the form of point doses or planar doses or projected on to a 3D image dataset to obtain volumetric dose. They either provide entrance dose or exit dose or dose inside the natural cavities of a patient. In external beam radiotherapy, there are four different established platforms whereby the delivered dose information can be obtained: (1) Collimator; (2) Patient; (3) Couch; and (4) Electronic Portal Imaging Device. Current real-time dosimetric techniques available in radiotherapy have their own advantages and disadvantages and a combination of one or more of these methods provide vital information about the actual dose delivered to radiotherapy patients.

Key words: Cancer; Radiotherapy; External beam; Dosimetry; Real-time

Core tip: Treatment outcome in radiotherapy is highly dependent on the dose delivered to the tumor volume with minimal dose to the surrounding critical structures. Real-time dosimetry plays a crucial role in assessing the accuracy of dose delivered to patients undergoing radiotherapy. Several radiotherapy accidents would have been avoided if real-time dosimetry was part of the radiotherapy treatment procedure. This article highlights different approaches to assess real-time dosimetry in external beam radiotherapy.

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INTRODUCTION

Radiotherapy plays a vital role in the treatment of cancer. Advances in external beam radiotherapy, such as

three-dimensional conformal radiotherapy and intensity modulated radiation therapy (IMRT), tightly conforms dose to the target volume, in turn reducing dose to the surrounding critical structures. Highly conformal dose distribution in the presence of critical structures is possible with IMRT due to its capability of achieving a very rapid dose fall-off. Clinical studies have demonstrated that conformal and high dose radiation treatments equate to an increase in the tumour control probability with reduced normal tissue complication probability[1-3]. This can only be achieved if the dose is delivered precisely to the target volume. Whilst there are a number of factors that affect precision in delivered dose, usually the most important factor is misalignment of the patient. Any misalignment or wrong patient setup during high dose radiotherapy may have serious consequences on the treatment outcome. Thus, it is increasingly important to position the patient precisely and to regulate or monitor the position of the internal organs. Image guided radiotherapy aids in precisely positioning the patient to the treatment isocentre. The local control, morbidity and survival rates of radiotherapy patients depend on the accuracy of radiation dose delivered to the tumor volume and avoidance of dose to peripheral normal tissue. Knowledge of the actual dose delivered is critical to our understanding of the physical parameters that determine the radiation response of a tumor. This knowledge will assist in optimizing the dose delivered to the tumor volume on an individual patient basis. Verification of the actual treatment delivery can prevent errors that may entail severe consequences to the patient and achieve the efficacy of treatment. Several radiotherapy incidents have led to serious injury or death such as in Panama[4], Exeter (United Kingdom)[5] and Costa Rica[6]. Moreover, it is reasonable to suggest that recent accidents in Epinal (France)[7] and Glasgow (United Kingdom)[8] could have been avoided if the delivered dose had been verified during treatment. Several international agencies such as IAEA, ICRP, WHO and professional societies of radiation oncology such as AAPM, ESTRO, NACP *etc.*, recommend the use of *in vivo* dosimetry as a possible solution to avoid radiotherapy accidents.

It has become mandatory to check each and every component of a treatment plan before implementing clinically. This process is currently administered as secondary check and as a pre-treatment quality assurance (QA) with IMRT and volumetric modulated arc therapy treatment plans. Although pre-treatment IMRT QA is aimed to ensure the correct dose is delivered to the patient, it does not necessarily predict the clinically relevant patient dose errors during treatment as the measurement is usually performed on a water equivalent phantom[9]. During radiotherapy, treatment uncertainties arise from setup error, tumor deformation or shrinkage, and organ motion that ultimately lead to dose variation. This variation affects tumor control and the chance of increased normal tissue complications. To combat this, image guided radiotherapy helps ensure the plan conditions are mimicked on the treatment machine. However, it does not provide information regarding whether the plan dose is delivered to the tumor correctly. There are several means of evaluating the dose delivered, but currently there is no system developed to allow for rapid real-time assessment. Within the linear accelerator there are four established platforms whereby the delivered dose information can be obtained: (1) Collimator; (2) Patient; (3) Couch; and (4) Electronic Portal Imaging Device (EPID).

At the collimator level, dose information could be obtained by two methods. The first method involves ascertaining the leaf positions and/or field defining apertures during treatment delivery. The dose information could be obtained with simple dose calculation by simulating the position of these leaves and or apertures onto the planning computed tomography (CT) or cone beam computed tomography (CBCT) scans. Alternatively, the relevant dose information could be achieved by the application of external attachments to the collimator. Such external attachments may include a multi-wire transmission ionization chamber[10] or a 2D-array of detectors[11] attached to the collimator. These methods rely on the patient CT data for 3D dose calculation and require either pre or post treatment CBCT to estimate the real-time dose delivered to the patient. The measured dose at the collimator level is projected onto the image datasets to obtain the 3D dose distribution. The most commonly employed methodology in radiotherapy to estimate the dose during radiotherapy is at the patient level and often called as *in-vivo* dosimetry. It is performed by directly placing the detectors on the patient surface or inside the natural cavities of a patient during treatment. There are a number of detectors (dosimeters) commonly used for determining the dose that includes thermoluminescence detectors[12], diodes[13], MOSFETs[14], diamond detectors[15], films[16], optical stimulated luminescence detectors[17], scintillation detectors[18,19] and radio photoluminescence detectors[20] *etc.* In most cases, the measured dose from these dosimeters is usually assessed at one or more points on the patient skin surface or inside the natural body cavities. The main aim of *in-vivo* dosimetry is to detect large errors and prevent potential misadministration. Usually an action level of ± 5% is used for simple treatments and ±7% for complex treatments. *In-vivo* dosimetry acts a potential tool for detecting systematic errors that may escape data transfer/MU calculation checks[21]. The *in-vivo* dosimeters are usually used for estimating the dose to organs at risk and in certain cases to verify the dose to the target volume. It is routinely used for most of the time to ensure that the dose to critical structure does not exceed its tolerance dose. The measured critical structure dose can also be used to correlate with toxicity. *In-vivo* dosimetry is also widely used to assess the out-of-field doses (gonads, spinal cord, lens *etc.*,) during radiotherapy which may predict complications/associated risk of second cancers with high energy photon beam[22,23].

Recently, a couch-based real time dosimetry system has been proposed that can be used for verifying the dose delivered to the patient by embedding a 2D array of detectors in the treatment couch[24]. It provides either exit or entrance dose depending on the gantry or couch position and it is a viable tool for performing daily quality assurance in radiotherapy. This device has the potential of measuring the doses for non-coplanar beam but has limitations in measuring the dose at lateral cardinal angles. Another device that can be used to obtain dose information is an EPID, which was originally designed to verify patient positioning and is currently used for quality assurance and transit dosimetry (such as in the pre-treatment verification of IMRT)[25]. In the instance of transit dosimetry, the EPID creates a fluence map and converts this to dose via calibration of the EPID image using an appropriate algorithm. The energy fluence maps acquired from these devices are back projected and deposited to a volumetric dataset (CT/CBCT) captured either during treatment or initial planning CT. The delivered dose is reconstructed from the deposited energy fluence in each voxel of the volumetric dataset after correcting for attenuation coefficients. One of the important drawbacks of EPIDs is the practical difficulty in measuring the dose to most of the non-coplanar beams due to physical limitations as the imager would collide with the treatment couch. This disadvantage could be overcome by combining a couch-based dosimetry system with EPID for real-time dosimetry. With existing technology, 3D *in-vivo* dosimetry can be achieved with collimator based/EPID based methodology. In clinical situations, 3D *in-vivo* dosimetry helps in assuring the prescribed dose is delivered as expected by the treating physician and also for adaptive radiotherapy. Especially for tumors that are prone to movement during treatment, 4D real-time dosimetry is currently being investigated as a possible solution[26,27,28]. With evolving technology, the implementation of real-time dosimetry routinely is becoming a reality and this may avert major accidents in radiotherapy. Current real-time dosimetric techniques available in radiotherapy have their own advantages and disadvantages and a combination of one or more of these methods may provide vital information about the dose delivered to radiotherapy patients. Real time dosimetry in conjunction with image guidance will be the perfect combination in moving forward towards high-precision radiotherapy.

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REVIEW

Sonographic markers for early diagnosis of fetal malformations

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Abstract

Fetal malformations are very frequent in industrialized countries. Although advanced maternal age may affect pregnancy outcome adversely, 80%-90% of fetal malformations occur in the absence of a specific risk factor for parents. The only effective approach for prenatal screening is currently represented by an ultrasound scan. However, ultrasound methods present two important limitations: the substantial absence of quantitative parameters and the dependence on the sonographer experience. In recent years, together with the improvement in transducer technology, quantitative and objective sonographic markers highly predictive of fetal malformations have been developed. These markers can be detected at early gestation (11-14 wk) and generally are not pathological in themselves but have an increased incidence in abnormal fetuses. Thus, prenatal ultrasonography during the second trimester of gestation provides a "genetic sonogram", including, for instance, nuchal translucency, short humeral length, echogenic bowel, echogenic intracardiac focus and choroid plexus cyst, that is used to identify morphological features of fetal Down's syndrome with a potential sensitivity of more than 90%. Other specific and sensitive markers can be seen in the case of cardiac defects and skeletal anomalies. In the future, sonographic markers could limit even more the use of invasive and dangerous techniques of prenatal diagnosis (amniocentesis, *etc.*).

Key words: Prenatal diagnosis; Prenatal sonography; Chromosome abnormalities; Nuchal translucency; Fetal echocardiography; Skeletal dysplasia

Core tip: The aim of this paper is to review sonographic markers associated with the most frequent fetal abnormalities (chromosomal anomalies, cardiac defects, skeletal dysplasia) and their sensitivity in prenatal diagnosis. Fetal malformations are very frequent in industrialized countries and the only effective approach for prenatal screening is currently represented by an ultrasound scan. Early detection of abnormalities can optimize pregnancy management and childbirth timing, give the possibility of performing simpler procedures for termination of pregnancy in those patients in whom findings are abnormal, and plan therapeutic treatment of objectively selected diseased fetuses.

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INTRODUCTION

Congenital malformations of different types and severity occur in 2%-3% of fetuses in industrialized countries, leading to perinatal death in 25%-30% of cases, and these percentages are increasing, mainly because of the marked increment of pregnancies in women older than 40 years. However, although advanced maternal age may affect pregnancy outcome adversely, with increased miscarriages, ectopic pregnancies, twinning, fetal and chromosomal abnormalities, low birth weight and prematurity, 80%-90% of fetal malformations occur in parents with no specific risk factor. A further cause of legal litigations starting in the delivery room is represented by the unexpected birth of a disabled child; in such cases, parents often denounce the gynecologist that did not provide a prenatal malformation diagnosis, but it is clear that ultrasound (US) potential in the field of obstetrics and gynecology is still far from being fully exploited. The only effective approach for prenatal screening is currently represented by prenatal US examinations[1] as the only possible way to reduce both child disability and perinatal mortality through early malformation diagnosis. US techniques definitely have the potential to provide accurate early diagnosis of fetal malformations, but their employment is significantly hindered by two main limitations: the substantial absence of fully objective approaches and the very low number of available quantitative parameters. It is also clear that pregnancy management needs new approaches and new guidelines to rely on, exploiting objective indications through suitable methods and technologies for standardized quantitative monitoring and appropriate medical decision taking[2]. Quantitative monitoring of pregnancy is improving by the use of sonographic markers that are objective and predictive of specific fetal malformations becoming a powerful tool of prenatal diagnosis.

Early detection of abnormalities can optimize pregnancy management and childbirth timing with timely referring of pregnant woman to specialized facilities for specific disease treatment.

The state of art

US monitoring of pregnancy consists of at least three scans, one for each trimester of gestation. The most important US examination for the study of fetal anatomy is the second trimester scan[3], whose sensitivity in different malformation detection is highly variable: 70%-90% for central nervous system malformations, 40%-50% for heart disease (*e.g.,* aorta coarctation), 25%-70% for urinary tract, 46%-100% for abdomen and gastrointestinal abnormalities (*e.g.,* obstructive anomalies, omphalocele or gastroschisis), 20%-50% for bone dysplasias (*e.g.,* spina bifida, limb reduction defects) and 7%-55% for cleft lip and palate[4]. US examination in the second trimester may show markers of suspected chromosomopathies, with a detection rate of 16%-45%[5], but until now its actual clinical usefulness is limited to an indication for more accurate but also more invasive cytogenetic tests[6] (Figure 1). However, invasive testing with a detection rate of 95%, such as amniocentesis, chorionic villus sampling or cordocentesis, is associated with a risk of miscarriage of about 1%-2%. Moreover, the false positive rate of about 0.2% is calculated only on the 20% of women selected to receive DNA testing. If all pregnant women had DNA testing, the false-positive rate would be 30 times greater. Therefore, cytogenetic tests are carried out only in pregnancies considered to be at high-risk for chromosomal defects[7,8].

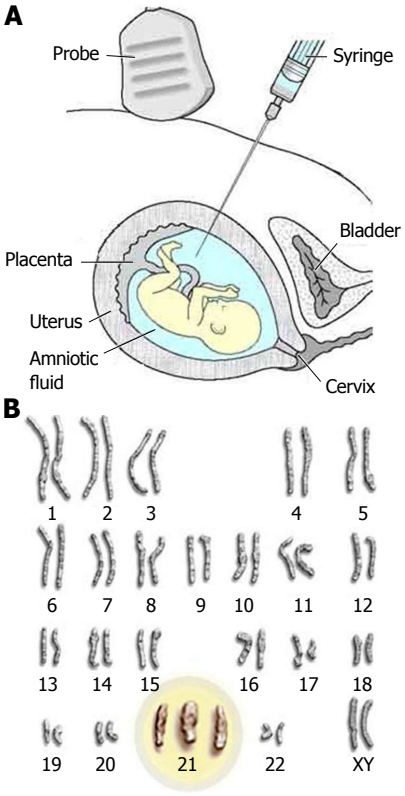

Figure 1 Prenatal cytogenetic tests. A: Amniocentesis: a small amount of amniotic fluid surrounding the baby during pregnancy is removed by a long needle for testing; B: Karyotype: the presence of an extra chromosome 21 is shown (diagnosis of Down's syndrome)[111,112].

Then, on the one hand, the effectiveness of available US methods for prenatal malformation diagnosis is limited by a number of factors, such as period of gestation, variability of the fetal morphogenesis, natural history of the disease, thickness of maternal abdominal wall, possible unfavorable fetus position, but, above all, by the absence of objective parameters for most malformation types and by the strong dependence on operator experience[9]. On the other hand, US examinations are non-invasive and safe and there is a growing international interest in the development of new methods for US detection of malformations, driven also by recent improvements in transducer technology that through increased lateral resolutions and optimized transvaginal probes[2] has enabled examinations of first trimester fetus with an unprecedented level of detail. As a consequence, since the introduction of these technologies together with quantitative sonographic markers, there have been advances in first trimester prenatal diagnosis of major fetal anomalies, in

particular concerning chromosomal abnormalities (80% detection rate), cardiac defects (57% detection rate) and skeletal anomalies (69% detection rate)[10,11].

