VOLUME 3 | ISSUE 4

Women's Imaging REVIEW

Imaging of ovarian cancer: Current concepts.

Rui Tiago Gil, Teresa Margarida Cunha, Mariana Horta

Serviço de Radiologia do Instituto Portugues de Oncologia de Lisboa, Francisco Gentil, Lisbon, Portugal

SUBMISSION: 17/5/2018 | ACCEPTANCE: 17/9/2018

ABSTRACT

Despite the advances in medicine over the past decades, ovarian cancer remains a major clinical and radiological challenge worldwide, with the highest mortality rate among gynaecologic malignancies. Modern histopathological and molecular genetic studies contributed to understand the pathogenesis of ovarian cancer, which now includes a heterogeneous group of malignant epithelial tumours that share the same origin as tubal cancer and peritoneal primary cancer. Based on this knowledge, the International Federation of Gynaecology and Obstetrics (FIGO) staging system was revised in 2014, providing better prognostic information and reinforcing personalised management of ovarian cancer. In accordance, there are now evidence-based imaging recommendations that provide accurate characterisation of adnexal masses that all radiologists should be aware of. Accurate mapping of tumour burden and distribution of disease by imaging plays a central role in treatment stratification and in predicting the success of cytoreductive surgery. The purpose of this article is to review the clinicopathological characteristics of ovarian cancer and their impact on radiological assessment, staging and therapeutic approach.

KEY WORDS | ovarian cancer; gynaecologic diseases; cancer; imaging

CORRESPONDING AUTHOR, GUARANTOR

Rui Tiago Gil, Serviço de Radiologia do Instituto Portugues de Oncologia de Lisboa, Francisco Gentil, Rua Prof. Lima Basto, 1099-023 Lisbon, Portugal
Email: ruitiagogil@gmail.com

1. Introduction

Ovarian cancer is the seventh most common type of cancer in women but represents the fourth most common cause of cancer death in women, having the highest mortality rate among gynaecologic malignancies [1]. Ovarian cancer is often clinically silent and about 75% of women present with advanced-stage disease and metastatic spread beyond the pelvis [2]. Moreover, ovarian masses are a common finding in daily practice, incidentally detected or identified in symptomatic patients. Fortunately, most of ovarian masses correspond to benign lesions, mainly functional or haemorrhagic cysts. However, differentiating ovarian masses is frequently not easy and the clinical impact of defining whether an adnexal mass is benign or malignant is enormous [3].

Advances in the knowledge about the clinicopathology and molecular biology of ovarian cancer contributed to understand its pathogenesis. Most of this review will focus on epithelial ovarian cancer that remains the most frequent type of ovarian cancer accounting for about 90% of malignant tumours. The other types, including germ cell and sex-cord stromal cell ovarian cancer, are much less frequent (<5%) and have particular features, although they share the same staging classification with epithelial ovarian cancer. Epithelial ovarian cancer is divided in different subtypes (high-grade serous, low-grade serous, endometrioid, clear cell and mucinous ovarian cancer) that are distinguished by molecular, genetic and morphologic characteristics that comprise important prognostic information [4]. Moreover, there is increasing evidence that high-grade serous ovarian cancer has the same origin as tubal cancer and primary peritoneal cancer. According to the "serous tubal intraepithelial carcinoma" (STIC) theory, these cancers derive from tubal epithelial cells and they currently share the same staging system [5]. The 2014 revised International Federation of Gynaecology and Obstetrics (FIGO) staging system provides now more accurate prognostic information and better guidance on the management of ovarian cancer [6, 7].

In this article, we intend to review the pathogenesis, classification and staging of ovarian cancer, as well as the diagnostic approach of ovarian masses, according to the most recent knowledge and international guidelines.

2. Pathology

Ovarian cancer is predominantly a disease of postmenopausal women, with more than 80% of cases being diagnosed in women over 50 years. The aetiology of ovarian cancer remains unknown, but different risk factors have been identified. Family history represents the most important risk factor, with the lifetime risk of developing ovarian cancer increasing from 1 in 70 to 1 in 30 if a first-degree relative has ovarian cancer. Less significant risk factors include infertility, nulliparity, late menopause and early menarche [8, 9]. Approximately 90-95% of ovarian cancers are sporadic and only 5-10% are associated with inherited familial syndromes. From ovarian cancers with an identifiable genetic mutation, BRCA 1 and BRCA 2 tumour suppressor genes account for the vast majority (85-90%) [10]. Ovarian cancer also occurs in almost 10% of patients with Lynch syndrome II (hereditary nonpolyposis colorectal cancer associated with other cancers of the gastrointestinal or reproductive system) [11].

