GE Healthcare

Ultrasound in Gynecological Oncology

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INTRODUCTION

In recent years ultrasound has developed into the most utilized imaging technique in gynecology, and its potentialities are in continual growth. In the field of oncological gynecology, it is extensively used for the pre-operative evaluation study of pelvic masses, as well as in post-treatment management and follow-up.

The use of high frequency endovaginal probes consents a very accurate investigation. At present, ultrasound can be considered as a sort of "macroscope" which provides an "in vivo" morphological evaluation of a lesion, the assessment of its vascularization, and offers the advantage of being a dynamic and interactive examination. Unlike other standard imaging methodologies, as computed tomography (CT) and magnetic resonance imaging (MRI), ultrasound permits the evaluation of the mobility, elasticity and deformability of a lesion with respect to contiguous organs, and the creation of "pain mapping" (with the movement of the endovaginal probe, retraction or exertion of pressure, one can record areas of pelvic tenderness), which can be determinant in making a specific diagnosis of a lesion.

OVARIAN PATHOLOGY

IOTA AND THE DIAGNOSIS OF OVARIAN NEOPLASMS

The ultrasound differentiation of ovarian masses, in benign and malignant, is mainly based on morphological parameters. Since 1989, many authors thought to put together a scoring system, in the attempt of improving the accuracy of the examination and to express the risk of malignity in numbers. The resulting systems, in fact, provided a good sensitivity, but were deficient in specificity.

In addition, it was difficult to compare results as they had no common language in gathering the ultrasound parameters of adnexal masses.

In 1998, in the course of a Consensus Conference, the IOTA (International Ovarian Tumor Analysis) group standardized a methodology for the ultrasound evaluation of an adnexal mass. This consensus considers the following parameters for the evaluation of an ovarian neoformation:

1) **LOCALIZATION** in the pelvis, the mono-bilaterality, the relationship with the ovarian parenchyma and with the adjacent organs;

2) **MEASUREMENT** and quantitative assessment of the morphology: the size of both ovaries and the lesions are measured taking the largest three diameters in two perpendicular planes;

3) **MORPHOLOGY** can be classified into five groups: unilocular, multilocular, unilocular-solid, multilocular-solid, solid;

4) **SEPTUM** (thin strand of tissue running across the cyst cavity from one internal surface to the controlateral side) or **INCOMPLETE SEPTUM** (thin strand of tissue running across the cyst cavity from one internal surface to the controlateral side, which appears incomplete on some scanning planes). The thickness is measured where it appears to be at its widest;

5) **SOLID PAPILLARY PROJECTIONS**, into the cyst cavity from the cyst wall, with a height greater than, or equal to 3 mm (smooth or irregular). The largest projection is measured in height and base. The number of separate papillary projections and the presence of detectable blood flow have to be reported;

6) **CYSTIC CONTENTS:** anechoic, low-level echogenicity, ground glass appearance, haemorrhagic, mixed;

7) **ACOUSTIC SHADOWS:** loss of acoustic echo behind a sound-absorbing structure;

8) Subjective semiquantitative **ASSESSMENT OF VASCULARIZATION**, evaluated by means of color Doppler analysis, and registered with a "color score" variable from 1 (absence of flow) to 4 (hypervascularization);

9) FLUID in the pouch of Douglas or **ASCITES** (fluid outside the pouch of Douglas).

DISCRIMINATION BETWEEN BENIGN AND MALIGNANT ADNEXAL MASSES

Positive familiar history of breast and ovarian carcinoma, age, parity, the menopausal state, hormonal therapy, pain and serological data (Ca125) are the clinical data recorded in the IOTA protocol.

After the publication of the consensus, the IOTA group carried out a study where all the above-mentioned parameters have been prospectively analyzed, with the aim of identifying significant differences between benign and malignant masses. On the basis of the morphology of the lesion, malignant prevalence resulted to be 0.6% in unilocular neoformations, 10% in multilocular ones, 33% in unilocular-solid, 41% in multilocular-solid, and 62% in solid masses. At logistic multivariate regression analysis, the parameters which resulted to be significantly independent are the following:

Factors which increase the risk of malignancy
- Age of the patient,
- Positive anamnesis of ovarian carcinoma,
- Maximum diameter of the lesion,
- Diameter of the solid component,
- Ascites,
- Presence of solid vascularized tissue,
- Completely solid aspect of the lesion,
- Color score.

Factors which diminish the risk of malignancy:
- Cone shadow,
- Pelvic pain during examination,
- Hormonal therapy.

These variables have been used to elaborate a mathematical model with a formula to calculate the objective risk of malignancy which provided a high diagnostic accuracy (area under the ROC - Receiver operating characteristic - curve equal to 0.946).

At present, the applicability and accuracy of this model is being studied in centers which were not involved in its original development, so that it could later be distributed for application to the general population.

SPECIFIC DIAGNOSIS

The optimal treatment management does not only demand the distinction between benign and malignant pathology, it also needs to differentiate the various subgroups of benign, as well as malignant pathologies. In recent years great effort has been employed to define the main sonographic features of each category. The following are the salient data of the principal characteristics concerning various malignant neoformations, as described in recent studies.

BENIGN EPITHELIAL NEOFORMATIONS

Cystadenomas and endometrioid cysts usually appear as unilocular or multilocular cysts. A detailed description of these formations does not fall within the objectives of the present topic.

BORDERLINE AND MALIGNANT EPITHELIAL NEOFORMATIONS

Borderline ovarian tumors

Borderline ovarian tumors (BOT) constitute 10-15% of all malignant neoplasms and are considered one of the most difficult group of masses to classify correctly. In recent years, numerous studies have been performed to identify useful ultrasound characteristics that distinguish borderline ovarian tumors from primitive ovarian tumors.

At histology, borderline ovarian tumors are characterized as serous (sBOT) and mucinous (mBOT), and the latter as endocervical and intestinal type.