Chromosomal abnormalities

The main part of fetal malformations are related to chromosomal abnormalities that occur in 0.1%-0.5% of live births[12,13]. The risk for many of the chromosomal defects increases with maternal age. Additionally, because fetuses with chromosomal defects are more likely to die *in utero* than normal fetuses, the risk decreases with gestation[7]. There is a great deal of interest in the US detection of aneuploidy and a second trimester US scan is able to detect, prior to karyotyping, two types of sonographic markers suggestive of aneuploidy[12]. The first group includes those that have a high rate of association with fetal chromosome abnormalities, whether in isolation or present with multiple other sonographic anomalies, and the second includes those that are much more likely to have associated chromosome abnormalities when seen in combination with other markers than in isolation[14].

Examples of data for the latter group are: ventriculomegaly, 2% (isolated) *vs* 17% (combined with other anomalies); holoprosencephaly, 4% *vs* 39%; choroid plexus cyst, 1% *vs* 48%; posterior fossa cyst, 0% *vs* 52%; facial clefting, 0% *vs* 51%; micrognathia, unknown percentage *vs* 62%; diaphragmatic hernia, 2% *vs* 49%; echogenic bowel, 7% *vs* 42%; renal abnormalities, 3% *vs* 24%; and exomphalos, 8% *vs* 46%. Examples of the former group are: cystic hygroma, 52% *vs* 71%; nuchal edema, 19% *vs* 45%; duodenal atresia, 38% *vs* 64%; and in a less pronounced way, for cardiac defects, 16% *vs* 66%[15].

Multiple anomaly associations, in particular cardiovascular anomalies, together with other markers are a more powerful indicator of aneuploidy[14]. Sonographically detectable aneuploidies include Down's syndrome (trisomy 21), trisomy 13 and 18, Turner syndrome (monosomy X), and triploidy.

Sonographic markers of Down's syndrome

The most common clinically significant aneuploidy among live-born infants is Down's syndrome, with an estimated prevalence of 1.21 in 1000 live births[16]. Trisomy 21 is associated with a tendency for brachycephaly, mild ventriculomegaly, nasal hypoplasia, cardiac defects (mainly atrioventricular septal defects), duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the femur and, more so, of the humerus, sandal gap and clinodactyly or mid-phalanx hypoplasia of the fifth finger[7]. There are different screening methods to identify this "high risk group": advanced maternal age, maternal serum biochemical screening in the first and second trimester, and US screening in the first and second trimester[17]. US screening has recently been shown to decrease the prevalence of fetal Down's syndrome in the second trimester to less than 85% by early identification of affected fetuses[18]. Sonographic findings in fetuses with Down's syndrome or another detectable aneuploidy include both structural abnormalities and nonstructural abnormalities or "markers." In themselves, these markers are not pathological but have an increased incidence in infants with chromosomal abnormalities and can be readily detected during the second-trimester US scan, although they are nonspecific and often transient.

Table 1 Sensitivity of sonographic markers of aneuploidies

Markers of aneuploidy	DR (%)	FPR (%)
NT	83	
NT+ PAPP-A + β-hCG + AFP + estriol	94	5
Femoral length	40-50	7
Humeral length	50-54	5-6
Humeral length + NT	75	
Pyelectasis	17-25	2-3
Hyperechoic bowel	3.3-27	1
Absence of nasal bone	73	0.5
Nasal bone + NT + PAPP-A + β-hCG + AFP + estriol+ maternal age	97	
Aberrant right subclavian artery	37.5	1.4

DR: Detection rate; FPR: False-positive rate; NT: Nuchal translucency; PAPP-A: Pregnancy-associated plasma protein; β-hCG: Chorionic gonadotropin; AFP: Alpha-fetoprotein.

The first reported marker associated with Down's syndrome was the thickening of the neck area (nuchal fold)[19]: 40%-50% of affected fetuses have, in the second-trimester, a thickened nuchal fold measuring ⩾ 6 mm, with a false-positive rate of 0.1%[20,21]. Nicolaides subsequently developed the measurement of the fetal nuchal soft tissues for use in the first-trimester, calling it the nuchal translucency (NT) and measuring it in the longitudinal midline plane of the fetus, using a very standardized technique (Figure 2A). NT, defined as the transient subcutaneous collection of fluid behind the fetal neck seen ultrasonographically at 11-14 wk, became a highly specific marker of Down's syndrome. After the introduction of screening by NT, 83% of trisomy 21 pregnancies were identified in the first trimester[22]. Later, it was demonstrated that screening by a combination of maternal age, fetal NT and bi-test [pregnancy-associated plasma protein (PAPP-A) with second-trimester free chorionic gonadotropin (β-hCG)] or tri-test [alpha-fetoprotein (AFP), estriol and free β-hCG] has a potential sensitivity of 94% for a 5% false-positive rate[23].

In addition to nuchal thickening, sonographic findings that are generally accepted as potential markers of trisomy 21 during the second trimester include shortened femur or humerus, renal pyelectasis, hyperechoic bowel, echogenic intracardiac focus, and, recently, nasal bone ossification[24]. The effectiveness of these markers are detailed in Table 1.

Ultrasound studies have shown that fetuses with Down's syndrome have a shorter femur and even shorter humerus when compared with normal fetuses[18]. The sensitivity for detecting trisomy 21 using the femoral length is 40%-50%, with a false-positive rate of up to 7%[25,26]. The humeral length is considered a slightly more efficient marker, with a sensitivity of 50%-54% and a

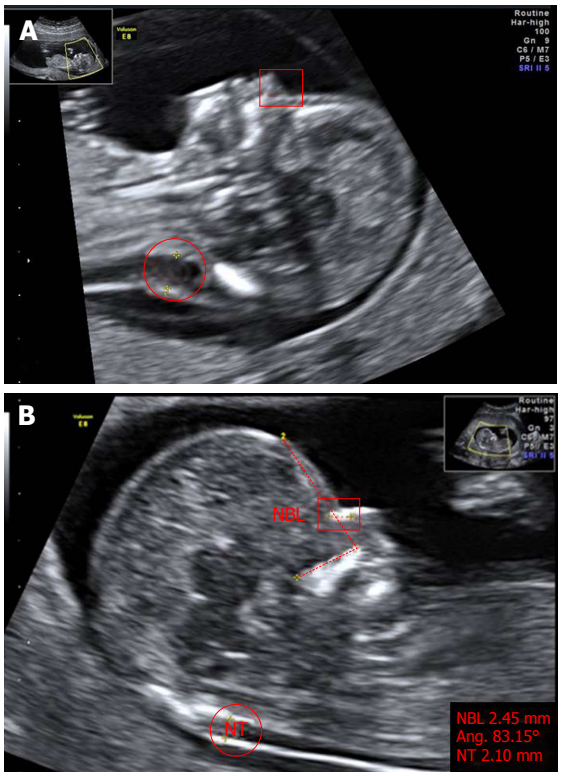

Figure 2 Markers of chromosomal defects. A: Fetus with Down's syndrome: increased NT (red circle), and absent nasal bone (red square where nasal bone was expected) at 11 wk of pregnancy; B: Normal fetus: measurements of nuchal translucency (NT, red circle), facial angle (red dashed line) and nasal bone length (NBL, red square) at 13 wk of pregnancy. The image has been certified by the Fetal Medicine Foundation. Photos taken by Wolfgang Moroder. Creative Commons[113].

false-positive rate of 5%-6%[27-29]. The combination of humeral length and nuchal fold increases the sensitivity to 75%, without substantially changing the false-positive rate based on humeral length alone[18,30].

Pyelectasis, defined as a diameter of the renal pelvis measuring ⩾ 4 mm, is another second-trimester marker; in fact, renal dilatation has a higher incidence among fetuses with Down's syndrome. However, pyelectasis remains a minor marker because the sensitivity is 17%-25%, with a false-positive rate of 2%-3%[31,32].

The sensitivity of hyperechoic bowel in Down's syndrome ranges from 3.3% to 27.0% depending on the sonographer and of the frequency of the US transducer[33-36]. Its false-positive rate is less than 1%[33,37]. Hyperechoic bowel also conveys an increased risk of cystic fibrosis, cytomegalovirus and severe early growth issues[18].

The echogenic intracardiac focus is the least efficient marker among those used for detecting Down's syndrome. It occurs in 16% of fetuses with Down's syndrome, 29% of those with trisomy 13% and 2% of normal fetuses[38]. A recent study also confirms that the finding of an isolated echogenic intracardiac focus on prenatal sonography does not significantly increase the risk for fetal trisomy 21[39]. The false-positive rate is 17%[40].

In the literature, there are important examples of soft markers that have been successfully incorporated into fetal abnormality screening. The case of the nasal bone is the most recent and most powerful marker (Figure 2B). The absence of nasal bone in fetus at the 11-14 wk scan is related to Down's syndrome (Figure 2A); this marker, initially, was found in 73% of trisomy 21 fetuses and in only 0.5% of chromosomally normal fetuses[41] and, subsequently, it was estimated that the combination of maternal age, NT, maternal serum biochemical screening (by bi-test or tri-test) and examination of nasal bone could increase the detection rate to 97%[42]. After the completion of further confirmation studies, it is generally accepted that fetal nasal bone is a very good sonographic marker, even if there are racial differences in the length of this bone[43,44].

Furthermore, there are minor markers of Down's syndrome used less to screen the general population. These include iliac angle, specific cardiac features, choroid plexus cysts and others. The mean iliac wing angle is a useful marker in prenatal screening in fetuses with trisomy 21. A recent study demonstrates that in affected fetuses it is 90.32°, significantly higher than those seen in fetuses with normal karyotype in which the mean iliac wing angle was 63.72°[45]. The specific cardiac features associated with an increased risk of Down's syndrome are primarily ventricular disproportion and the presence of septal defects[18]. In addition, the phenomenon of tricuspid regurgitation is highly associated and its prevalence increases with the NT[46]. Other findings suggest that the mitral valve-tricuspid valve distance could prove useful as an additional marker at the time of the second trimester sonogram. It increases with gestational age and is lower in fetuses with trisomy 21[47]. Fetal aberrant right subclavian artery is another potential marker because in a small group its prevalence in fetuses with Down's syndrome is 37.5% *vs* 1.4% in a low-risk population[48]. Choroid plexus cysts were suggested as a possible minor marker but it has been demonstrated that the risk of Down's syndrome is not raised in their presence[49,50]. Anyway, choroid plexus cysts are a well-known marker for trisomy 18. Finally, ear length at 11-14 wk of gestation has been evaluated in screening for chromosomal defects but the degree of deviation from normal is too small for this measurement to be useful as a marker for trisomy 21[51].

Other aneuploidies

Trisomy 18 is the second most common autosomal trisomy syndrome after trisomy 21. The estimated prevalence is 1 in 6000-8000 live births but the overall prevalence is higher (1 in 2500-2600) due to the high frequency of fetal loss and pregnancy termination after prenatal diagnosis. Currently, most cases of trisomy 18 are prenatally diagnosed, based on screening by maternal age, maternal serum marker screening or detection of sonographic abnormalities. The prenatal sonographic pattern of trisomy 18 is characterized by growth retardation, polyhydramnios, "strawberry-shaped" cranium, choroid plexus cyst, absent corpus callosum, enlarged cisterna magna, facial cleft, micrognathia, nuchal edema, heart defects, diaphragmatic hernia, esophageal atresia, overlapping of fingers, congenital heart defects, omphalocele, renal

defects, echogenic bowel and single umbilical artery[52-55]. The prevalence of growth retardation and polyhydramnios increases with gestational age: 28% and 29% in the second trimester and 87% and 62% in the third trimester, respectively[56]. In particular, choroid plexus cyst is detected in about 50% of trisomy 18 fetuses, while hand abnormalities, exomphalos and single umbilical artery have been found in more than 30% of affected fetuses[55,56]. The most common soft sonographic markers detected in the early second trimester are, as in Down's syndrome, the increased NT thickness and the absence or hypoplasia of the nasal bone[57,58]; the screening by assessment of nuchal fold and nasal bone identifies 66.7% of cases with trisomy 18 (and 13)[58]. Combining NT with bi-test or tri-test sensitivity is at least 78%[59,60]. Anyway, one or more sonographic anomalies are detected in over 90% of fetuses; two or more abnormalities are present in 55% of cases[61].

In trisomy 13, common defects include holoprosencephaly and associated facial abnormalities, microcephaly, cardiac and renal abnormalities with often enlarged and echogenic kidneys, exomphalos and postaxial polydactyly[7]. In particular, among craniofacial malformations detected by prenatal sonography, cleft deformities are found in 65.2% and ocular and orbital abnormalities were found in 28%[62]. Fetal tachycardia is observed in about two-thirds of cases and early-onset intrauterine growth restriction in about 30% of cases[63]. In trisomy 13, as well as in trisomy 18, maternal serum free β-hCG and PAPP-A are decreased[7,63-65].

Turner syndrome, usually due to loss of the paternal X chromosome, is the most common monosomy (45, X) in the fetus, with a prevalence of 25-55 cases per 100000 females and, unlike that of trisomies, is unrelated to maternal age[66]. Characteristic sonographic markers are highly predictive in early pregnancy: huge septated cystic hygroma, hydrops, subcutaneous edema, narrowed aortic arch, renal anomalies and short femur are detected in about 90% of affected fetuses. Some studies have reported that fetuses with Turner syndrome have cystic hygromas much larger than in trisomy 18 or trisomy 21[67]. The classic webbed neck in Turner syndrome is probably the end result of the huge fetal cystic hygroma. Coarctation of the aorta is observed in approximately 20% of the affected fetuses at 14 to 16 wk of gestation[68] and tachycardia observed in about 50% of cases.

Polyploidy is extremely rare and lethal and affects about 2% of recognized conceptions. In particular, triploidy is associated with molar placenta if the extra set of chromosomes is paternally derived. While in cases of double maternal chromosome contribution, the fetus demonstrates severe asymmetrical growth restriction. Ventriculomegaly, micrognathia, cardiac abnormalities, myelomeningocele and syndactyly are also common[7].

CONGENITAL HEART DISEASES

Congenital heart disease (CHD) is one of the most common congenital anomalies and incidence in different studies varies from about 0.4%-5.0% live births[69], while the prevalence rate in the general population is 0.8%-1.0%[70]. Approximately half of infant deaths are due to CHD and 3.0-4.4 per 1000 live births require intervention during the first year of life[71]. Most fetal CHDs occur in patients without any risk factors. Because of this, prenatal US screening of CHD is justified in the general low-risk population. Fetal echocardiography (echoCG) is considered to be an accurate diagnostic tool, reflecting postnatal outcomes well. Fetal echoCG is now widely used in pediatric cardiology and perinatology and even for fetal cardiac intervention, improving the preoperative condition, morbidity and mortality of patients with CHD[72].