Primary ovarian tumours are divided into three major categories: epithelial tumours, germ cell tumours (GCTs) and sex cord-stromal tumours [6]. Epithelial tumours are the most common, accounting for about 60% of all ovarian tumours and 90% of malignant ovarian tumours [12]. Epithelial tumours are further divided into seven subtypes: serous, mucinous, endometrioid, clear cell, Brenner, seromucinous and undifferentiated. The first six types can be further subdivided into benign, borderline and malignant tumours [6]. Malignant epithelial tumours include by order of frequency: high-grade serous carcinoma -HGSC- (70%), endometrioid carcinoma (10%), clear cell carcinoma (10%), low grade serous carcinoma –LGSC– (<5%), mucinous carcinoma (3%), malignant Brenner tumour (<1%), seromucinous carcinoma (<1%) and undifferentiated carcinoma (<1%). Differentiation of these subtypes is important because they have different clinical presentation, prognosis and response to treatment [13]. Radiologists should understand this differentiation, because these subtypes usually manifest with distinct radiologic findings and different patterns of metastatic dissemination. HGSC is associated with TP53, BRCA 1 and BRCA 2 mutations and usually develop in few months. At presentation, HGSC is commonly disseminated, with peritoneal deposits throughout the abdominal cavity [14]. Conversely, LGSC is frequently associated with KRAS and BRAF mutations and

seems to develop from a benign precursor lesion with slow growth (from serous cystadenoma to serous borderline cancer) and is often confined to the ovary [7].

Recent clinicopathological and molecular genetic studies demonstrate that HGSC, tubal cancer and peritoneal primary cancer share molecular, morphologic and clinical features [5]. Evidence that many of these cancers derive from tubal epithelial cells led to the formulation of the STIC theory [15]. The proportion of HGSCs of ovarian and tubal origin is unknown because tumour growth in advanced stages of cancer obscures the primary site. Although there is no described impact on therapy and prognosis, the identification of the primary site of origin should be designated when possible. The primary site of the other subtypes is usually easier to detect because they are often confined to the ovary [7].

GCTs originate from primordial germ cells and are mainly diagnosed in the first two decades of life. These tumours recapitulate the steps of development, from undifferentiated germ cells to adult tissues. GCTs account for 25% of all ovarian tumours and 3-7% of malignant ovarian tumours [16]. The primitive GCTs, composed of undifferentiated germ cells, and tumours with extra-embryonic differentiation are all malignant (dysgerminoma, yolk sac tumour and embryonal carcinoma). Teratomas are the most common GCTs and are benign. Immature teratomas are much less common and contain embryonic tissues with malignant potential. Immature teratomas are typically larger (14–25 cm) than mature cystic teratomas (average 7 cm) and demonstrate a prominent solid component with cystic areas and intratumoural fat. Peritoneal implants, lymph node metastasis, ascites and extra-capsular spread also differentiate immature from mature teratomas. Older age at diagnosis, advanced stage and high-grade histology are the most important prognostic factors [17].

Sex cord-stromal tumours constitute a heterogeneous group of neoplasms that accounts for about 7% of all malignant ovarian tumours. These tumours originate from gonadal primitive sex cords (granulosa cells and Sertoli cells) and from stromal cells (theca cells, fibroblasts and Leydig cells), that can be present separately or in combination, with different degrees of differentiation [18]. They are often associated with hormonal abnormalities and occur in a wide range of age, although in specific tumour types the age range is often more limited [19]. Tumours formed from granulosa cells and theca cells are often hyperestrogenic and usually present with isosexual precocity in children, abnormal uterine bleeding, endometrial hyperplasia and carcinoma in older women. Tumours comprising of testicular cell types (e.g. Sertoli and Leydig cells) are usually hyperandrogenic and may present with virilisation signs (hirsutism, acne, irregular menstrual periods, male-pattern baldness and hoarse voice) [18].