It has been observed that the different BOT histotypes are characterized by particular sonographic characteristics: the serous and endocervical mucinous types share a similar morphology; both are frequently represented as unilocular-solid lesions, with an elevated number of papillae and a

smaller number of locules (figure 1), with respect to the intestinal mBOT type; the mucinous intestinal type is instead characterized by unilateral multilocular masses, with regular septa having large dimensions and an elevated number of concamerations (figure 2).

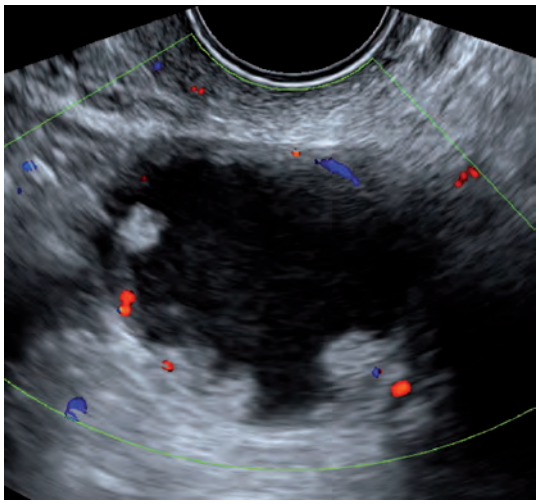


Figure 1: Serous borderline ovarian tumor

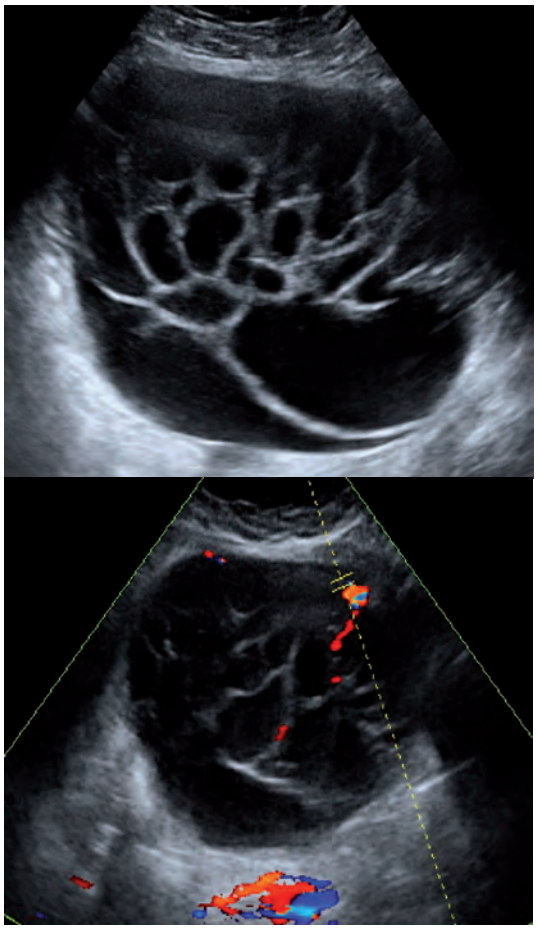


Figure 2: Mucinous borderline ovarian tumor

Epithelial ovarian carcinomas

Early-stage borderline tumors and ovarian carcinomas present numerous common ultrasound characteristics. They are similar in terms of dimensions and morphology, and present a high prevalence of papillary projections.

The solid tissue of the neoplasm increases in proportion to the rising levels of malignancy, from borderline tumors to the different stages of ovarian carcinoma, and the solid component progressively presents an increase in echo-genicity and more irregular borders.

On the contrary, more advanced staged ovarian tumors have smaller dimensions and generally present a solid morphology (figure 3).

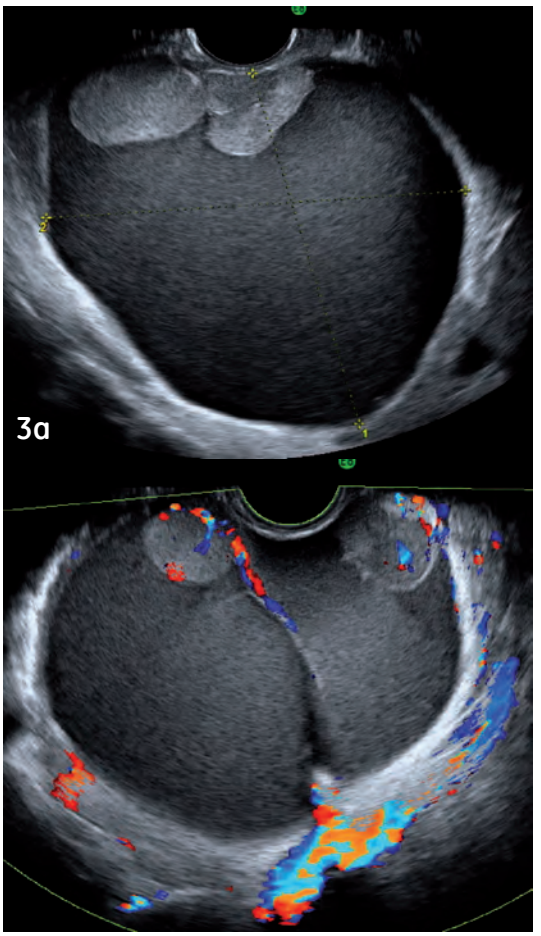
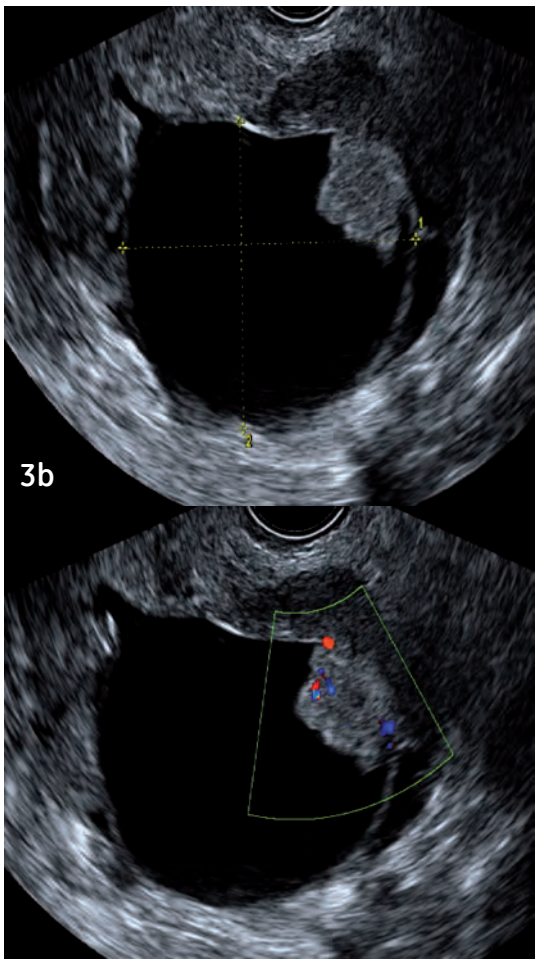