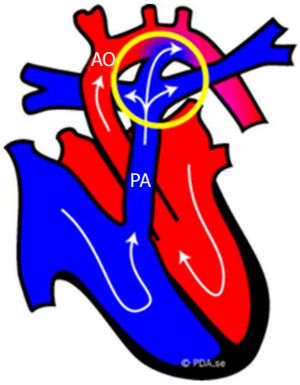

Figure 3 Fetal normal heart. Schematic representation of the blood circulation in fetus: the blood that comes into the right side of the fetal heart (blue part) is pumped into the pulmonary trunk (PA) and flows through the ductus arteriosus (circled in yellow) directly out into the aorta (AO). The ductus arteriosus is an extra blood vessel of the fetal heart that creates a bypass for the blood oxygenated not by the lungs, but through the placenta[114].

The fetal heart is the organ that presents the most problems in diagnosis[73]. This is undoubtedly reflected in the low detection rate of cardiac abnormalities compared to those of most other organ systems in the fetus[74]. It is still a challenge, even for the most experienced ultrasonographer, to visualize the different cardiac structures at an early stage in gestation. All the changes producing the venous connections, the atrial and ventricular chambers, the arterial roots and the intrapericardial arterial trunks have been completed by 8 wk of gestation when the total length of the heart is no more than 8 mm and the distance between different structures is of the order of millimeters. At 12 wk of gestation, the fetal heart is positioned within the chest normally and, fortunately, between the 12th and 17th week, the heart doubles in size and triples in size by the 21st wk[75]. At this time, cardiac structures can be visualized and identified (Figure 3).

The application of an extended basic US cardiac examination improves the detection of CHD, in particular the conotruncal anomalies. The stepwise method suggested for fetal heart US screening during the mid-second trimester sonogram is based on 4 routine axial views of the heart and great vessels: (1) a transverse view of the superior abdomen (Figure 4A); (2) a 4-chamber

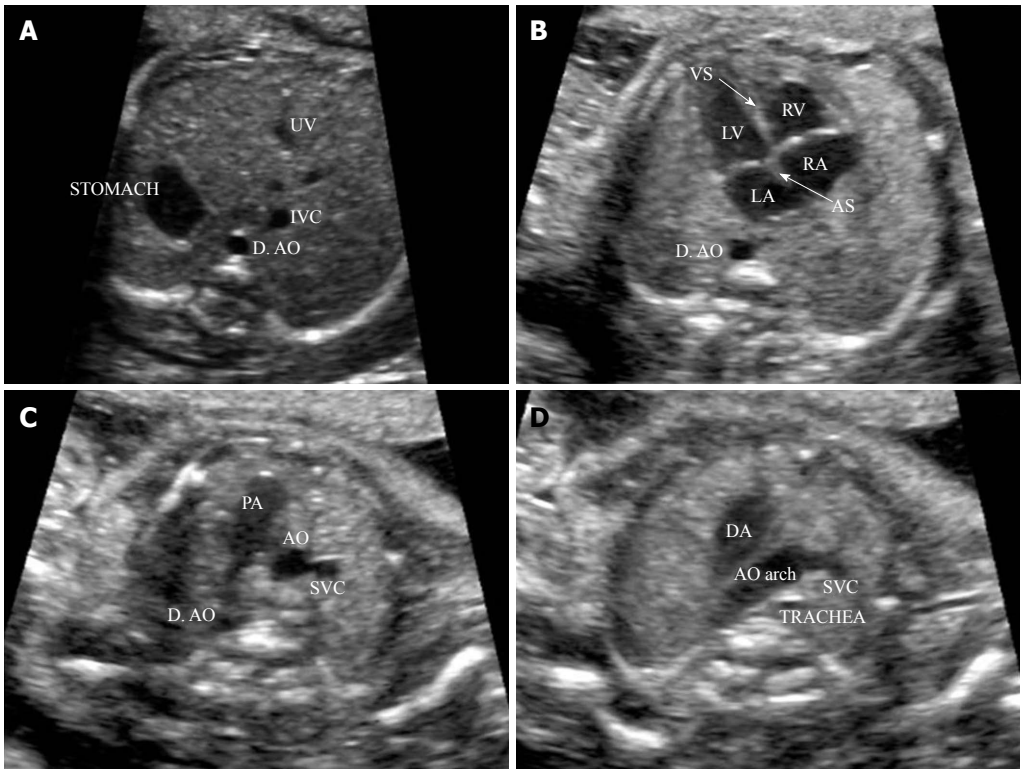

Figure 4 Four routine axial views of heart and great vessels. A: Transverse view of the superior abdomen: the stomach on the fetal left side; the descending aorta (D. AO) to the left side and inferior vena cava (IVC) to right side of the spine, respectively; B: Four-chamber view: in a normal fetal heart, approximately equal size of the right and left chambers, intact intact ventricular septum (VS) and normal offset of the two atrioventricular valve; C: Three-vessel view: pulmonary artery (PA), aorta (AO) and superior vena cava (SVC) in the correct position and alignment; PA, to the left, is the largest of the three and the most anterior, whereas the SVC is the smallest and most posterior; D: Transverse view of the aortic arch: in the normal heart, both the AO arch and the ductal arch (DA) are located to the left of the trachea, in a 'V'-shaped configuration. (Adapted from ISUOG Practice Guidelines[115]). UV: umbilical vein; RV: right ventricle; LV: left ventricle; LA: left atrium; RA: right atrium; AS: Atrial septum.

view (Figure 4B); (3) a 3-vessel view (Figure 4C); and (4) a transverse view of the aortic arch (Figure 4D)[70].

Abnormalities of the right heart

Anatomically, the right atrium possesses all its morphological characteristics from at least 10 wk gestation and is usually a triangular structure, whereas the left atrium is more tubular and meandering.

In the structurally normal heart (Figure 3), the right atrium accepts the superior and inferior cava vein at its cranial and caudal ends. The third systemic veins to enter the right atrium are the coronary sinus[74]. Generally, abnormalities of the coronary sinus are rare but there can be fenestrations within its walls creating the second interatrial communication or else dilation when it drains the pulmonary venous return anomalously[76]. The most frequent anomaly, however, is the dilation of the coronary sinus (Figure 5A) in the setting of persistence of the left superior cava vein. Actually, this anomaly is present in up to one-thirtieth of the normal population but is many times more common when the heart is malformed[77].

The right ventricle is usually easily identified on US by the coarse trabeculations found within its apex. One trabeculation is usually particularly prominent but it is the multiple prominent muscle bundles present within the apex of the right ventricle that give it a 'filled-in' appearance on US. In almost all structurally abnormal hearts, the trabeculated portion of the right ventricle is also present[78]. In some forms of cardiac disease, such as pulmonary atresia (PA) (Figure 5B) or stenosis with intact ventricular septum (IVS), the apical muscle bundles become even more prominent during fetal life, eventually obliterating completely the apical portion of the right ventricle. In others, such as tricuspid atresia or double inlet left ventricle, they are hypoplastic as well as the whole right ventricle[74]. The tricuspid valve is very important in recognizing the right ventricle. In this side of the heart, the tricuspid valve closes in trifoliate fashion, although a discrete septal leaflet is not seen prior to 12 wk gestation. When formed, the septal leaflet has multiple cordal and muscular attachments to the right side of the ventricular septum. On US, the septal leaflet appears to be hinged from the right side of the ventricular septum, more towards the ventricular apex than the mitral valve. The displacement of the tricuspid valve, seen in a four-chamber section, is largely caused by draping of the right atrium over the right side of the ventricular septum as a result of the atrioventricular canal closure, and the creation of discrete right and left inlets to the heart[79]. Consequently, in fetuses with atrioventricular septal (or canal) defects (Figure 5C), this draping cannot occur since there is no offsetting of the atrioventricular valves at the center of the four-chamber view. Similarly, in fetuses with a large ventricular septal defect

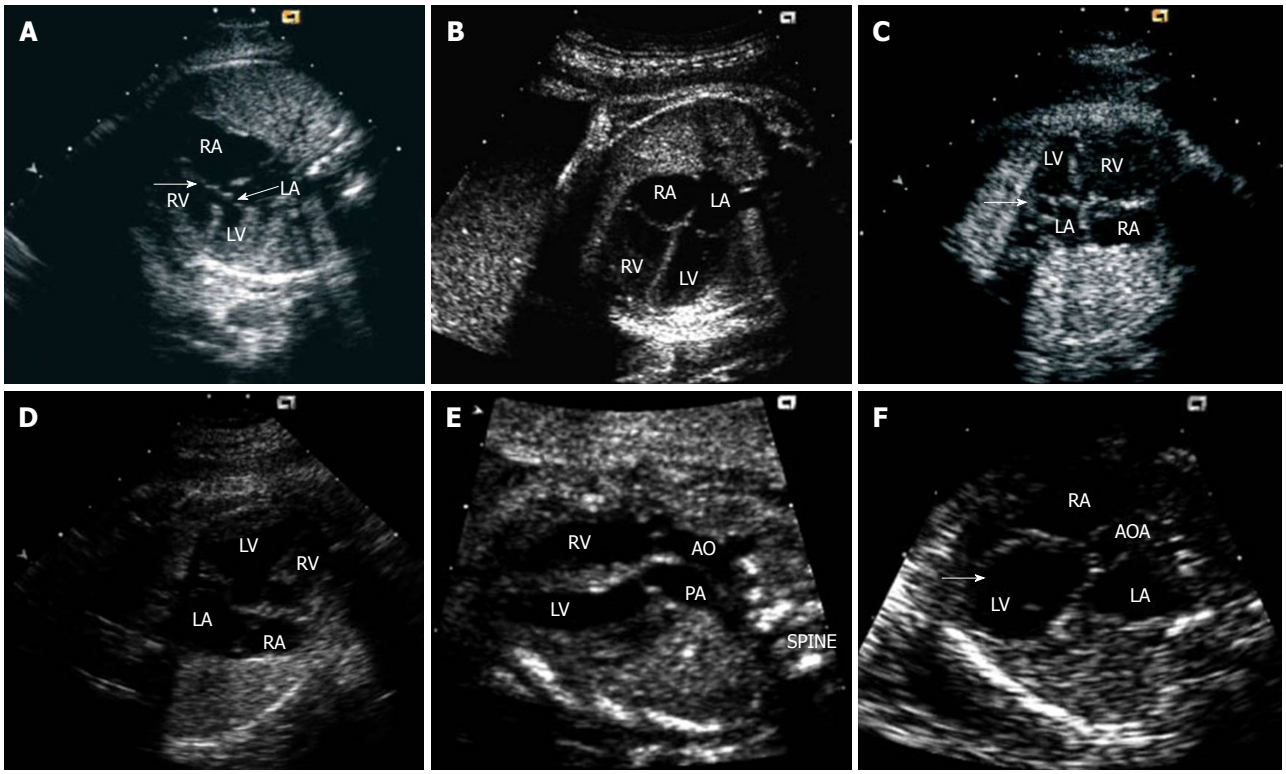

Figure 5 Markers of congenital heart disease. A: Atrioventricular septal defect with a common junction leading to loss of off-setting of the atrioventricular valves (arrows); B: Four-chamber echo view in a normal mid-trimester fetus; C: Enlarged coronary sinus seen as a circular structure (arrow) within the left atrium adjacent to the mitral valve; D: Pulmonary atresia with intact ventricular septum: apical muscle bundles are prominent in the apical portion of the right ventricle with trabeculations coarser than usual; E: Transposition of the great arteries (discordant ventriculoarterial connections): the arteries are parallel to one another with the aorta arising from the right ventricle and positioned to the right of the pulmonary trunk; F: Severe aortic stenosis with patent mitral valve: the left ventricle becomes bulb-shaped (arrow). LA: left atrium; RA: right atrium; RV: right ventricle; LV: left ventricle; AO and AOA: Aorta; PA: Pulmonary trunk. Adapted from Cook *et al*[74].

(VSD), asymmetry of the atrioventricular valves is also lost, principally because there is no septum over which the tricuspid valve can be draped. The Ebstein's defect is characterized by an apically displaced septal insertion of the tricuspid valve leaflet with an atrialized portion of the right ventricle. Closely related to this, is the tricuspid valve dysplasia. In this situation, the delamination of the leaflets of the tricuspid valve is normal, but there is a marked dysplasia of their leaflets and cords. Moreover, in some fetuses, the connection between the right atrium and ventricle is entirely lacking, creating classical tricuspid atresia. In others, a right-sided atrioventricular valve may be formed, but malalignment of the ventricular and atrial septums leads to double inlet left ventricle or straddling tricuspid valve[74].

Abnormalities of the left heart

The left ventricle is characterized by fine trabeculations and the leaflets of the mitral and aortic valves are in fibrous continuity in the roof of the left ventricle. The three or four pulmonary veins enter at the left atrium in the form of a cross and the lower ones can be seen in a standard four-chamber section of the heart (Figure 5D). A narrow junction of the pulmonary veins, or a wide separation between the pulmonary venous confluence and the left atrium, can indicate anomalous pulmonary venous connection. Usually, such anomalous veins drain either *via* an ascending channel to the superior vena cava, or through a descending channel to the hepatic portal venous system. They can also drain directly to the heart *via* a dilated coronary sinus. In ultrasonic four-chamber sections, the two unequal leaflets forming the mitral valve are also seen. In the structurally normal heart, the arterial leaflet is long and with an apron-shaped structure and the second leaflet is shallower than the first one but appreciably longer. Both the leaflets are supported by the same paired papillary muscle groups, leaving the left side of the ventricular septum smooth in contrast to its right-sided counterpart. Abnormalities of the mitral valve are very similar to those in the right heart. In mitral atresia, there is the complete atresia of the connection between the left atrium and ventricle or a malalignment of its orifice leading to double inlet right ventricle[74]. In some malformations, a complex and abnormal connection of the cardiac segments can be seen. Isolated dysplasia of the mitral valve leaflets is rare and is usually encountered in the setting of aortic valve stenosis or atresia[80].

Major abnormalities of the left ventricle usually involve the spectrum of left heart hypoplasia. On the one hand, the left ventricle is slitlike, with both the mitral and aortic valves being atretic. On the other hand, there is patency of the mitral valve, aortic valve stenosis or atresia and a thick-walled and calcific left ventricle. However, the first marker of abnormalities involving

arterial malformations, such as discordant ventriculoarterial connections ("transposition") or double outlet right ventricle, is often the lack of crossover of the arterial valves[74]. Finally, in assessment of the left ventricle, it is important to distinguish between real and false outflow in the region of the membranous septum. In fact, the ventricular septum is abnormal in many malformations of the outflow tract, including the tetralogy of Fallot, most forms of double outlet, common arterial trunk and the type of perimembranous ventricular defect seen in many chromosomal abnormalities[81]. Unfortunately, this region is filled by thin, fibrous tissue and is therefore prone to loss of signal when imaged in some orientations by US[74].