Pure stromal tumours are mostly benign, with more than 50% being fibromas and thecomas. Fibromas are the most common sex-cord-stromal tumours (4% of all ovarian neoplasms) and can be present at any age (although the mean age is in the late forties). Fibromas are composed of spindle stromal cells and are almost always endocrine-inert. Thecomas account for 0.5%–1% of all primary ovarian tumours and are more likely to occur in postmenopausal women. They are composed of lipid-laden stromal cells that resemble theca cells and can produce oestrogen-related symptoms such as uterine bleeding, endometrial hyperplasia and endometrial carcinoma. Tumours with sex cord elements are usually malignant, with granulosa cell tumours being the most frequent histological subtype [16]. Granulosa cell tumours are the most common oestrogen-producing tumours and can be divided into two histologic subtypes, the adult form, that usually occurs in early postmenopausal women, and the juvenile form, that predominantly occurs in children and young women. Sertoli-Leydig cell tumours are mixed sex cord-stromal tumours and account for about 0.5% of all ovarian neoplasms. They are the most common virilising ovarian tumour, as 30%-50% of these tumours produce androgens (testosterone and androgen precursors) [18].

3. Role of Imaging

Adnexal tumours are a frequent finding in daily practice and commonly represent a clinical and diagnostic challenge. Although most of adnexal tumours are benign lesions, the clinical impact of defining whether an adnexal mass is benign or malignant is enormous [3]. While benign adnexal masses may be either managed conservatively or undergo resection by a general gynaecologist, malignant masses should be evaluated in a dedicated oncology centre, to decide if neoadjuvant chemotherapy is required, followed by interval debulking or direct radical cytoreductive surgery by a specialist surgeon with expertise in gynaecological oncology [20].

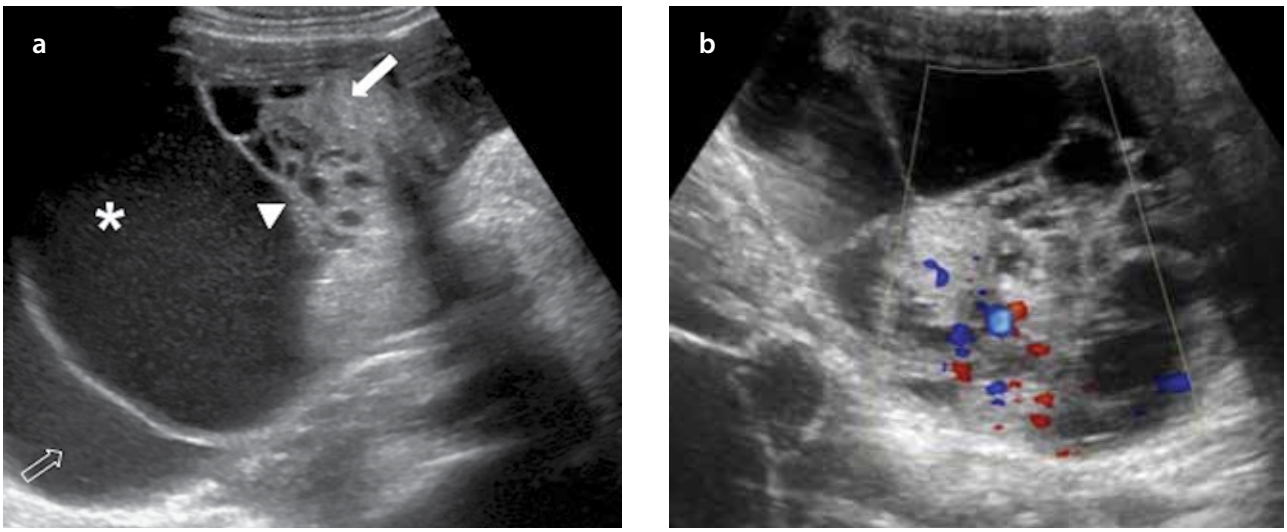

Fig. 1. *Bilateral high grade serous carcinoma in a 61-year-old woman. Transvaginal US scan shows a right adnexal complex cystic-solid tumour* ***(a)*** *with solid component (arrow), thick septa (arrowhead), cystic areas (asterisk) and ascites (open arrow). Colour Doppler US* ***(b)*** *confirmed flow within the solid components, typical of malignancy.*