Figure 3 (a,b): Epithelial ovarian carcinomas with papillary projections vascularized at Color Doppler examination



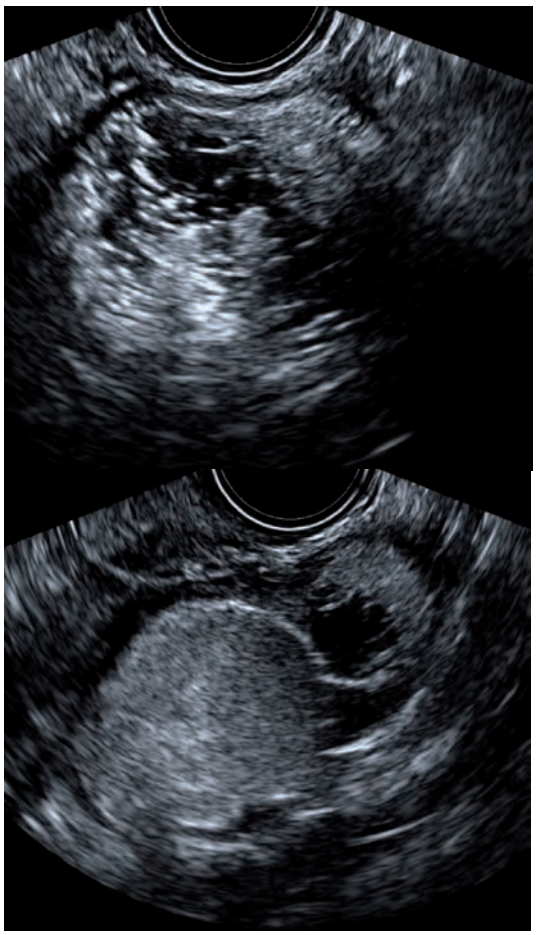


Figure 4: Cystic teratoma

Germinal ovarian tumors

THE CYSTIC TERATOMA

The cystic teratoma is a benign neoformation which originates from the three embryonic layers (the ectoderma, mesoderma and endoderma); it is prevalently constituted by sebaceous material and pilifereous structures, and it is not uncommon to find teeth, bones and muscular tissue.

At ultrasound, the lesions appear unilocular with inhomogeneous content, and with horizontal hyperechogenic stria, referable to hair. At times, the piliferic content is gathered inside the formation forming the Rokintanski nucleus which, at ultrasound, typically appears as a hyperechogenic roundish formation, ("white ball"), which should not be wrongly interpreted as solid parenchymal tissue (figure 4). Nevertheless, 9-18% of dermoids can manifest a prevalently cystic echopattern, indistinguishable from other formations.

MALIGNANT GERMINAL TUMORS

These are rare tumors which can be divided in disgerminomas, yolk sack tumors and choriocarcinomas. From a sonographic point of view, given the rarity of the neoplasm, there are no specific sonographic characteristics reported in the literature; they are usually observed as multilocular-solid lesions, with large dimensions, and a rich vascularization within the fibro-vascular septa.

Stromal tumors

FIBROMAS, FIBROTECOMAS AND BRENNER TUMORS

The most frequent category of stromal tumors is represented by benign forms. Ovarian fibromas and fibrotecomas are often reported as "difficult" masses to diagnose at ultrasound examination, however ovarian fibromas often present characteristic morphologies which consent diagnosis, such as a solid spheric or ovoidal structure and hypo-anechoic stripes (figure 5).

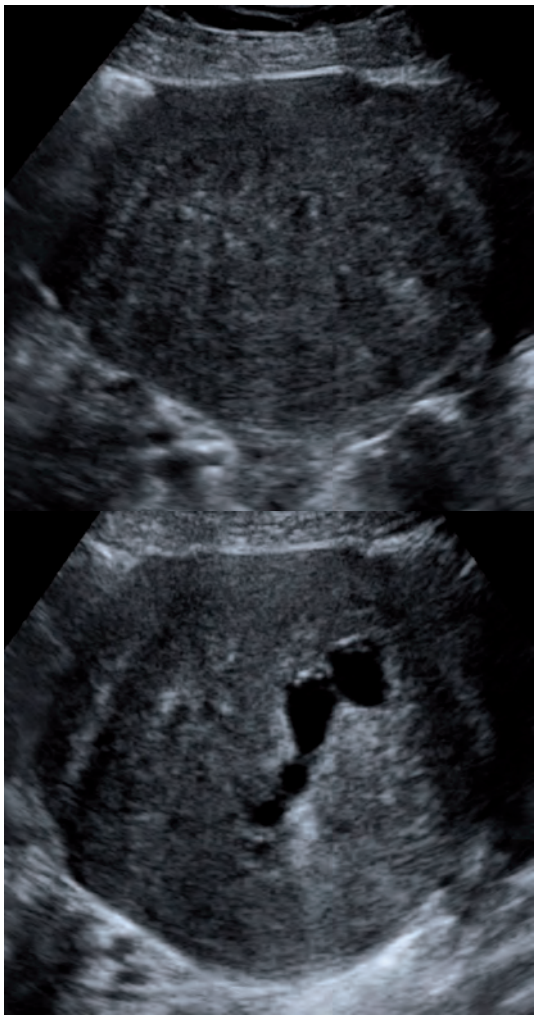


Figure 5: Ovarian fibroma

The ultrasound characteristics of fibrotecomas are still not well defined; they often present cystic concamerations. At times however, the echostructure of these formations is so inhomogeneous, that it makes it difficult to discriminate these lesions from malignant ovarian masses.