Abnormalities of the great arteries

The arrangement and branching of the distal great arteries is altered in many cardiac abnormalities. Normally, by an US oblique view of the fetal thorax, it is easy to see the aortic arch running to the left of the trachea and to the right of the arterial duct. Other inferior views show the branching pattern of the pulmonary trunk, as well as the linear relationship between the pulmonary trunk, aorta and superior cava vein. In case of discordant ventriculoarterial connections (Figure 5E) and in some forms of double outlet right ventricle, the pattern of branching that allows recognition of the pulmonary trunk from the aorta is the reverse of that seen in the normal fetal heart. Alterations in the size and shape of the distal arteries are seen when there is an abnormal balance of aortic to pulmonary blood flow. The size of the aortic or ductal arches also reflects the flow of blood through them. For instance, in fetuses with aortic coarctation (Figure 5F) or hypoplasia of the left heart, the aortic arch is small and enters into the side of a dominant ductal arch. In contrast, in fetuses with obstruction to the pulmonary outflow tract, the ductal arch is usually hypoplastic and enters into the underside of a dominant aortic arch.

Fetal echocardiography: Markers and diagnostic outcomes

Fetal echoCG becomes more consistently successful at a later gestational age and therefore early scanning does require justification. Cardiac examination is carried out in high-risk fetuses by a fetal cardiologist and/or gynecologist with particular experience in fetal echocardiography. Risk factors for a cardiac defect are increased NT $\geqslant$ 4 mm, a first-degree relative with a significant CHD and suspicion of a cardiac or extracardiac abnormality on the 10-14 wk scan. Occasionally, a full cardiac examination is performed at the parent's request[82]. The NT measurement is only a modestly effective screening tool for all CHD when used alone; however, the combination of an increased NT, tricuspid regurgitation (TR) and an abnormal ductus venosus (DV) Doppler flow profile is a strong marker for CHD. Generally, an increased NT is considered a marker of fetal chromosomal aneuploidies, although the nuchal edema can be caused by the fluid accumulation due to a cardiac failure[83]. The phenomenon of TR is also associated with aneuploidy and its prevalence increases with the NT thickness and is substantially higher in fetuses with than in those without CHD. In chromosomally normal fetuses, the finding of TR at 11 to 13 + 6 wk gestation is associated with an eight-fold increase in the risk of CHD[84]. Moreover, an abnormal DV Doppler flow profile, where during late diastole, coincident with atrial contraction, reduced or reversed flow is seen, has been interpreted as indicative of cardiac failure as it was assumed to reflect increased central venous pressure[85]. The performance of a complete fetal echocardiogram at the end of the first trimester requires expertise. With modern equipment, it is usually possible, using the abdominal approach, to define the situs and cardiac connections, identify the cardiac chambers and their symmetry, the crossing of the great vessels, and to evaluate the flow in the chambers and the great vessels using Doppler and color flow mapping[46].

Table 2 Classes of fetal cardiac anomalies

Complex CHD	Moderate CHD	Simple CHD
Transposition of the great arteries	Mild or moderate AS or aortic incompetence	Small VSD
Tetralogy of Fallot, Hypoplastic right heart	Moderate PS or incompetence	Small PDA
SV, DORV, Truncus arteriosus	Noncritical Coarc	Mild PS
Total anomalous pulmonary venous connection	Large ASD	BAV without AS or aortic incompetence
AVSD, Large VSD, Large PDA Critical or sever PS, Critical or severe AS, Critical Coarc	Complex forms of VSD	Small or spontaneously closed ASD

CHD: Congenital heart disease; AS: Aortic stenosis; VSD: Ventricular septal defect; PS: Pulmonary stenosis; PDA: Patent ductus arteriosus; SV: Single ventricle; DORV: Double outlet right ventricle; ASD: Atrial septal defect; BAV: Bicuspid aortic valves; AVSD: Atrioventricular septal defect.

Fetal echoCG results have been ranked in 5 classes: normal, minor abnormalities, simple cardiac anomalies, moderate cardiac anomalies, and complex cardiac anomalies (Table 2). The criteria of this classification are as follows. Simple cardiac anomalies are defined as a defect able to be corrected by medical treatment or percutaneous cardiovascular interventions and only sometimes by surgery, such as VSD, atrial septal defect (ASD) and possible coarctation of the aorta (possible CoA). Moderate cardiac anomalies are defects able to be corrected surgically with a low risk for reoperation, such as tetralogy of Fallot, CoA, atrioventricular septal defect (AVSD) and complete transposition of the great arteries (TGA). Complex cardiac anomalies are defined as defects able to be corrected anatomically by surgery but with a high risk for sequelae or a Fontan operation candidate, such as double outlet right ventricle, TGA with pulmonary stenosis (PS), critical PS and Fontan candidates (PA with IVS), functional single ventricle, hypoplastic left heart

syndrome][72].

The relative frequency of different major forms of CHD differs greatly from study to study because of many reasons. Some studies are restricted to infancy and so miss patients who present later in life; others do not detect patients with a small ventricular or ASD, an abnormal patent ductus arteriosus (PDA) or many with CoA. Moreover, the increasing use of fetal echocardiography also leads to therapeutic abortion for complex heart diseases and can substantially reduce the incidence of specific lesions. However, isolated VSDs are the most common form of CHD and the incidence of these varies from 2% to 5%[86,87]. About 85%-90% of these defects close spontaneously by one year of age[88,89]. PDA is another common lesion, the incidence of which varies with the age at the time of study and the gestational age of the subject. Preterm infants have an increased incidence of PDA based on abnormal physiology rather than on a structural abnormality. In term infants, the normal ductus may stay open for some time after birth. Isolated partial anomalous pulmonary venous connection is a rare lesion clinically and it resembles an ASD in producing a right ventricular volume overload. Some studies, however, have shown an incidence of 0.6%-0.7%. AVSDs (endocardial cushion defects, common atrioventricular canal) have an incidence that varies with the age of the involved mothers. Trisomy 21 is much more common in mothers older than 34 years old and AVSDs are much more frequent in fetuses with trisomy 21 than with normal chromosomes. Bicuspid aortic valves (BAV) are important because of their frequency and their late complications. Most subjects with BAVs develop stenosis or incompetence after 40 years of age. There is some variation in incidence from about 0.40%-2.25%. Mitral incompetence as an isolated congenital lesion is rare in children; however, mitral valve prolapse is common, occurring in perhaps 4%-5% of the population[69,90,91].

With the recent advances in fetal echoCG on both technical and educational sides, the prenatal diagnosis of rare CHD, as well as the left isomerism, is also increasing. Left isomerism is associated with paired left-sided viscera, whereas right-sided viscera may be absent. Typical findings in left isomerism are bilateral morphological left atrial appendages, visceral-cardiac heterotaxy, multiple cardiac anomalies, congenital heart block, bilateral morphological left lungs with hyparterial bronchi, polysplenia, intestinal malrotation and interruption of the inferior vena cava with azygos continuation. By these markers, prenatal diagnosis of left isomerism is feasible with high accuracy[92].

Generally, the diagnostic accuracy of fetal echoCG is in the range 94.3%-99.0%[93-95]. Also, considering discrepancies between prenatal and postnatal echoCG results in the diagnostic accuracy of 98.6%[72]. Moreover, the diagnostic accuracy of fetal echoCG performed by a pediatric cardiologist is much higher than the reported diagnostic accuracy of sonographic screening performed by an obstetrician (59%)[95]. Anyway, paramount in the approach to the fetus with CHD is a multidisciplinary team composed of an obstetrician, geneticist, perinatologist, pediatrician, pediatric cardiologist and cardiac surgeon that review each case of fetal malformation, refining the diagnosis, establishing management plans and facilitating issues relating to the delivery of the patient[96]. The three main types of cardiovascular malformations in which prenatal diagnosis has been shown to be beneficial are coarctation of the aorta, hypoplastic left ventricle and TGA.

Recently, upgrades to commercially available equipment have improved image quality in order to use high-resolution real-time three-dimensional echocardiography in evaluation of fetal cardiac anatomy and function. With conventional imaging, the accuracy and reproducibility of quantifying ventricular size and function are limited by image plane positioning errors and geometric assumptions. Three-dimensional ultrasonography (3D-US) has been shown to provide more accurate measurements of volume and area than two-dimensional methods, possibly even for volumes encountered in the fetal heart. Moreover, by minimizing some of the time and imaging expertise demands compared to conventional fetal echocardiography, real-time 3D-imaging also may represent a more effective way for sonographers to screen for congenital heart disease in low risk pregnancies[97].

Early diagnosis of CHD gives the parents more time to make an informed decision regarding continuation of the pregnancy. Should they decide to interrupt the pregnancy, this can then be performed earlier, more safely and with less long-term psychological sequelae. If the pregnancy is continued, the timing, location (hospital with neonatal intensive care, pediatric cardiology and pediatric cardiac surgery facilities), mode of delivery and direct postnatal care can be planned. In this way, the postnatal outcome of these babies can be improved. Where the early fetal echocardiogram shows no evidence for a cardiac defect, it allows earlier reassurance of couples considered at high risk for CHD[46].

SKELETAL DYSPLASIAS

Skeletal dysplasias are a heterogeneous group of conditions associated with various anomalies in shape and size of the skeleton[98]. These conditions are caused by widespread disturbance of bone growth, beginning during the early stages of fetal development and evolving throughout life[99]. The prevalence of skeletal dysplasias is low, approximately 3.2 in 10000 live births[100], and the overall frequency of skeletal dysplasias among perinatal deaths is about 9 per 1000[98]. Based on postnatal radiological classification, more than 150 different conditions have been described[101]. Despite recent advances in imaging, fetal skeletal dysplasias are difficult to diagnose before birth (especially in the absence of a familial history) due to a number of factors, including their large number, their phenotypic variability with overlapping features, lack of precise molecular diagnosis for many disorders, lack of a systematic approach and variability in the time at which findings manifest the inability of US to provide an inte-

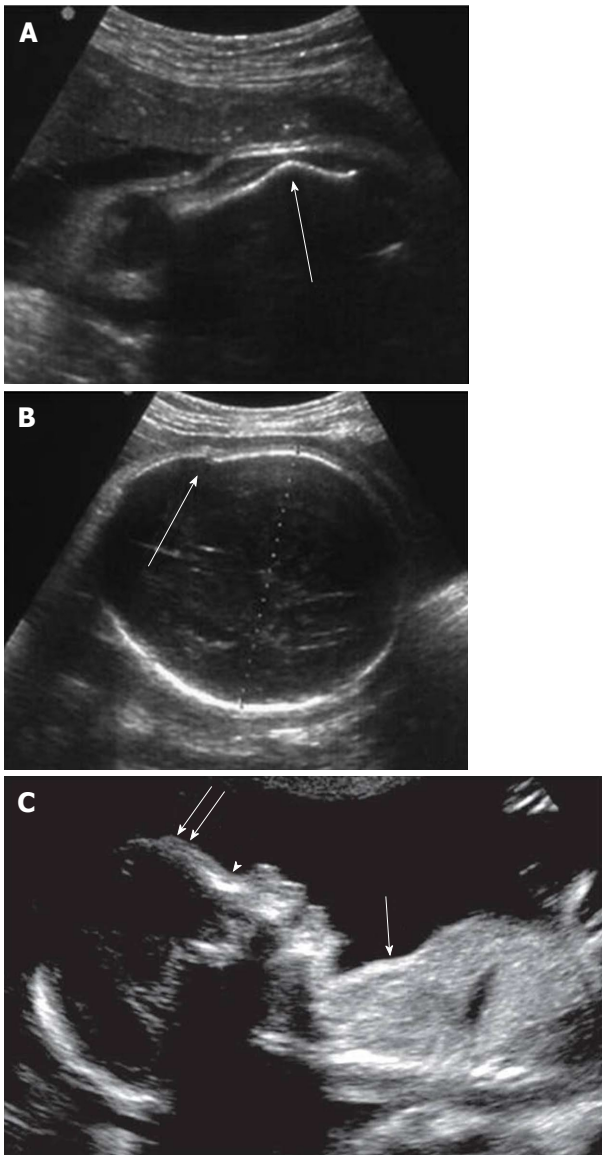

Figure 6 Marker of skeletal dysplasia by two-dimensional ultrasound. A: Abnormal angulated femur; B: Osteogenesis imperfecta: cranial vault distortion upon probe pressure. (Adapted from Cassart[98]); C: Features of thanatophoric dysplasia: depressed nasal bridge (arrowhead), prominent forehead (double arrows), and undersized thorax (single arrow) compared with the abdomen. Adapted from Dighe *et al*[99].

grated view. It must be emphasized that the analysis of bone anomalies requires expertise and great knowledge of postnatal features. At present, accurate prenatal diagnosis of skeletal dysplasia remains a challenge, with only approximately 65% of cases being accurately diagnosed by conventional two-dimensional ultrasound (2D-US)[102]. US of suspected skeletal dysplasia involves systematic imaging of the long bones, thorax, hands and feet, skull, spine and pelvis[99].

Long bones

The bones should be assessed for the presence, curvature, fractures and degree of mineralization[99]. All the long bones of each limb and segment should be examined and measured. The shortened segments must be identified (rhizo-, meso- or acromelic shortening). A femur length-abdominal circumference ratio < 0.16 suggests lung hypoplasia and a femur length-foot length ratio < 1 is in favor of dysplasia[98]. In achondroplasia, femur length becomes abnormally short only in the third trimester. The presence of abnormal angulation (Figure 6A) suggests a fracture and joint deformities or disruption or incongruence are compatible with luxations. Anterior angulation of the tibia and the short fibula are pathognomonic features of campomelic dysplasia[103]. Abnormal epiphyseal calcification should also be looked for but bone mineralization is still very difficult to appreciate on US scans[98].

Thorax

The thorax must also be measured; in fact, a chest circumference less than the 5th percentile has been proposed as an indicator of pulmonary hypoplasia which is the main cause of neonatal death in many lethal skeletal dysplasias[104]. Hypoplastic thorax occurs in many skeletal dysplasias, such as thanatophoric dysplasia (Figure 6C), achondrogenesis, hypophosphatasia, camptomelic dysplasia, chondroectodermal dysplasia, osteogenesis imperfecta and short-rib polydactyly and may lead to pulmonary hypoplasia[99]. The shape and size of the ribs, clavicles and scapula should be analyzed, since the absence or hypoplasia of the clavicles is seen in cleidocranial dysplasia[105] and the absence of the scapula is a useful defining feature of camptomelic dysplasia[106].

Hands and feet

The hands and feet should be carefully analyzed to exclude the presence of pre- or postaxial polydactyly (the presence of more than five digits), syndactyly (soft-tissue or bone fusion of adjacent digits) and clinodactyly (deviation of a finger). Foot deformities, such as 'hitchhiker' thumb, rocker-bottom or clubbed feet, should also be evaluated[98]. Clubbing of the hand is suggestive of the spectrum of "radial ray" anomalies, which include an abnormal thumb (Holt-Oram syndrome), hypoplasia and absence of the thumb and sometimes, absence of the radius or of both the radius and the hand[99]. In diastrophic dysplasia, the fingers are short, with ulnar deviation and 'hitchhiker' thumbs. There are clubfeet and micrognathia. In achondroplasia, the phalanges are short; typical gaps between the fingers and digital deviation lead to the appearance of a "trident" hand[103].