In a radiologic perspective, ultrasonography (US) with transvaginal approach remains the first-line imaging tool to study adnexal masses. Distinct models have been created to optimise the diagnosis of adnexal tumours and to classify them as benign or malignant [21]. Among these models, the International Ovarian Tumour Analysis (IOTA) "simple rules" are currently considered one of the best US-based modes for use in clinical practice, with excellent prediction of malignancy (pooled sensitivity 93% and specificity 96%) [22]. US features that indicate malignancy include the presence of a solid component (particularly if there is visible central flow on colour Doppler evaluation), thick or irregular septa, and ascites (**Fig. 1**) [23]. However, even using accurate US models with grey-scale and colour Doppler, 5-25% of adnexal masses remain indeterminate and need further examination [24, 25]. These tumours are usually large, unilocular or multilocular, with solid components, irregular walls and papillary projections [26].

Magnetic resonance imaging (MRI) improves the characterisation of adnexal masses and is considered the best second-line technique to evaluate indeterminate or complex adnexal masses detected on transvaginal US [27]. An algorithmic approach using basic and problem-solving MR sequences was proposed in 2010 by the European Society of Urogenital Radiology (ESUR) and recently updated in 2017 (**Table 1**) [3, 28]. This revision incorporated diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI in the characterisation of adnexal masses, based on the added value of these functional techniques provided by different studies [29-31].

Before the examination, patients should fast for 4-6 hours. Data support the value of intramuscular or intravenous smooth muscle relaxants (hyoscine butylbromide or glucagon) to reduce bowel movements and improve image quality [32]. The diagnostic algorithm starts with basic morphologic sequences, including sagittal T2-weighted (T2W) imaging of the pelvis, and a pair of T1-weighted (T1W) imaging and T2W imaging covering the indeterminate mass and its relationship to the uterus in the same orthogonal plane (axial or coronal or oblique) with identical slice thickness [3, 28]. When performed, DWI and DCE-MRI (or contrast-enhanced T1-weighted - CET1W - images, should be obtained in the same orientation of the pair of T1W and T2W imaging [28]. On DWI, high signal using b values higher than 800 s/mm^2 with corresponding low ADC signal indicate diffusion restriction, which should alert for malignancy. However, interpretation of DWI should be carefully performed, particularly in the possibility of benign conditions that can also demonstrate diffusion restriction (e.g. haemorrhagic lesions, epidermoid components and pelvic inflammatory disease). On DCE-MRI, a time-intensity curve (TIC) type 1 represents a weak and progressive enhancement compared to that of myometrium, a

Table 1. MR imaging protocol (adapted from ESUR recommendations 2016)

Patient preparation	Intravenous smooth muscle relaxant Placement of intravenous cannula
Basic MR sequences	Sagittal T2W of the pelvis Pair of T1W, T2W through the indeterminate mass ± T2W sequences in the long axis of the uterus
Problem-solving sequences	T1 "bright" mass – FST1W T2 "dark" solid mass (site of origin) – oblique T2W T2 "dark" solid mass (nature) - DWI T2 solid mass – DWI ± CET1W/DCE Cystic-solid mass – DWI and CET1W/DCE

ESUR – European Society of Urogenital Radiology; T2W – T2-weighted; T1W – T1-weighted; FST1W – fat-suppressed T1-weighted; DWI – diffusion-weighted imaging; CET1W – contrast-enhanced T1-weighted; DCE – dynamic contrast enhanced

TIC type 2 represents a moderate initial enhancement relative to that of myometrium, followed by a plateau, and a TIC type 3 represents a rapid and steeper enhancement than that of myometrium. Whereas a TIC type 1 predicts benignity, a TIC type 3 strongly predicts malignancy. Type 2 curves are mainly associated with benign or borderline tumours [30, 31, 33].

The decision tree identifies three groups of adnexal masses according to their main characteristics on T1W and T2W sequences: T1 "bright" masses, T2 solid masses, and complex cystic or cystic-solid masses.

T1 "bright" masses.