GRANULOSA CELLS AND SERTOLI LEYDIG TUMORS

Granulosa cell (GCTs) and Sertoli-Leydig tumors are rare cancers, and in literature there are few studies regarding specific ultrasound markers. According to a recent multicenter study GCTs were reported as large tumors with a median largest diameter of 102 mm. Few GCTs have been described as unilocular solid or multilocular whilst the vast majority were reported as multilocular–solid or purely solid, with a large number (>10) of small locules. The echogenicity of the cyst content is most often mixed or low level. Papillary projections are found in a small percentage of cases. At color Doppler examination a moderate-high vascularization (color score 3-4) is detected (figures 6-7).

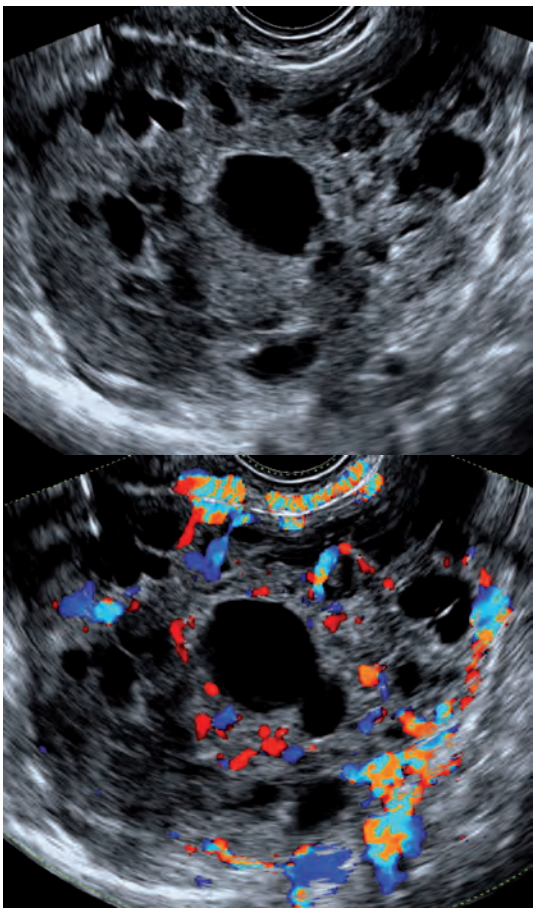


Figure 6: Granulosa cells tumor

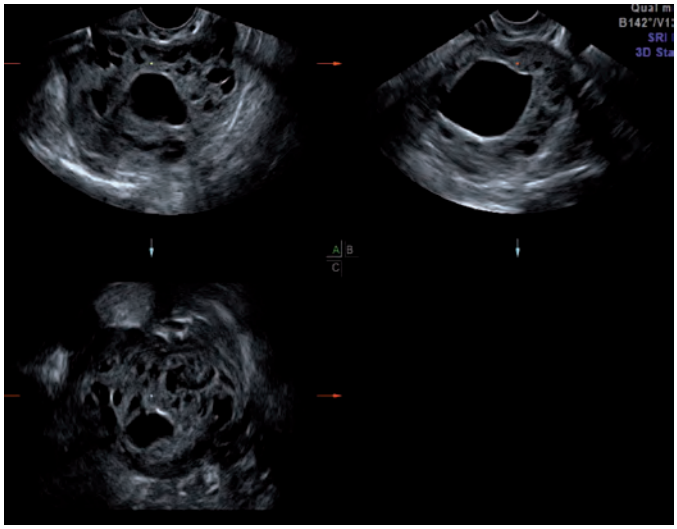


Figure 7: 3D orthogonal planes of granulosa cells tumor

Metastatic ovarian tumors

Ovarian masses result to be metastases in 4-5% of cases and the majority originate from intestinal tract or breast neoplasms. The descriptions provided by pathologists demonstrate that ovarian metastases which derive from tumors localized in other organs, are observed as bilateral lesions, with solid multiple nodules (in the ovary), or partly cystic, or less frequently, totally cystic. Within these lesions, it is common to observe extended areas of necrosis or hemorrhage. Krukenberg tumors are typically solid, with a polilobated external surface (figure 8).

A recent multicenter study analyzed the ultrasound characteristics of 67 patients with histologically diagnosed ovarian metastatic tumors and nearly all the tumors (93%) derived from the stomach, the breast, lymphoma or the uterus, resulted to be solid; in contrast, the metastases from colon-rectum, appendix and biliary tract tumors resulted multilocular or multilocular-solid.

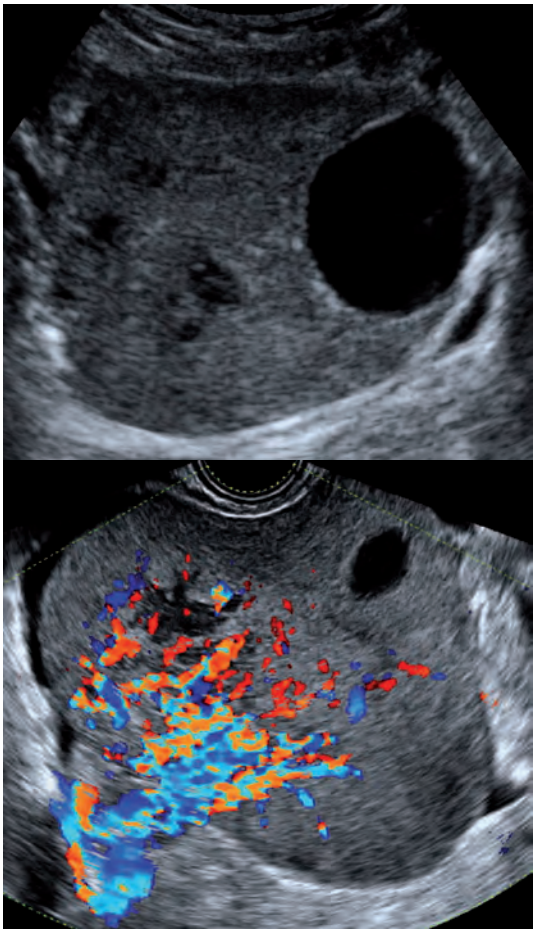


Figure 8: Metastatic ovarian tumor (krukenberg tumor) and the "lead vessel"