Skull

Head circumference and biparietal diameter should be measured to exclude micro- or macrocephaly. The shape, mineralization and degree of ossification of the skull should be evaluated; osteogenesis imperfecta can be suspected in cases of cranial vault distortion upon probe pressure (Figure 6B). Interorbital distance should be measured to exclude hyper- or hypotelorism[99]. Other features, such as clover-leaf deformity, brachycephaly or scaphocephaly, should suggest craniosynostosis (premature fusion of the sutures). In thanatophoric dysplasia,

Table 3 Comparison between two-dimensional ultrasound and three-dimensional ultrasound detection power of skeletal dysplasia markers

Markers of skeletal dysplasia	Power of detection	
	2D-US	3D-US
Shortening of long bones	+++	+++
Increased thickness of femoral metaphysis	-	+++
Bone fracture	++	+++
Bowing of long bones	++	+++
Decreased mineralization	-	++
Phalangeal hypoplasia	+	+++
Point-calcified epiphysis	+	++
Macrocephaly	++	+
Frontal bossing	++	+++
Facial dysmorphism	+	+++
Narrow thorax	+++	+++
Increased intervertebral space	++	++
Deformation of the fetal pelvis	+	++

+++: Height; ++: Medium; +: Low; -: Very low.

the head circumference is large in half of cases, with the nasal bridge depressed, and an abnormal sonographic translucency can be detected[103]. Facial dysmorphisms may be better depicted by 3D-US[107-109].

Spine

The spine should be carefully imaged to assess the relative total length and the presence of curvature or incomplete closure of the neural tube. Mineralization of vertebral bodies and neural arches should be evaluated. Only marked platyspondyly (vertebral body height < disk height) which is typically seen in thanatophoric dysplasia can be diagnosed.

Pelvis

In the pelvis, the presence of the three ossification points (iliac, pubic and ischial bones) and the shape of the iliac bone (round, flat, lack of iliac flaring) can be important in certain dysplasias and dysostoses, such as limb-pelvic hypoplasia, femoral hypoplasia - unusual face syndrome and achondroplasia. Pelvic shape may be difficult to evaluate at routine US and 3D-US may be necessary[99].

Technical improvement in early diagnosis of skeletal dysplasias

In the absence of a previous history of skeletal dysplasia, fetal morphological examination by conventional 2D-US remains the screening test of choice[100]. As observed in different studies, most skeletal dysplasias are detected late in the second or third trimester of pregnancy[102]. Assessment of the fetus with 3D-US has been shown to improve diagnostic accuracy, since additional phenotypic features not detectable at 2D-US may be identified[107,108] (Table 3).

3D-US provides a global rather planar view of the anatomy by means of depth perception cues, rotation, surface-rendering techniques and multiplanar displays. In particular, multiplanar viewing capability allows to identify scapular anomalies, appreciate limb abnormalities, evaluate fetal facial profile and improve visualization of the spine[107]. 3D-US is superior in elucidating some of the features typical of each skeletal dysplasia. For example, brachydactyly, almost pathognomonic for achondroplasia, is under-appreciated by 2D-US, while 3D-US allows precise measurements of the phalanges, palms and feet and captures the trident configuration of the hands (Figure 7A); 3D-imaging also has the significant advantage of showing the relative disproportion of limb segment. Moreover, surface rendering of fetal facies allows the evaluation of the metopic prominence contour, bony structure, nasal contour and overall relationship of facial features. Facial dysmorphisms such as frontal bossing and mid-face hypoplasia are found by 3D-US in achondroplasia and thanatophoric dysplasia (Figure 7B). The Binder facies (depressed nasal bridge, mid-face hypoplasia, small nose with upturned alae) that is part of the spectrum of chondrodysplasia punctata is also visualized. The very rare case of laryngeal stippling found in some case of chondrodysplasia punctata is preferentially seen by 3D-imaging because of the ability to rotate the image 180°; multiple punctuate calcifications are visualized throughout the larynx[108]. The great advantage of 3D-US is the lower cost and the absence of fetal irradiation. However, this examination is more dependent on the amniotic fluid volume and fetal position[102].

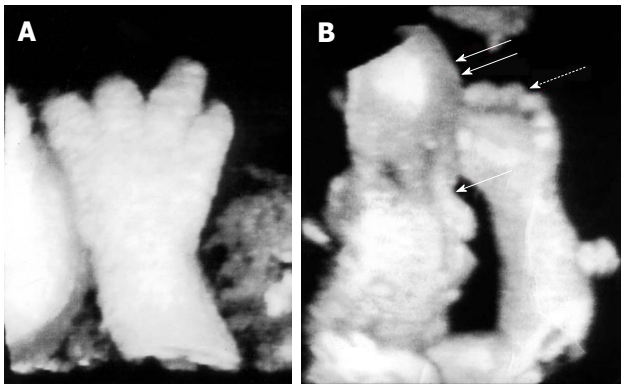

Figure 7 Skeletal anomalies detected by three-dimensional ultrasonography. A: Trident configuration of the digits and brachydactyly suggestive of achondroplasia; B: Facial dysmorphisms: frontal bossing (double arrows) and flattened mid-face (single arrow), disproportionate limb segments and brachydactyly (dotted arrow) typical of achondroplasia. Adapted from Krakow *et al*[108].

Sometimes US and genetic data are inconclusive to diagnose or exclude a suspected skeletal dysplasia[98]; then radiological findings are required in cases of a possible termination of pregnancy. For example, long bone deformities (curvature, fractures), cranial deformities (clover leaf skull) and spinal angulations (segmentation anomalies) are good indications for prenatal three-dimensional helical computer tomography (3D-HCT)[110]. Indeed, 3D-HCT can image the entire fetal skeleton, while 3D-US can image only limited and specific fetal parts[102] (Figure 8).

Nevertheless, this technique has important limitations since it requires ionizing radiation and additionally the image quality is dependent on bone mineralization (better

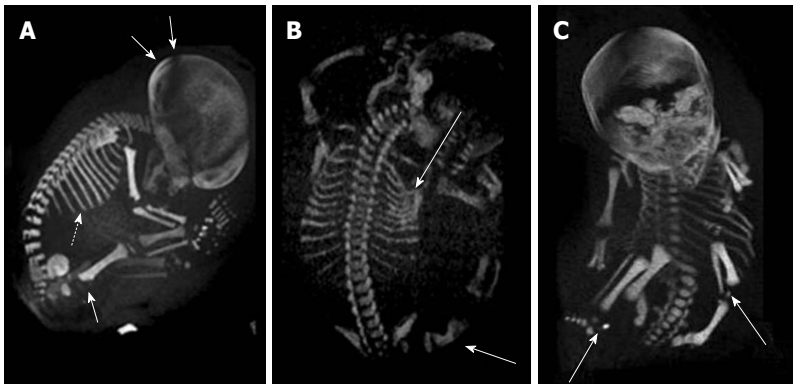

Figure 8 Prenatal diagnosis by three-dimensional helical computer tomography. A: Achondroplasia (sagittal view): macrocephaly (double arrows), short ribs (dotted arrow) and increased thickness of the femoral metaphysis (single arrow); B: Osteogenesis imperfecta (posterior view): fractures of ribs and femur (arrows); C: Chondrodysplasia punctata (frontal view): epiphyseal calcifications of long bones (arrows). Adapted from Ruano *et al*[102].

after 30 wk gestation) and fetal immobility. CT is still often insufficient in the precise and complete visualization of the fetal extremities (hands and feet)[98].

CONCLUSION

Despite the advances in US technology, the diagnosis of multiple fetal structural defects and genetic syndromes currently still depends on the experience of physicians and sonographers. New diagnostic protocols are required to improve the accuracy of US detection of fetal abnormalities. In particular, an objective method based on quantitative parameters is of paramount importance to increase the use of US in prenatal diagnosis. In the last years, quantitative and objective sonographic markers highly predictive of specific fetal malformations have been studied and adopted in order to increase the sensitivity of sonography. US scan represents the most safe and non-invasive method for prenatal diagnosis. Then, innovative research approaches will need to allow the quantitative exploration of several new parameters and the identification of new sonographic markers for aneuploidy or other pathologies. In the future, highly innovative systems with respect to the state of the art of US-based prenatal diagnosis should be able to generate appropriate combinations of multiple sonographic markers with expected significant improvements in both sensitivity and specificity of the corresponding diagnoses. Moreover, these innovative methods should perform automatic comparisons among the values of the same parameter measured at different gestation ages, so automatically providing the temporal evolution of selected parameters, in order to easily check if fetal growth resembles an expected path and also if there are some "disproportions" between different anatomical regions. Therefore, research in prenatal diagnosis should introduce into clinical practice a number of new prenatal diagnostic parameters that must be quantitative, accurate and independent from operator experience. Early diagnosis of fetal malformations based on these new systems will be also useful for parental counseling and fetal treatment planning. In particular, main specific benefits will be related to optimized pregnancy management and childbirth timing, the possibility of performing simpler procedures for termination of pregnancy in those patients in whom findings are abnormal (reducing physical and psychological morbidity associated with late abortions), extension of malformations identifiable already in the first trimester of pregnancy and timely therapeutic treatment of objectively selected diseased fetuses.

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BRIEF ARTICLE

Contrast-enhanced ultrasonography in peripheral lung consolidations: What's its actual role?

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Abstract

AIM: To evaluate the diagnostic accuracy of contrast-enhanced ultrasonography (CEUS) in the differential diagnosis between neoplastic and non-neoplastic peripheral pleuro-pulmonary lesions.

METHODS: One hundred patients with pleural or peripheral pulmonary lesions underwent thoracic CEUS. An 8 microliters/mL solution of sulfur hexafluoride microbubbles stabilized by a phospholipid shell (SonoVue®) was used as US contrast agent. The clips were stored and independently reviewed by two readers, who recorded the following parameters: presence/absence of arterial enhancement, time to enhancement (TE), extent of enhancement (EE), pattern of enhancement (PE), presence/absence of wash-out, time to wash-out, and extent of wash-out. After the final diagnosis (based on histopathologic findings or follow-up of at least 15 mo) was reached, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) of each CEUS parameter in the differential diagnosis between neoplastic and non-neoplastic lesions were calculated. Furthermore, an arbitrary score based on the ratio between the PPVs of each CEUS parameter was calculated, to evaluate if some relationship could exist between overall CEUS behaviour and neoplastic or non-neoplastic nature of the lesions.

RESULTS: Five patients were lost at follow-up before a conclusive diagnosis was reached, 53 lesions resulted neoplastic and 42 non-neoplastic. Enhancement in the arterial phase was observed in 53/53 neoplastic lesions and 30/42 non-neoplastic lesions. On the whole, 40/42 non-neoplastic lesions showed absence of enhancement or early enhancement (95.2%) *vs* 3/53 neoplastic lesions (5.7%). EE was marked in 29/53 (54.7%) neoplastic lesions and 25/30 (83.3%) non-neoplastic lesions, moderate in 24/53 (45.5%) and 5/30 (16.7%), respectively. PE was homogeneous in 6/53 (11.3%) neoplastic lesions and 18/30 (60%) non-neoplastic lesions, inhomogeneous in 47/53 (88.7%) and 12/30 (40%), respectively. 19/30 (63.3%) non-neoplastic lesions enhancing in the arterial phase had no wash-out in the venous phase, 11/30 (36.7%) had late and mild wash-out. Wash-out was early in 26/53 (49%) neoplastic lesions, late in 26/53 (49%), absent in 1 (2%); marked in 16/53 (30.2%), and moderate in 36/53 (67.9%). The delayed enhancement in the arterial phase showed a sensitivity of 94.32%, specificity of 95.2%, PPV of 96.2%, NPV of 93%, PLR of 19.81, and NLR of 0.06 in identifying the neoplastic lesions. All other parameters individually considered showed unsatisfactory values of sensitivity, or specificity, or both, in differentiating neoplastic from non-neoplastic lesions. The median of the overall arbitrary score was 3 (range 0-14) in non-neoplastic lesions, and 16.5 (range 7.0-17.5) in neoplastic le-

sions (P < 0.001). The correlation between the diagnosis of neoplastic *vs* non-neoplastic lesion and the score value was statistically significant (r = 0.858, P < 0.001). Based on the score distribution, a cut-off of 7.5 enabled to reach a sensitivity of 98.1%, specificity of 95.1%, PPV 96.3%, NPV 97.5%, PVR 20.1 and NVR 0.02 in differentiating neoplastic from non-neoplastic lesions.

CONCLUSION: CEUS could be useful in the diagnostic workup of pleuropulmonary lesions. A delayed TE or a score ⩾ 7.5 suggest the neoplastic nature of a lesion.

Key words: Thoracic ultrasonography; Contrast-enhanced ultrasonography; Pleuropulmonary diseases; Neoplastic lesion; Diagnostic accuracy

Core tip: Contrast-enhanced ultrasonography (CEUS) is widely used to characterize focal liver lesions. The lung has dual blood supply (pulmonary arteries and systemic bronchial arteries), and theoretically it should be suitable for CEUS evaluation of arterial vascularity. This study suggests that a delayed time to arterial enhancement or an arbitrary score based on the overall CEUS behaviour ⩾ 7.5 have high sensitivity and specificity in suggesting the neoplastic nature of pleural or peripheral pulmonary lesions. CEUS could allow for discriminating between lesions which need invasive diagnostic procedures, and those which can be monitored with clinical and instrumental follow-up.

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INTRODUCTION

Despite the limits caused by the sound reflection at the aerated lung surface, in the last years transthoracic ultrasonography (US) has gained increasing interest in the evaluation of peripheral pulmonary lesions abutting the pleura[1,2]. However, the correlation between the US pattern of lung consolidations and their specific pathology is quite poor, and transthoracic US is mainly used as an alternative to computed tomography (CT) to guide percutaneous needle biopsy of the lesions, when endoscopic biopsy fails in yielding adequate tissue specimens[3,4,5].

Contrast-enhanced ultrasonography (CEUS) with second generation US contrast agents is increasingly used in the diagnostic imaging of abdominal organs. In particular, in Europe, Eastern Countries, and Canada it is recommended as the first-line technique for the characterization of focal liver lesions[6-8]. The lung has dual blood supply (pulmonary arteries and systemic bronchial arteries), and this peculiarity could theoretically be exploited by CEUS to characterize and differentiate lesions with different arterial supply. However, at present only few preliminary studies on the role of CEUS in the characterization of peripheral lung masses have been reported in literature, and most of them were mainly descriptive and gave conflicting results[9-14]. This prospective pilot study was planned to evaluate the possible role and diagnostic accuracy of CEUS in the differential diagnosis between neoplastic and non-neoplastic pleural and peripheral pulmonary lesions.