They include masses with high T1 signal and require additional fat-suppressed T1-weighted (FST1W) imaging to distinguish fat in mature teratomas, which show signal drop on the FST1W images, from blood, mucin or other proteinaceous material (rarely melanin), which remain "bright". Products of haemorrhage result in T2* effects, with dependent darkening, dependent graded "shading" and even bright-dark fluid–fluid levels in cysts and/or T2 darkening in the walls of haemorrhagic cysts. Blood products of differing ages and such striking sedimentation of blood products indicate endometriosis [34]. The T2 dark spot sign -hypointense foci within the cyst on T2W images with or without T2 shading– is an indicator of chronic haemorrhage and has very high specificity in helping to distinguish ovarian endometriomas from non-endometrioma haemorrhagic adnexal lesions **(Fig. 2)** [35]. Another T1 "bright" mass is mucinous cystadenoma, that usually has a multilocular appearance containing fluid of various viscosity that produces variable signal intensities on both T1W and T2W sequences ("stained-glass" appearance). When there is concern for a solid nodule within a T1 "bright" mass, it must be regarded as a complex cystic or cystic-solid mass. CET1W imaging, or preferably DCE-MRI should be performed and reviewed on subtracted images to distinguish a blood clot from a vegetation **(Fig. 3)** [3, 28]. Application of DWI and DCE-MRI should always be careful in the assessment of T1 "bright" masses. Components of benign teratomas may show diffusion restriction similar to malignant lesions (usually epidermoid components) and may also rapidly enhance with type 3 TIC curves on DCE-MRI. Haemorrhagic lesions may also have a confusing appearance on DWI, showing diffusion restriction similar to malignant lesions [31].

T2 solid masses.

For these masses, the first consideration is to define their anatomic origin, whether ovarian or uterine. An oblique T2W imaging through the maximum point of contact between the mass and the uterus should be performed. An adnexal tumour separated from the uterus with the beak sign within the ovary indicates ovarian origin. The claw sign, or in broad-based leiomyomas the bridging vessels sign, indicates uterine origin [28, 36]. On T2W imaging, ovarian solid masses may be divided in homogeneous T2 "dark" solid masses, and T2 "intermediate" or "mixed signal solid masses", in comparison to muscle signal. Most of T2 "dark" solid adnexal masses are ovarian fibromas or uterine leiomyomas.