ASSESSMENT OF THE EXTENSION OF OVARIAN CARCINOMA

In recent years, ultrasound has assumed ever greater importance in the preoperative evaluation of patients affected by ovarian carcinoma in assessing the extension of the disease. Peritoneal carcinomatosis can be diagnosed on the basis of the presence of solid hypoechoic nodules which grow on the perinoteal surface, or a band of thickened tissue which traps the intestinal loops and can cause retraction towards the mesenteric root (figure 9). Carcinosis is often associated with the presence of ascites.

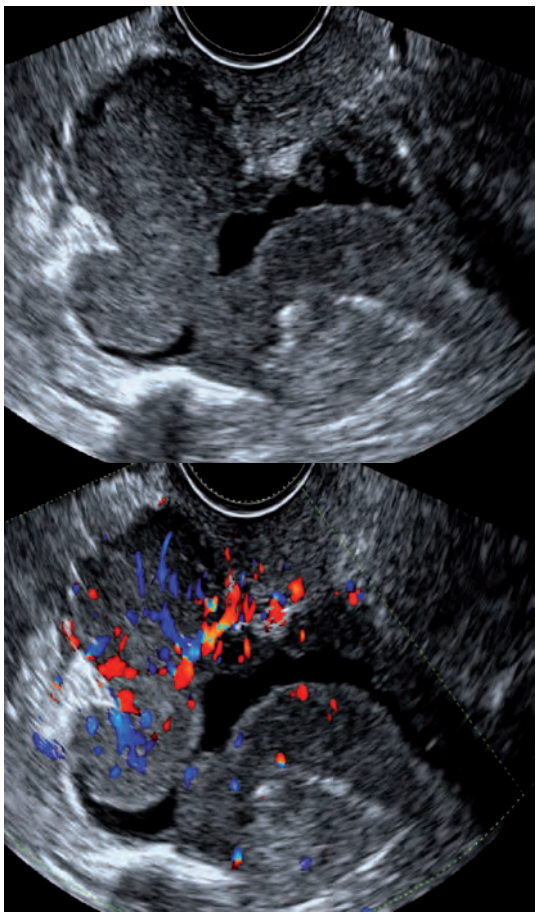


Figure 9: Carcinomatosis in the pouch of Douglas

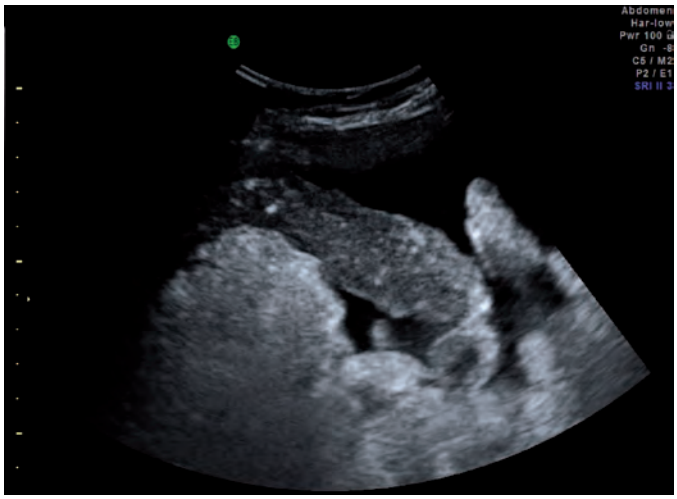


Figure 10: metastatic omentum

The infiltrated omentum generally presents as solid aperistaltic tissue, situated between the peritoneum wall and intestinal loops, having an inferior echogeneity, or in some cases equal in respect to the surrounding loops (figure 10). At times, hypoechogenic nodules are identified. A recent study has evaluated the capacity of ultrasound in predicting the omental infi ltration, and it demonstrated reliable accuracy.

The standard treatment for patients with ovarian carcinoma consists in surgery performed by a gynecological oncologist followed by chemotherapy, based on platinum. This first surgical stage is of outmost importance in the oncological history of these patients, as the most significant prognostic factor is represented by residual tumor at surgery. For a certain percentage of patients, however, the extension of the disease is such, that it is impossible to carry out an optimal cytoreduction of the neoplastic pathology. Hence, these patients are first referred to neoadjuvant chemotherapy and cytoreduction is carried out later on. In particular, the main criteria for non surgical cytoreduction are represented by multiple hepatic metastases, mesenteric root infiltration, extensive carcinomatosis requiring multiple small intestine resections. A preoperative selection of these patients would be of great clinical value, in order to avoid the morbidity correlated to the surgery and, delay in starting chemotherapy.

There are at present studies being carried out aimed at defining the capacity of ultrasound, to select patients who cannot be optimally cytoreduced.

ENDOMETRIAL PATHOLOGY

Transvaginal ultrasound examination consents the analysis of the endocavital tissue echotexture, the dimensions of the neoplastic tissue, the myometrial infiltration and its extension to the cervix, the extension to nearby organs and the intraparenchimal vascularization. The preoperative staging of endometrial carcinoma is fundamental in planning the modalities and extension of the surgical procedure (figures 11-12).