MATERIALS AND METHODS

Participants

From October 2009 to October 2011, 100 consecutive patients (56 males and 44 females, mean age 61 years, range 24-89 years) with pleural lesions or peripheral pulmonary consolidations abutting the pleura were enrolled into this prospective study. The study was approved by Ethics Committee of our hospital and informed consent was obtained from each patient. The inclusion criteria were the following: age > 18 years; presence of a pulmonary peripheral mass depicted by chest Rx or CT, and visible at transthoracic US; diagnostic course still running; absence of known hypersensitivity to sulfur hexafluoride, pulmonary hypertension, class IV New York Heart Association heart failure[15], unstable angina, acute or recent myocardial infarction, or adult respiratory distress syndrome.

Test methods

A preliminary US evaluation of the lesions was performed using a real-time sonography system equipped with a 3.5 to 5.0 MHz convex transducer and a 5.0 to 7.5 MHz linear transducer (Mylab 70 XVG Gold, Esaote, Genova, Italy) to identify the optimal acoustic window for CEUS examination, according to the lesion location and patient's body size[16-18]. CEUS was performed with a low mechanical index contrast-specific nonlinear technique (CnTI, Esaote, Genova, Italy) and an 8 microliters/mL solution of sulfur hexafluoride microbubbles stabilized by a phospholipid shell (SonoVue®, Bracco, Milan, Italy) was used as US contrast agent. Acoustic power was set at 40 kilo pascal for both high-frequency linear transducer and low-frequency convex transducer. All US and CEUS examinations were performed by one of two physicians (PT and SP) with at least 5 years of experience in CEUS examination of abdominal organs, and well experienced with US of the lung.

After *iv* administration of a bolus of 2.4 mL of Sonovue, the lesions were continuously examined for at least 180 s taking care to include a portion of normal surrounding parenchyma in the same US scan, in order to examine contemporaneously both the lesion and normal lung. If normal parenchyma could not be included in the same scan, or the mass was located at the basis of the lung, the surrounding chest wall, or the liver or spleen,

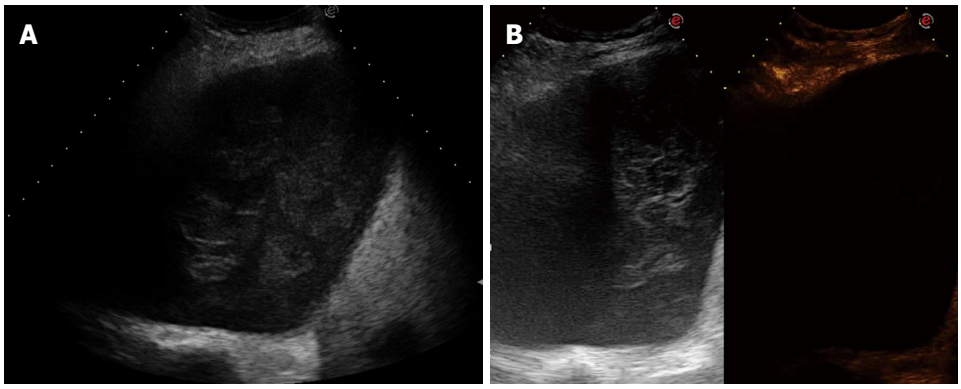

Figure 1 Absence of arterial enhancement. A: transverse sonogram of the right chest wall in the sixth posterior intercostal space showing an inhomogeneous mass in the pleural space; B: transverse contrast-enhanced sonogram of the mass showing complete absence of enhancement in the arterial phase. Final diagnosis was haemothorax with a large clot.

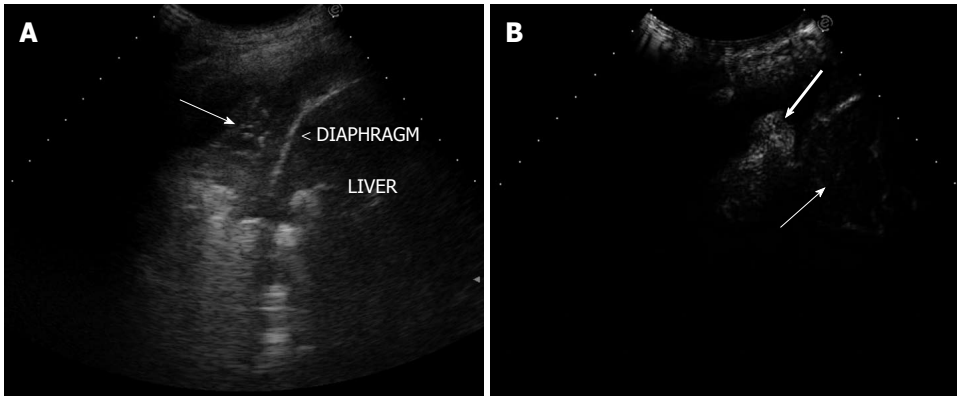

Figure 2 Early arterial enhancement. A: Transverse sonogram showing parenchymal consolidation of the lower lobe of the right lung (arrow); B: Transverse contrast-enhanced sonogram in the arterial phase showing clear enhancement of the lung consolidation (large arrow); the enhancement of the liver is still starting (thin arrow). Final diagnosis was slow resolution pneumonia.

Table 1 Contrast-enhanced ultrasonography parameters

	TE		EE		PE	TW		EW		
Enhancement present	Early (0-1 s with respect to normal lung)	Late (≥ 2 s later than normal lung)	Marked	Moderate	Homogeneous	-	-	-	-	-
Enhancement absent	Stop assessing CEUS parameters					-	-	-	-	-
Wash-out						Early (< 60 s)	Late (≥ 60 s)	Marked	Mild	Absent

TE: Time to enhancement; EE: Extent of enhancement; PE: Pattern of enhancement; TW: Time to wash-out; EW: Extent of wash-out; CEUS: Contrast-enhanced ultrasonography.

were examined contemporaneously to the lesion. All CEUS examinations were recorded, stored and independently reviewed by the two operators.

First, each lesion was assessed for the presence or the absence (Figure 1) of enhancement in the arterial phase, defined as the twenty s period following the appearance of the first microbubbles in the lesion or the surrounding parenchyma (or the chest wall, the liver, or spleen). If the lesion showed arterial enhancement, the following parameters were then recorded: time to enhancement (TE), extent of enhancement (EE), pattern of enhancement (PE), time to wash-out (TW), and extent of wash-out (EW). TE was defined as early if it was observed contemporaneously to the normal lung, or before the enhancement of the chest wall, liver or spleen (Figure 2); and as delayed if it was observed at least 2 s after the enhancement of the normal lung, or contemporaneously to the enhancement of the chest wall, liver or spleen (Figure 3). EE was defined marked (Figure 4) or moderate (Figure 3B) with respect to the EE of the normal lung, the chest wall, the liver or spleen. PE was classified as homogeneous (Figure 4) or inhomogeneous (Figure 3B). TW was defined as early if it occurred within 60 s after the injection of Sonovue, as late if it occurred later,

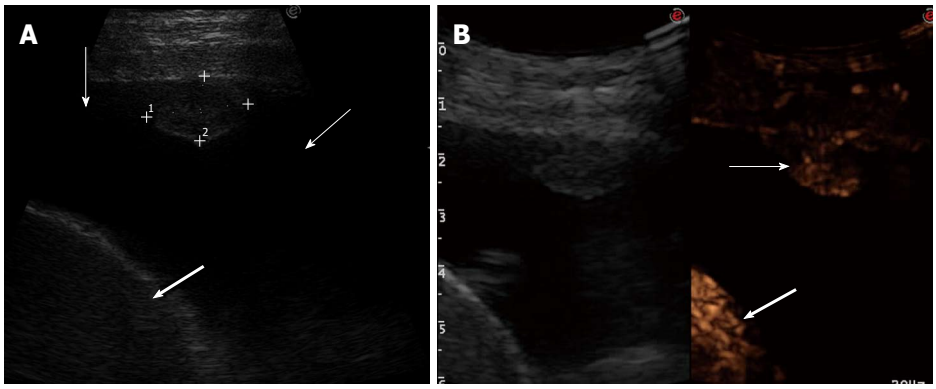

Figure 3 Delayed arterial enhancement. A: Tranverse sonogram of the left chest wall in the seventh intercostal space along the mid-axillary line showing an isoechoic pleural nodule, pleural effusion (thin arrows), and spleen (large arrow); B: Transverse contrast-enhanced sonogram in the arterial phase showing inhomogeneous enhancement of the nodule (thin arrow) that occurs contemporaneously to the enhancement of the spleen (large arrow) (left side of the split-screen); the enhancement of the nodule is less marked than that of the spleen. Final diagnosis was pleural metastasis from colon cancer.

and as absent if it was not observed within 180 s after the bolus. EW was classified as marked or mild according to its entity with respect to the entity of the arterial enhancement. The parameters examined are reported in Table 1. If some discordance in the evaluation of the CEUS parameters occurred between the two readers, the clip was reviewed and discussed with a third reader (SS) and the final decision was reached by consensus.

The final diagnosis was based on histopathologic findings (by endoscopic or percutaneous imaging-guided biopsy, or surgical exploration), or clinical follow-up. Clinical proof of malignant lesion was accepted if the patient was treated for malignancy and the clinical course and response to therapy were appropriate. Clinical proof of benign lesion was accepted if the lesion disappeared spontaneously or after treatment other than antineoplastic chemotherapy, or no change in size was observed for more than 15 mo.

Statistical analysis

After the final diagnosis was reached, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative PLR of each CEUS parameter in the differential diagnosis between neoplastic and non-neoplastic lesions were calculated. First, the presence *vs* the absence of arterial enhancement was evaluated. If the lesion showed arterial enhancement, each distinctive feature of TE (*i.e.*, early or delayed) was compared to the other one plus the absence of enhancement. The other parameters of arterial enhancement were analyzed as well (marked *vs* moderate enhancement, and homogeneous *vs* inhomogeneous enhancement). Finally, wash-out features were evaluated (presence *vs* absence, early *vs* late, and marked *vs* mild or absent) for the lesions that had enhancement in the arterial phase.

Furthermore, an arbitrary score based on the features of all CEUS parameters examined was conceived, in order to evaluate if some relationship could be found between the overall CEUS behaviour and the neoplastic or non-neoplastic nature of the lesions. The absence of arterial enhancement or wash-out (when arterial enhancement was present) was scored 0. For each parameter of enhancement or wash-out, the feature with lower PPV was scored 1 and the other one was scored according to the ratio between the two PPVs (for instance, homogeneous enhancement: PPV 25%, score 1; inhomogeneous enhancement: PPV 79.7%, score 3.2). The sum of the scores assigned to each CEUS parameter yielded the overall score, and the median values of the overall scores of neoplastic and non-neoplastic lesions were compared by using the non-parametric Mann Whitney test. Finally, the relationship between neoplastic or non-neoplastic nature of the lesions and overall CEUS score was analysed by using the non-parametric Spearman test. An alfa error $< 5\%$ was assumed as statistically significant in both analyses. All statistical analyses were performed with a statistical software program (Stata 11.0 for Windows, Stata Corp., College Station, TX, United States).

RESULTS

Participants

The quality of CEUS examination was good in all patients and no adverse reaction to Sonovue was observed. Both high-frequency linear transducer and low-frequency convex transducer yielded the same quality of CEUS examinations. There was no concordance between the readers in TE and EW evaluation in 5/100 cases and 4/100 cases, respectively ($r = 0.899$, and $r = 0.9$, respectively). In all these cases final consensus was reached after collegial review and discussion of the CEUS clips.

Mean diameter of the lesions was 3.5 cm (range 1-12 cm). Five patients were lost at follow-up before a conclusive diagnosis was reached. The final diagnosis was based on a median clinical follow-up of 17 mo (range 7-26 mo) in 23/95 cases (3 neoplastic and 20 non-neoplastic lesions), and histopathological findings (63 endoscopic or percutaneous biopsies, and 9 surgical explorations) in 72/95 cases (50 neoplastic and 22 non-neoplastic

Table 2 Final diagnoses

Non-neoplastic lesions	*n*	Neoplastic lesions				Lost at follow-up (*n*)
		Primary tumors	*n*	Metastatic tumors (origin)	*n*	
Slow resolution pneumonia	19	Adenocarcinoma	18	Colon	5	5
BOOP	5	Squamous carcinoma	5	Stomach	2	
Abscess	4	Small-cell lung cancer	3	Testis (seminoma)	2	
Pulmonary infarction	3	Indifferentiate carcinoma	6	Liver (HCC)	1	
Organized pleural effusion	4	Sarcomatoid carcinoma	2	Breast	1	
Post-surgical fibrosis	4	Mesothelioma	2	Indeterminate	2	
Obstruction atelectasys	2	Schwannoma	2			
Fibrotic plaque of the pleura	1	Plasmacytoma	1			
		Lymphoma	1			
			40		13	
Total	42		53			5

BOOP: Bronchiolitis obliterans organizing pneumonia; HCC: Hepatocellular carcinoma.

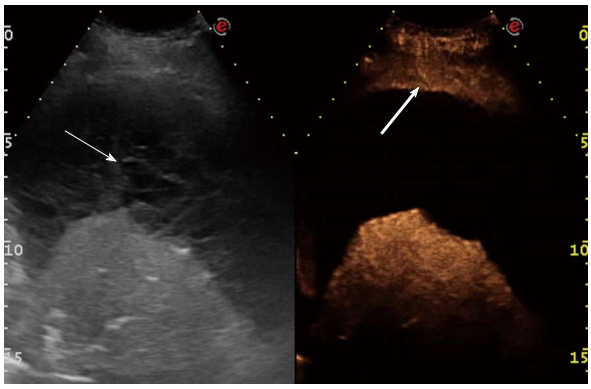

Figure 4 Marked and homogeneous arterial enhancement. Left side of the split-screen: transverse sonogram of the left chest wall in the sixth intercostal space showing loculated pleural effusion (thin arrow) and pulmonary consolidation. Right side of the split screen: contrast-enhanced sonogram showing homogeneous and marked enhanced of the pulmonary consolidation with respect to the chest wall (large arrow). Final diagnosis was compressive atelectasis.

lesions). On the whole, fifty-three lesions resulted neoplastic (40 primary tumors, 13 metastatic tumors), and 42 resulted non-neoplastic. All the 22 biopsy diagnoses of non-neoplastic lesion were confirmed by the clinical follow-up. The final diagnoses are reported in detail in Table 2.

Test results

Enhancement in the arterial phase was observed in 53/53 neoplastic lesions and 30/42 non-neoplastic lesions. Arterial enhancement resulted absent in four organized pleural effusions, 1 abscess, 3 pulmonary infarctions, 3 post-surgical fibroses, and 1 fibrotic plaque of the pleura. TE was delayed in 50/53 neoplastic lesions (94.3%), and early in 28/30 non-neoplastic lesions (93.3%). On the whole, 40/42 non-neoplastic lesions showed absence of enhancement or early enhancement (95.2%) *vs* 3/53 neoplastic lesions (5.7%). EE was marked in 29/53 (54.7%) neoplastic lesions and 25/30 (83.3%) non-neoplastic lesions, moderate in 24/53 (45.5%) and 5/30 (16.7%), respectively. PE was homogeneous in 6/53 (11.3%) neoplastic lesions and 18/30 (60%) non-neoplastic lesions, inhomogeneous in 47/53 (88.7%) and 12/30 (40%), respectively. 19/30 (63.3%) non-neoplastic lesions with enhancement in the arterial phase had no wash-out in the venous phase, 11/30 (36.7%) had late and mild wash-out. Wash-out was early in 26/53 (49%) neoplastic lesions, late in 26/53 (49%), absent in 1 (2.0%); marked in 16/53 (30.2%), and moderate in 36/53 (67.9%). The results are summarized in Table 3.