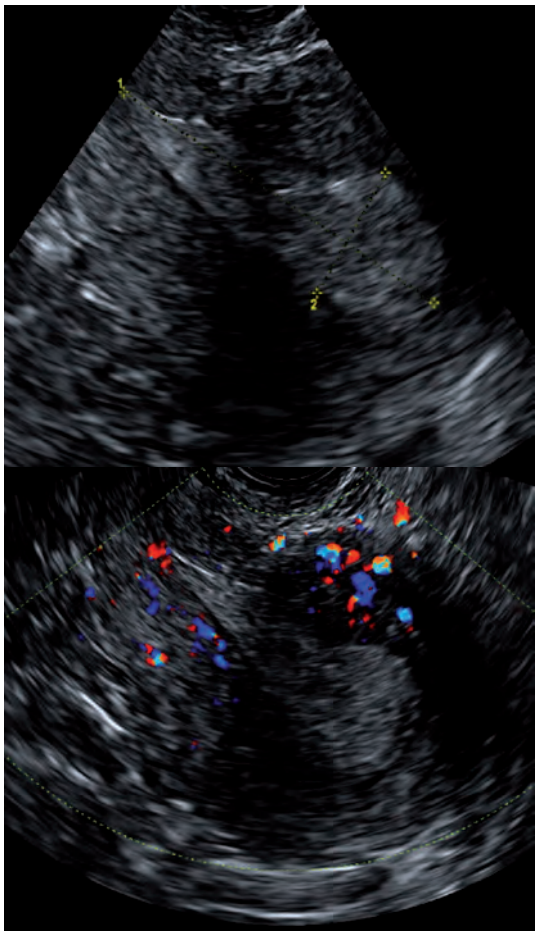


Figure 11: Endometrial carcinoma with myometrial infiltration less than 50% (stadio FIGO IB)

Endocavital echotexture:
at sonographic observation, endometrial carcinoma could assume the aspect of an irregular polipoid neoformation, or appear as a localized or diffused inhomogeneous tissue with irregular margins, and in each case characterized by a marked thickening of the endometrial rima. The presence of an endometrial neoplasm, with an endometrial rima inferior to 5 mm, is only found in a small percentage of cases. The echostructure of the neoplasm has been related to the degree of differentiation, and it has been demonstrated that in well-differentiated carcinomas (G1), the

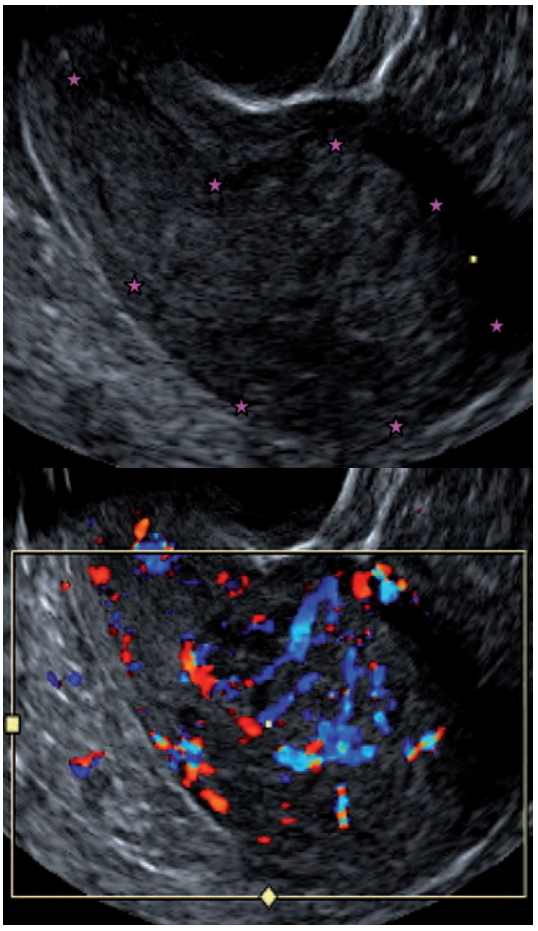


Figure 12: Endometrial carcinoma with deep myometrium infiltration (greater than 50%) and cervical involvement (stadio FIGO IIB)

echostructure is homogenously hyperechoic, whereas it is often iso-hypoechoic in moderately differentiated anaplastic adenocarcinomas (G2-G3). Probably, well-differentiated carcinomas produce a greater quantity of mucus, which facilitates the intracavital tissue to assume a dissimilar echogeneity. When the endometrial cancer infiltrates the cervical stroma, it is often characterized by a low echogeneity, which can be well distinguished from the surrounding normal cervical stroma.

Dimensions:
the volume of the tumor has been proposed as a prognostic factor and the transvaginal probe consents an accurate visualization and evaluation of the three spatial dimensions of the endometrial carcinoma.

Myometrial infiltration:
regarding the ultrasound study of myometrial infiltration,

Karlsson introduced a relationship between the antero-posterior diameter of the endometrium and the antero-posterior diameter of the uterus, to define whether the infiltration is more or less than 50%. This relationship results indicative and accurate in case of symmetrical growth of tumor, whilst it is not reliable when the tumor growth is asymmetrical. Therefore, in our experience, the maximum myometrial infiltration is evaluated subjectively, by studying the minimal point of myometrial infiltration.

The extrauterine extension:
transvaginal evaluation permits the analysis of the extension of the endometrial neoplasm both by simple visualization of the neoplastic tissue outside the uterine corpus (ovarian metastases, lymphadenopathies), as well as through the dynamic relational study of the pelvic organs. By exerting slow movements of the TV probe, one can observe the contiguous anatomic structures sliding towards the uterus and vice-versa; the adequate sliding of the planes reliably excludes extension to the adjacent organs. As to ovarian and lymph-node infiltration, US is characterized by a high specificity, but low sensitivity. In particular, in patients with an elevated body mass index, the low penetration of the ultrasound beams hampers the visualization of para-aortic lymph-nodes.

Intraparenchimal vascularization:
Angiogenesis plays a fundamental role in tumoral pathogenesis, and it is essential for tumor growth and metastasis. With respect to the endometrium, it has been demonstrated that the process which goes from simple hyperplasia to invasive carcinoma, is characterized by a gradual increment of the "angiogenetic process". Transvaginal sonography, with the help of color Doppler, permits the "in vivo" study of the intratumoral vascular flow, and even to characterize the distribution of vascularization within the endometrial carcinoma by documenting the anarchic disposition of the vessels, and the presence of artero-venous shunts. It has been demonstrated that the color score is significantly different between early and advanced stages of endometrial carcinomas.

Limitations:
many factors can interfere with the study of endometrial carcinoma and impede the evaluation of the parameters for staging:

- myomas and adenomyosis: determine myometrial inhomogeneity and hinder the visualization of the endometrial-myometrial interface;
- physical habitus: severe obesity often represents an obstacle in the visualization of the paraortic district;
- fluid in the endometrial cavity: the distension caused by the presence of fluid can determine a false image of deep myometrial invasion owing to the thinning of the myometrial wall, above all in cases of senile uterus.

In conclusion TVS, performed by expert hands, is able to offer reliable accuracy in the loco-regional staging of endometrial carcinoma. Nevertheless, US does not consent a sufficiently accurate evaluation of the disease at lymph-node level. MRI, at par with loco-regional staging accuracy, is more precise in defining the lymph-nodal involvement, however this diagnostic procedure is still costly, and unfortunately, not widely available in all Institutions.

CERVICAL PATHOLOGY

It is rather surprising, that we do not find much literature on the utility and accuracy of ultrasound in the evaluation of patients affected by carcinoma of the uterine cervix.

With the ultrasound equipment at our disposition today, it is common experience that transvaginal ultrasound obtains uterine cervix images at a high resolution.

The first ultrasound step in a patient affected by cervical carcinoma is the transabdominal evaluation of the renal pelvis: a locally advanced cervical cancer can determine a compression of the ureter in its distal part, causing hydronephrosis. By means of transvaginal ultrasound it is however possible to detect a series of other morphological parameters as: the three perpendicular diameters of the lesion calculating the tumoral volume, the stromal infiltration, the infiltration of the parametria, the integrity of the septum (rectum-vaginal and vesico-vaginal), the vascularization (figure 13).

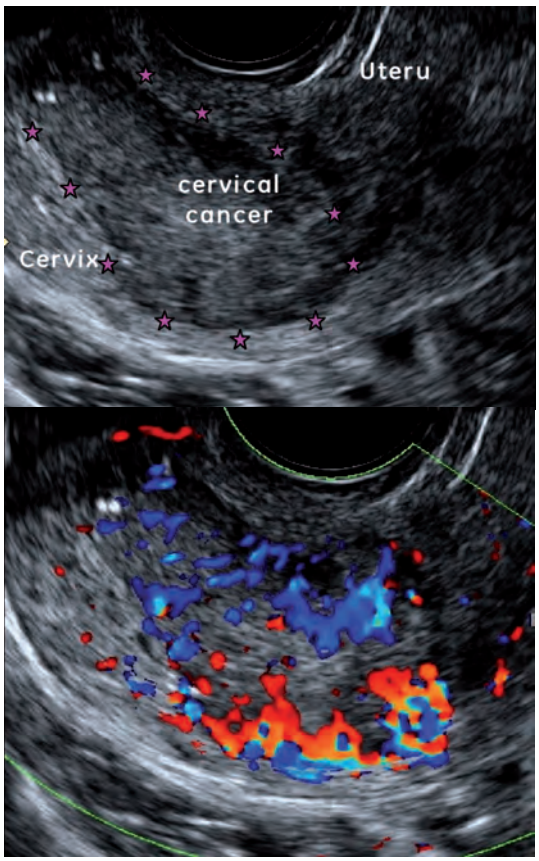


Figure 13: Cervical carcinoma

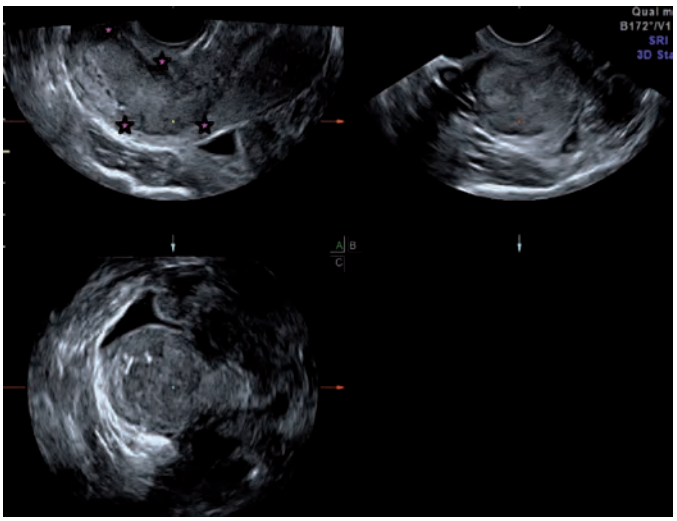


Figure 14: 3D orthogonal planes of cervical carcinoma

Thanks to the dynamicity of the examination, it is also possible to analyze the deformability and elasticity of the tissues, as well as the reciprocal movement of the various organs, obtaining an accurate evaluation of the loco-regional extension of the disease. Tridimensional ultrasound has been used for the analysis of the vascularization within the tumor volume, and other studies are currently being carried out to evaluate the prognostic value of 3D vascular parameters.

Moreover, the three perpendicular sections provided by 3D examination could provide important information on the morphological parameters of the neoplastic lesion (see infiltration of parametria) (figure 14).

FOLLOW-UP OF PATIENTS WITH GYNECOLOGIC NEOPLASMS

Though follow-up constitutes standard practice in the management of gynecologic tumors, the optimal methods to be used are still under discussion.

CT and MRI are accurate methods, but too expensive to be utilized in routine follow-up of gynecologic neoplasms. Also the recently introduced PET (Positron Emission Tomography) cannot be proposed as first-line diagnostic instrument.