Estimates

The delayed enhancement in the arterial phase showed a sensitivity of 94.32%, specificity of 95.2%, PPV of 96.2%, NPV of 93%, PLR of 19.81, and NLR of 0.06 in identifying the neoplastic lesions. All the other parameters individually considered showed unsatisfactory values of sensitivity, or specificity, or both, in differentiating neoplastic from non-neoplastic lesions. All analyses are reported in detail in Table 4.

The correlation data between PPV and values of the arbitrary score are reported in Table 5. The risk score was calculated in all the patients, with overall median value of 15 (range 0-17.5). In non-neoplastic lesions the median score was 3 (range 0-14), in neoplastic lesions it was 16.5 (range 7.0-17.5) ($P < 0.001$). The correlation between the diagnosis of neoplastic *vs* non-neoplastic lesion and the score value was statistically significant ($r = 0.858$, $P < 0.001$). Based on the score distribution, we found that a cut-off of 7.5 enabled to reach a sensitivity of 98.1%, specificity of 95.1%, PPV 96.3%, NPV 97.5%, PVR 20.1 and NVR 0.02 in differentiating neoplastic from non-neoplastic lesions.

DISCUSSION

Thoracic US has become a well-established method to guide percutaneous biopsy of peripheral pulmonary lesions abutting the pleura, and is considered as effective as CT-guidance in terms of sample accuracy, with the advantages of lower cost, lack of exposition to ionizing

Table 3 Enhancement and wash-out findings in non-neoplastic and neoplastic lesions *n* (%)

	Enhancement								Wash-out			
	Early	Delayed	Absent	Marked	Moderate	Homogeneous	Inhomogeneous	Marked	Mild	Absent	Early	Late
Non-neoplastic lesions	28/42	2/42	12/42	25/30	5/30	18/30	12/30	0/30	11/30	19/30	0/30	11/30
	(66.7)	(4.8)	(28.6)	(83.3)	(16.7)	(60)	(40)	(0)	(36.7)	(63.3)	(0)	(36.7)
Neoplastic lesions	3/53	50/53	0/53	29/53	24/53	6/53	47/53	16/53	36/53	1/53	26/53	26/53
	(5.7)	(94.3)	(0)	(54.7)	(4.3)	(11.3)	(88.7)	(30.2)	(67.9)	(1.9)	(49)	(49)

Table 4 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio of enhnacement and wash-out parameters

		Sensitivity	Specificity	PPV	NPV	PLR	NLR
		95%CI	95%CI	95%CI	95%CI	95%CI	95%CI
	Present	100	28.6	63.9	100	1.4	0
		100-100	14.9-42.2	53.5-74.2	100-100	1.21-1.59	--
	Early	5.7	6.7	9.7	3.8	0.06	14.15
		-0.719	-17.9	-20.8	-10.5	-2.24	12.8-15.5
	Delayed	94.3	95.2	96.2	93	19.81	0.06
Enhancement		88.1-100.6	88.8-101.7	90.9-101	85.4-100.6	18.4-21.2	-2.2
	Marked	54.7	16.7	53.7	17.2	0.66	2.72
		41.3-68.1	3.3-30	40.4-67	3.5-31	0.36-0.95	1.86-3.57
	Moderate	45.3	83.3	82.8	46.3	2.72	0.66
		31.9-58.7	70-96.7	69-96.5	33-59.6	1.86-3.57	0.36-0.95
	Homogeneous	11.3	40	25	20.3	0.19	2.22
		2.8-19.9	22.5-57.5	7.7-42.3	10.1-30.6	-1.62	1.77-2.67
	Inhomogeneous	88.7	60	79.7	75	2.22	0.19
		80.1-97.2	42.5-77.5	69.4-89.9	57.7-92.3	1.77-2.67	-1.62
	Marked	30.8	100	100	23.4	--	0.69
		18.2-43.3	100-100	100-100	11.3-35.5		0.5-0.87
Wash-out	Mild	69.2	0	76.6	0	0.69	--
		56.7-81.8		64.5-88.7		0.5-0.87	
	Absent	98.1	63.3	82.5	95	2.68	0.03
		94.5-101.8	46.1-80.6	73.2-91.9	85-104.6	2.2-3.15	-3.92
	Early	50	100	100	29.7	--	0.5
		36.4-63.6	100-100	100-100	15-44.5		0.23-0.77
	Late	50	0	70.3	0	0.5	--
		36.4-63.6		55.5-85		0.23-0.8	

PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

Table 5 Arbitrary score based on the ratio between the positive predictive value calculated for each contrast-enhanced ultrasonography parameter

		PPV	Score
Enhancement	Absent	63.9	0
	Early	9.7	1
	Delayed	96.2	9.9
	Marked	53.7	1
	Moderate	82.8	1.5
	Homogeneous	25	1
	Inhomogeneous	79.7	3.2
Wash-out	Marked	100	1.3
	Mild	76.7	1
	Absent	69.3	0
	Early	100	1.4
	Late	70.3	1

Absent enhancement or wash-out = 0; lower positive predictive value (PPV) = 1.

radiation, shorter procedure time, and lower rates of post-procedural pneumothorax[19]. Despite the increasing applications of CEUS in the characterization of focal lesions of the liver and other abdominal organs[6-8,20], to date the use of second generation US contrast media in pleuropulmonary diseases is limited to improve the diagnostic yield of percutaneous biopsy[21,22]. The role of CEUS in the characterization of peripheral pulmonary lesions has been scarcely investigated, and the few preliminary studies published in literature were mainly descriptive and gave inconclusive and disappointing results[9-14,23]. The lung is characterized by dual blood supply: the bronchial arterial system, which provides nutrition for the bronchi, pulmonary vessels, alveoli, interstitial tissue, and visceral pleura; and the pulmonary arterial system, which is responsible for gas exchange[10]. Such a peculiarity could theoretically be exploited to differentiate pleural-based non-neoplastic lesions from neoplastic lesions, as the formers are supplied by both arterial systems, whereas tumor angiogenesis usually rises from bronchial arteries[12]. Therefore, a different TE should be seen in real time imaging, as the tissue enhancement resulting from the pulmonary arteries starts before the

tissue enhancement resulting from the bronchial arteries. Moreover, a regular, dominant pulmonary arterial supply should lead to a more marked tissue enhancement than that observed in tissues only supplied by the bronchial arteries. CEUS represents the best imaging method to evaluate both the vascularity and transit time within an organ, as it enables the assessment of any time of enhancement during the arterial phase. Conversely, contrast-enhanced CT is an instant scanning modality, and can assess the vascularity only at a certain point in time during the arterial phase[24]

Although CEUS was shown to be as effective as CT in detecting peripheral lung cancer vascularisation[25] a prior study on 137 patients with pleural based lesions reported that CEUS did not allow to distinguish benign from malignant pulmonary consolidations[9]. However, 62% of malignant lesions had delayed TE, whereas 62% of inflammatory consolidations had early TE, and this observation was subsequently confirmed on larger and more recent series[10,11,26]. In our pilot study, delayed TE was observed in 94.3% of neoplastic lesions and in 4.8% of non-neoplastic lesions. A methodological defect could have biased the results of the above-mentioned studies. An arbitrary cut-off of six s after the *iv* bolus of the US contrast agent was used to define TE as early or delayed, because the time windows of pulmonary arterial vascularity and systemic bronchial arterial vascularity usually range from 1 to 5 s, and from 8 to 11 s, respectively[10,11]. However, a lot of physiological and pathological conditions, such as sitting or supine position of the patient, antiarrhythmic drugs, tachycardia, bradycardia, chronic heart failure, chronic pulmonary disease, hyperthyroidism and hypothyroidism, and so on, can modify the standard time window of both pulmonary and systemic bronchial arterial vascularities. Indeed, a wide variability in hepatic artery arrival time, ranging from 8 to 16 s, was observed even in healthy volunteers in a study investigating the hepatic transit time in healthy subjects and patients with liver metastases[27]. It follows that a cut-off based on the standard time windows of the pulmonary and systemic bronchial arteries can be misleading in the assessment of early or delayed TE. In our study, this potential bias was avoided defining TE as early if the enhancement in the lesion was contemporaneous to that of the normal lung, and as delayed if it appeared after the enhancement of the normal lung, or contemporaneously to that of the chest wall, liver, or spleen. In this way, a true early enhancement was observed in just three neoplastic lesions, probably due to a concomitant supply from pulmonary arteries, as described in some bronchioloalveolar carcinomas and adenocarcinomas[28]. Likewise, non-neoplastic lesions showed absence of arterial enhancement or early enhancement in all cases but two, in which the delayed enhancement was likely determined by a widespread vasoconstriction caused by hypoxia[10].

Conversely, and despite the theoretical rationale in favour of a more marked arterial enhancement in non-neoplastic lesions due to the dual blood supply, EE did not result useful to distinguish neoplastic from non-neoplastic lesions, as well as all the other CEUS parameters. The presence of enhancement and the absence of wash-out (when arterial enhancement was present) showed very good sensitivity in suggesting the neoplastic and the non-neoplastic nature of the lesions, respectively, but specificity of both parameters was quite poor; and the presence of early wash-out had a 100% specificity in predicting the neoplastic nature of the lesions, but an unacceptably low sensitivity. However, we analysed also the overall CEUS behaviour including all the CEUS parameters into an arbitrary score, either to limit the possible bias consequent to the subjective evaluation of a single parameter, or to explore the possibility of further improving the good performance yielded by the delayed TE. Indeed, the score was proven to be a reliable tool to differentiate the two populations, and the cut-off of 7.5 enabled to improve the sensitivity of the single CEUS parameter "delayed TE" in discriminating between neoplastic and non-neoplastic lesions.

Our study has several limits. First, US and even more CEUS are strictly operator-dependent techniques. However, an adequate learning curve can minimize the risk of high interobserver variability; indeed, in our study it resulted fairly low and limited to two CEUS parameters. Second, because of the low number of patients enrolled into this pilot study, benign neoplastic lesions were just 2/53, and both of them showed a CEUS behaviour comparable to that of malignant lesions. Consequently, our results suggest that CEUS can discriminate between neoplastic and non-neoplastic lesions, but it does not enable to distinguish benign from malignant neoplastic lesions. Finally, US and CEUS may represent useful tools to evaluate peripheral pulmonary masses, but they can not investigate central lung lesions.

Despite these limits, this prospective pilot study suggests that CEUS could play some role in the diagnostic work-up of peripheral lung lesions. If the results will be confirmed by wider series, a lesion with a CEUS score < 7.5 could undergo clinical and instrumental follow-up, whereas invasive diagnostic procedures could be reserved to lesions with delayed TE, or a score $\geqslant 7.5$ if TE is not delayed.

COMMENTS

Background

The lung has dual blood supply (pulmonary arteries and systemic bronchial arteries), and this peculiarity could theoretically be exploited by contrast-enhanced ultrasonography (CEUS) to differentiate non-neoplastic from neoplastic lesions, as the formers are supplied by both arterial systems, whereas tumor angiogenesis usually rises from bronchial arteries.

Research frontiers

CEUS represents the best imaging method to evaluate both the vascularity and transit time within an organ, as it enables the assessment of any time of enhancement during the arterial phase. Conversely, contrast-enhanced computed tomography is an instant scanning modality, and can assess the vascularity only at a certain point in time during the arterial phase

Innovations and breakthroughs

A different time to arterial enhancement (TE) should be seen in neoplastic

and non-neoplastic lesions, as the enhancement resulting from the pulmonary arteries starts before that resulting from the bronchial arteries. However, the few preliminary studies investigating the role of CEUS in the characterization of lung consolidations gave inconclusive and disappointing results. In all these studies, an arbitrary cut-off of six s after the bolus of the US contrast agent was used to define TE as early or delayed, because the time windows of pulmonary arterial vascularity and bronchial arterial vascularity usually range from 1 to 5 s, and from 8 to 11 s, respectively. However, a lot of physiological and pathological conditions can modify the standard time window of both pulmonary and bronchial arterial vascularities. Authors avoided this potential bias defining TE as early if the enhancement in the lesion was contemporaneous to that of the normal lung, and as delayed if it appeared after the enhancement of the normal lung, or contemporaneously to that of the chest wall, liver, or spleen. In this way, a true early enhancement was observed in just 3/53 neoplastic lesions, and the delayed TE showed a very high diagnostic accuracy in identifying neoplastic lesions. Moreover, a cut-off value of 7.5 obtained by a cumulative arbitrary score based on the ratio between the positive predictive values of all CEUS parameters investigated, was shown to further improve the diagnostic performance of TE.

Applications

The study results suggest that CEUS could play some role in the diagnostic work-up of peripheral lung lesions. Lesions with a CEUS score < 7.5 could undergo clinical and instrumental follow-up, whereas invasive diagnostic procedures could be reserved to lesions with delayed TE, or a score ⩾ 7.5 if TE is not delayed.

Terminology

Low mechanical index CEUS with second generation ultrasonography contrast agents is a technique that allows for real-time depiction of tissue micro- and microvascularity, and in the last years it is increasingly used worldwide in abdominal imaging; in particular it is recommended as the first-line technique for the characterization of focal liver lesions in most western and eastern countries.

Peer review

This is an interesting and somewhat unique study to identify neoplastic lesions in the lung using contrast-enhanced ultrasound.

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CASE REPORT

Endovascular interventions for traumatic portal venous hemorrhage complicated by portal hypertension

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Abstract

Life-threatening hemorrhage rarely occurs from the portal vein following blunt hepatic trauma. Traditionally, severe portal bleeding in this setting has been controlled by surgical techniques such as packing, ligation, and venorrhaphy. The presence of portal hypertension could potentially increase the amount of hemorrhage in the setting of blunt portal vein trauma making it more difficult to control. This case series describes the use of indirect carbon dioxide portography to identify portal hemorrhage. Furthermore, these cases illustrate attempted endovascular treatment utilizing a transjugular intrahepatic portosystemic shunt in one scenario and transmesocaval shunt coiling of a jejunal varix in the other.

Key words: Trauma; Portal vein; Portal hypertension; Transjugular Intrahepatic Portasystemic Shunt; Varix

Core tip: The significance of bleeding from a portal venous origin following blunt hepatic trauma in the setting of portal hypertension, the potential role of indirect carbon dioxide venogram in identifying massive portal hemorrhage, and the use of a multiphase computed tomography of the liver in a trauma case with suspected internal bleeding and known portal hypertension are discussed. These cases illustrate attempted endovascular treatment of portal vein injury utilizing a transjugular intrahepatic portosystemic shunt in one scenario and transmesocaval shunt coiling of a jejunal varix in the other. Further research is needed to elucidate outcomes of portal interventions in the setting of coexisting portal hypertension and hemorrhage.