Surprisingly, one finds scant data in the literature on the utility and accuracy of transabdominal and transvaginal sonography in the follow-up of gynecological cancer patients. If a high accuracy were to be demonstrated, considering the wide availability and the relative low-cost of the ultrasound technique, as well as the rapidity of the procedure and the possibility of a bed-side use of the ultrasound equipment, it would justify the introduction of this diagnostic tool in a routine surveillance protocol.

Gynecologic tumor recurrences can assume different morphological patterns, which go from a solitary neoformation to diffused carcinomatosis. In the case of single lesions, besides dimensional parameters, ultrasound examination is also able to provide "dynamic" parameters related to deformability, mobility and painfulness of the lesions, consenting a more accurate diagnostic differentiation. The description of the lesions' margins, which could be regular or infiltrated with respect to surrounding tissues, is essential from a therapeutic point of view, as it indicates the degree of susceptibility to surgical treatment (figures 15-16).

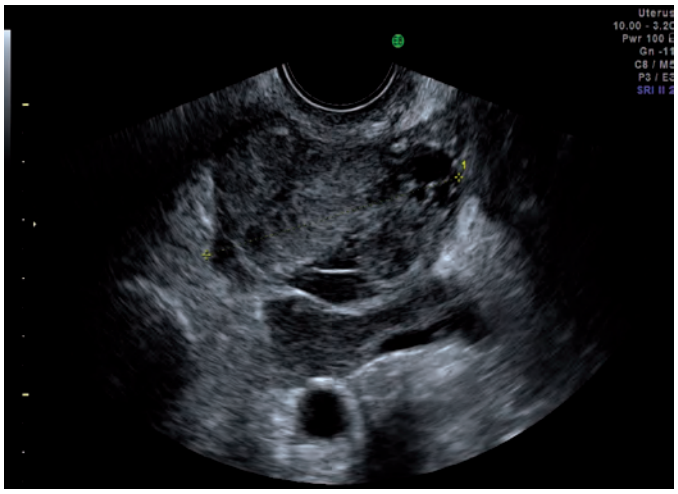


Figure 15: Pelvic recurrent lesion of endometrial carcinoma

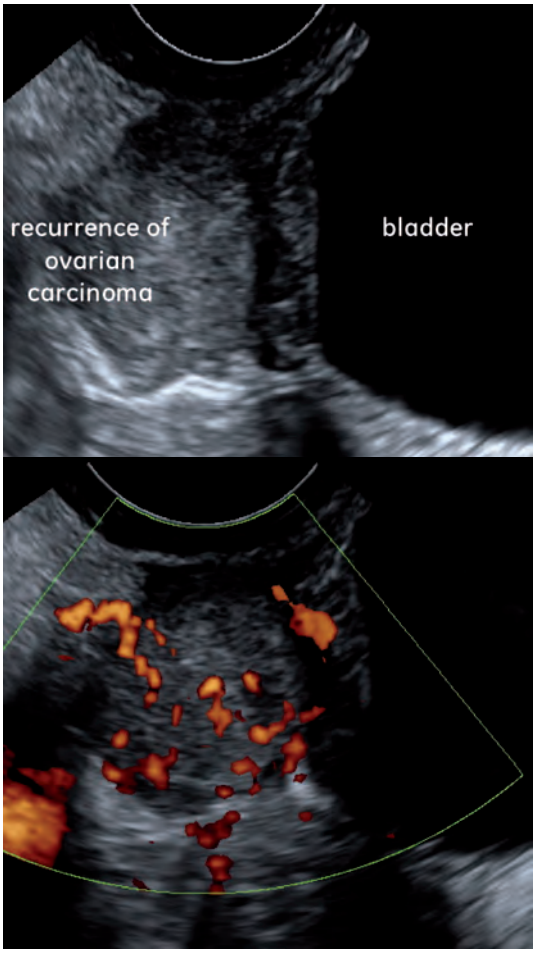


Figure 16: Pelvic recurrence of ovarian carcinoma adjacent to the bladder

Furthermore, TVS can offer the possibility of carrying out a guided transvaginal biopsy on a suspicious pelvic lesion, or the aspiration of peritoneal liquid for cytological analysis, thus permitting an easy and immediate diagnostic confirmation of the suspicious oncological recurrence (figure 17).

In conclusion the application of US as a routine follow-up tool in gynecologic neoplasms, can have a role to play, especially in the case of asymptomatic patients, whereas instrumental methods like CT and MRI appear to be more appropriately indicated for patients with clinical or serological evidence of the disease.

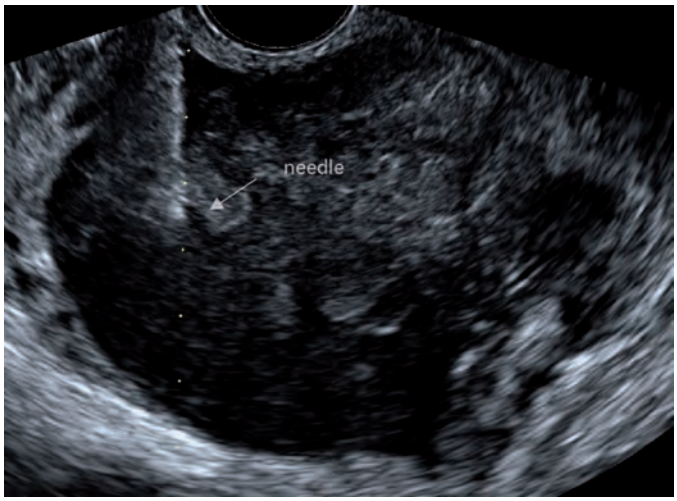


Figure 17: Transvaginal biopsy of a metastatic ovarian tumor.

However further studies still need to evaluate the effective impact of US routine use on the clinical outcome and on the overall survival of patients, as well the usefulness of 3D examination in the presence of a pelvic recurrence, to better assess the relationship between the recurrent lesion and the surrounding organs.

FURTHER READING

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