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INTRODUCTION

The hepatic arterial system is a common source of massive hemorrhage from blunt liver trauma[1]. However, significant bleeding from the portal venous vasculature is rare, with a reported incidence of 0.08%-0.10%[2]. The low pressure typically present in the portal system likely accounts for this difference. Portal venous injuries are generally associated with severe injuries affecting adjacent organs that often require surgical treatment. As a result, the mortality associated with portal venous injury following blunt trauma remains dismal, reportedly as high as 57%[2-4]. Intrahepatic portal venous bleeding is surgically controlled by the tamponade effect of peri-hepatic packing. In instances of pre-existing portal

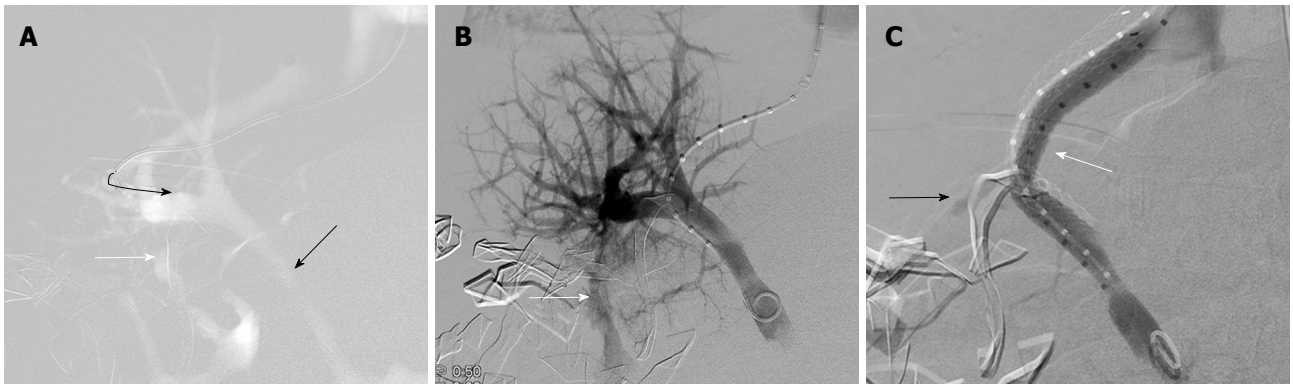

Figure 1 Case 1: Intra-hepatic portal venous injury. A: Wedged carbon dioxide venogram of the right hepatic vein shows main portal vein (arrow) and brisk active extravasation from the right branch of the portal vein (curved arrow) into the peritoneum (white arrow); B: Portal venogram from the marked pigtail using iodinated contrast confirms the active extravasation into the peritoneum (white arrow); C: Portal venogram obtained after successful deployment of 10 mm x 8 cm length Viatorr stent (white arrow) shows the patent shunt with a minimal residual extravasation (arrow) from the previously noted site of bleeding.

hypertension, injury to the portal vein and its tributaries can result in massive hemorrhage and shock. Although transjugular portosystemic shunt (TIPS) can effectively control variceal bleeding secondary to portal hypertension[5], its role in controlling bleeding secondary to blunt trauma remains unclear. These case reports describe two unusual cases of massive hemorrhage from a portal venous source in the setting of portal hypertension and illustrate techniques for diagnosis and potential management.

CASE REPORT

Case 1

A 58-year-old man with hepatitis C cirrhosis suffered severe blunt abdominal trauma in a motor vehicle collision. Limited history, which was later available from the family member suggested chronic liver disease due to Hepatitis C for 3 years without known history of gastrointestinal bleeding or hepatic encephalopathy. No prior medical records or images were available for review. He presented with circulatory shock due to massive intraperitoneal hemorrhage. After initial resuscitation, an emergent exploratory laparotomy was performed to control the intra-abdominal bleeding. Operative findings included multiple right hepatic lobe lacerations as well as a 5 cm hepatic mass, presumptively hepatocellular carcinoma. Massive mesenteric congestion due to portal hypertension was seen, and identification of the source of hemorrhage proved difficult. A clamp was placed across the hepatoduodenal ligament, hepatic artery, and portal vein (Pringle maneuver) and the peri-hepatic region was packed. Ongoing hemodynamic instability prompted emergent angiography. The abdomen was left open to unclamp the patient during angiography.

Angiography of the celiac axis, proper hepatic artery, and right hepatic artery did not reveal any active extravasation. However, given the patient's unstable status and severe right hepatic lobe injury, the arterial branches supplying the inferior segments of the right lobe were embolized using 100-300 micron Embospheres (Merit Medical Systems, Utah) in order to control a possible tumor related hemorrhage. Hemodynamic instability persisted despite arterial embolization, packing, and resuscitation. The portal venous system was subsequently evaluated for source of hemorrhage.

With the catheter in the right hepatic vein, a wedged carbon dioxide venogram demonstrated brisk extravasation of contrast from a branch of the right portal vein (Figure 1A). The right hepatic vein wedged pressure recordings revealed a portosystemic gradient of 50 mmHg (Free = 5 mmHg, wedged = 55 mmHg). Transhepatic access was obtained to the right portal vein. Direct portal venous pressure measurement and portogram confirmed the high portal venous pressure and brisk extravasation of contrast arising from the right branch of portal vein (Figure 1B). A 10 mm × 8 cm Viatorr endoprosthesis (WL Gore associates) was successfully placed across the hepatic tract and the stent was dilated to 10 mm. Following deployment of the stent, the porto-systemic gradient reduced to 0 mmHg. Post-TIPS portal venogram showed drastic reduction in the contrast extravasation from the portal vein (Figure 1C). Unfortunately, during the procedure, the patient's hemodynamic status further deteriorated, and he developed profound hypotension. The patient was transferred to the ICU for further cardiovascular resuscitation. Both surgical re-exploration and the possibility of portal vein embolization were contemplated. However, the patient expired three hours after the interventional radiology procedure secondary to refractory shock and acidosis.

Case 2

A 19-year-old man sustained blunt abdominal trauma in a motor vehicle collision and presented with massive hematemesis and shock. The patient's history was pertinent for a right liver lobe hepatectomy for hepatoblastoma with the creation of a hepatico-jejunostomy at 1 year old. At 4 years of age, he developed extra-hepatic portal hypertension due to the portal vein thrombosis with

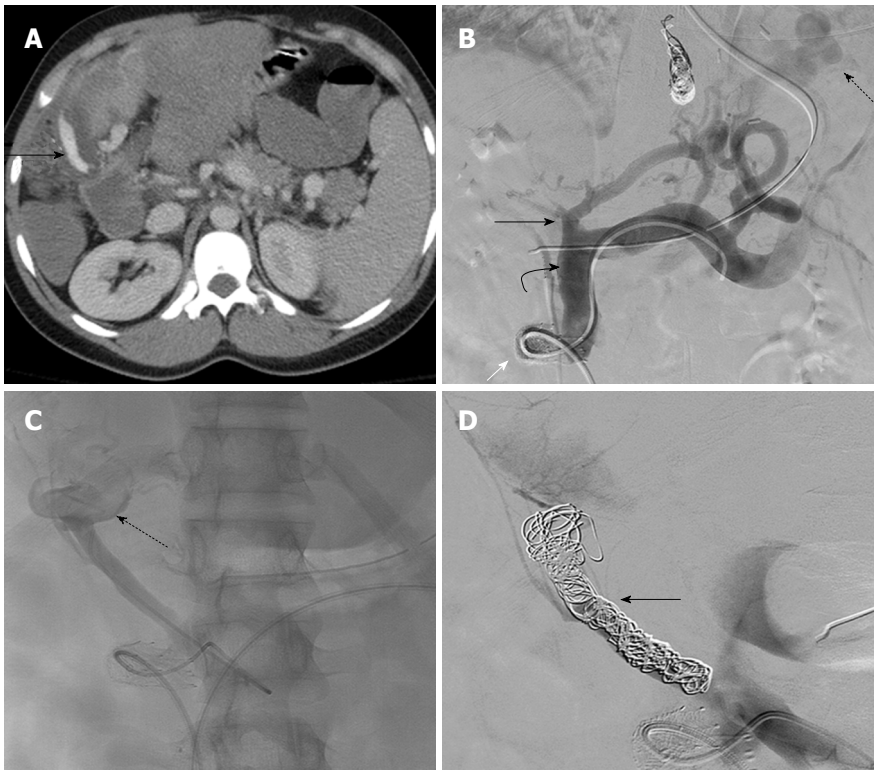

Figure 2 Case 2: Traumatic hemorrhage from a jejunal varix. A: Contrast enhanced computed tomography axial image shows contrast extravasation tracking along the outer wall of the hepatico-jejunostomy loop (arrow); B: Venogram performed by a trans meso-caval shunt (white arrow) approach shows large gastric fundal varices (dotted arrow), dilated superior mesenteric vein (curved arrow). The main portal vein is obliterated (black arrow); C: Selective venogram of the hepaticojejunostomy loop branch of the superior mesenteric vein shows dilatation of this branch with active extravasation of the contrast from the hepaticojejunostomy loop (dotted arrow); D: Multiple coils were used to occlude the branch (arrow).

cavernous transformation of the portal vein; this was treated with a mesocaval shunt. At 17 years old, stenosis of the shunt was identified and treated with angioplasty and stenting; large esophageal varices were also embolized concomitantly.

At the time of the traumatic presentation, contrast enhanced computed tomography (CT) revealed possible contrast extravasation from a dilated venous collateral into the peritoneum (Figure 2A). The patient was sent for angiography given ongoing hemodynamic instability. Hepatic and superior mesenteric artery angiography was negative for active extravasation or pseudoaneurysm. Next, the portal circulation was accessed through the preexisting mesocaval shunt. The pressure gradient across the mesocaval shunt measured 4 mmHg. A 5 French, 40 cm Ansel sheath (Cook, Bloomington, Ind) was advanced through the mesocaval shunt. Portal venogram showed a patent mesocaval shunt with severely dilated gastric varices (Figure 2B). Although no clear hemorrhage was identified, these varices were successfully embolized using multiple 6-8 mm Nester (Cook, Bloomington, Ind) coils. Subsequent venogram of a branch of the superior mesenteric vein revealed large venous collaterals in the hepaticojejunostomy loop with active extravasation (Figure 2C). This feeding vein was also successfully embolized using multiple Nester coils (Figure 2D). The patient stabilized after embolization. The remaining post-procedural period was uneventful and the patient was discharged two weeks later. There have been no further episodes of bleeding during the 2 year follow-up period.

DISCUSSION

Extravasation from an hepatic arterial source is more common, and is effectively managed by arterial embolization. Damage control surgery can be effective at managing hemorrhage in blunt abdominal trauma requiring laparotomy, allowing time for physiological recovery from coagulopathy, shock, and hypothermia[6]. But in cirrhotic patients with blunt abdominal trauma, this approach may prove insufficient. Portal hypertension, coagulopathy, varices, and splenomegaly caused by cirrhosis renders spontaneous arrest of bleeding difficult[7]. Significant bleeding from a portal venous origin is rare, and has a more complex management. In hemodynamically stable patients, primary portal venography, direct reanastomosis, porto-caval anastomosis, interposed grafts, and intraoperative temporary stenting of the injured segment of the portal vein have been performed to achieve continuity without causing mesenteric congestion[2,4,8]. These procedures involve prolonged surgical time, with many deaths resulting from intraoperative exsanguination[9]. Fraga *et al*[2] report the overall mortality associated with primary repair of the portal vein at 46.7%. A second approach to prompt control of portal hemorrhage involves ligation of the portal vein[9]. When used as a last line resort for controlling the portal hemorrhage, the survival rate is 13%[10]. Acute portal vein ligation increases the portal pressure which can cause mesenteric congestion, systemic hypotension due to sequestration of venous return, and occasionally bowel infarction[11]. The effects of portal ligation in portal hypertensive patients

were not reported, however, it is reasonable to speculate that exacerbating the baseline mesenteric congestion in cirrhotic patients would result in even higher mortality rates[10].

Not unexpectedly, mortality following hepatic trauma to the cirrhotic liver correlates with increasing Model for End Stage liver disease (MELD) score. Lin *et al*[7] studied the outcomes in 34 cirrhotic patients with blunt trauma and concluded that a MELD score of 17 or more correlates with increased post-operative mortality. In the presented case scenarios, portal hypertension may have led to, or at least intensified, massive portal vein hemorrhage.Endovascular treatment such as TIPS could thus potentially provide an alternative or adjunct to surgery in a portal hypertensive patient with proven portal hemorrhage. Although this approach increases the chances of liver failure in high MELD score cases, it also has the potential to avoid operative mortality and morbidity associated with portal venography, as well as avoiding the complications of increased mesenteric congestion caused by portal ligation. The endovascular technique attempted in the first case was based on the extrapolation of the success of emergent TIPS in controlling medically refractive spontaneous massive upper gastrointestinal hemorrhage due to portal hypertension[12]. However, reducing portal pressure using TIPS did not completely stop the extravasation in this patient. If he had been more stable, the next step may have included selective transhepatic portal vein embolization. While this move may have controlled hemorrhage, subsequent liver necrosis and/or fulminant hepatic failure would have been possible complications.

In the second case, the afferent loop of the hepaticojejunostomy was the source of jejunal variceal bleed. Ectopic varices in portal hypertension favor forming at sites of postoperative adhesions[13]. Spontaneous bleeding occurs in only 1%-5% of ectopic varices[14], and this type of hemorrhage is difficult to diagnose, as well as treat, by routine upper gastrointestinal endoscopic techniques. TIPS and balloon occlusion assisted retrograde transvenous obliteration are more effective methods of treating hemorrhage from ectopic varices[15]. The second patient responded well to transmesocaval shunt coiling of the bleeding varix.

In both of the presented case reports, arterial bleeding was ruled out with angiography before proceeding with portal venous evaluation and intervention. CT was not performed in the first patient because of hemodynamic instability, and only a single-phase contrast scan was performed in the second patient. Pre-procedural triple-phase CT in stable trauma patients with known portal hypertension and liver injury could help distinguish arterial versus portal hemorrhage. This could save the time and risks associated with conventional angiography; however, may not be feasible in unstable patients. On single-phase CT, the standard imaging protocol in trauma cases, imaging clues of intra-hepatic portal vein trauma include extension of hepatic laceration through the portal vein, abrupt cut off the portal vessels, vessel wall contour irregularity, and periportal hypodensity[16].

These case reports illustrate the significance of bleeding from a portal venous origin following blunt hepatic trauma in the setting of portal hypertension, and describe some of the challenges associated with diagnosis and treatment. The potential role of indirect carbon dioxide venogram in identifying massive portal hemorrhage was described. However, if clinically permissible, a multiphase CT of the liver could be valuable in differentiating arterial from portal venous hemorrhage as well as planning a potential intervention. Further research and larger case series are clearly desirable to delineate the imaging protocols and to elucidate outcomes of portal interventions in the setting of coexisting portal hypertension and hemorrhage.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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