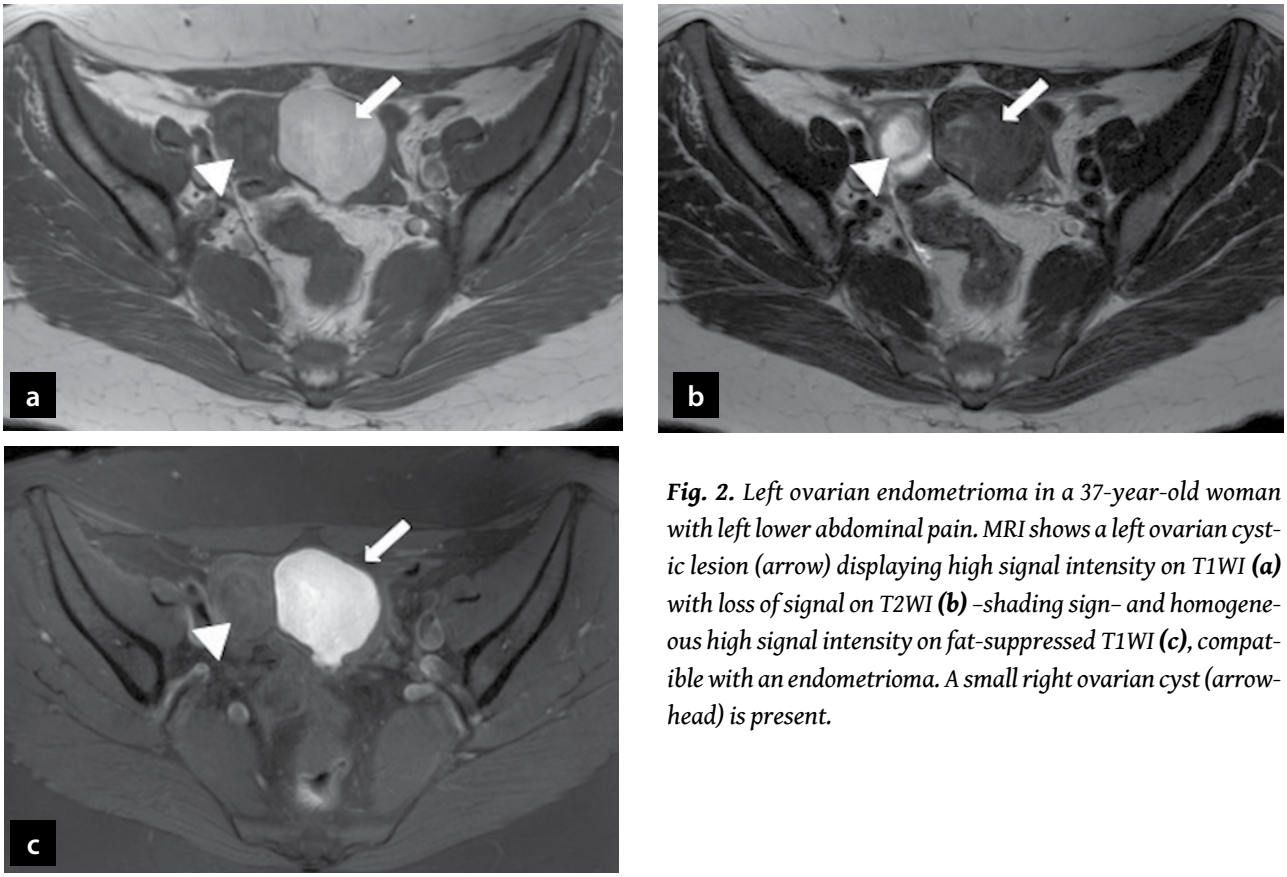

Fig. 2. *Left ovarian endometrioma in a 37-year-old woman with left lower abdominal pain. MRI shows a left ovarian cystic lesion (arrow) displaying high signal intensity on T1WI* ***(a)*** *with loss of signal on T2WI* ***(b)*** *–shading sign– and homogeneous high signal intensity on fat-suppressed T1WI* ***(c)****, compatible with an endometrioma. A small right ovarian cyst (arrowhead) is present.*

Their origin can be diagnosed only with T2W imaging as previous described, but in clinical practice many radiologists feel more comfortable using CET1W imaging or DCE-MRI. Ovarian fibromas typically show slow and minimal enhancement, with type 1 TIC on DCE-MRI, whereas pedunculated subserosal leiomyomas enhance parallel to the adjacent myometrium and are supplied by the "bridging vessels", which are better depicted on enhanced studies [37]. Because Brenner tumours (rarely malignant) and ovarian metastases may also display low signal intensity on T2W imaging, DWI is now recommended in T2W low-signal solid ovarian masses. If the solid mass has low signal on DWI sequences with high b values (≥800 s/mm^2) it can be considered benign and CET1W imaging or DCE-MRI are not necessary (**Fig. 4**). T2 "intermediate" or "mixed signal" solid masses may represent either benign tumours which have undergone degeneration, cellular fibromas or endocrine active tumours (e.g. thecoma, Sertoli-Leydig cell or granulosa cell tumour), but also primary or secondary malignant tumours. Therefore, T2 "intermediate" or "mixed signal" solid masses", as well as T2 "dark" solid masses with other than low DWI signal, should be assessed by CE-T1W imaging, or preferably DCE-MRI. From these, tumours with enhancement and/or type 3 curves on DCE-MRI should be considered as malignant. Finally, there are specific features for T2 solid masses that may guide for a particular diagnosis: fibrovascular septa and a fibrotic capsule in dysgerminomas, an early peripheral enhancement with centripetal progression in sclerosing stromal tumours and small haemorrhagic foci in granulosa cell tumours [38].

Complex cystic or cystic-solid masses.

This group includes masses with characteristics suggestive of malignancy: solid components within cystic masses, nodular/irregular thickening of internal septa and/or tumour wall. The differential diagnosis includes benign masses with complex imaging presentation such as multilocular benign cysts, lesions in the adenofibroma-cystadenofibroma spectrum and complex tubal disease, including acute and chronic tubo-ovarian infections [39]. Therefore, the first step in approaching complex cystic and cystic-solid masses is to evalu-

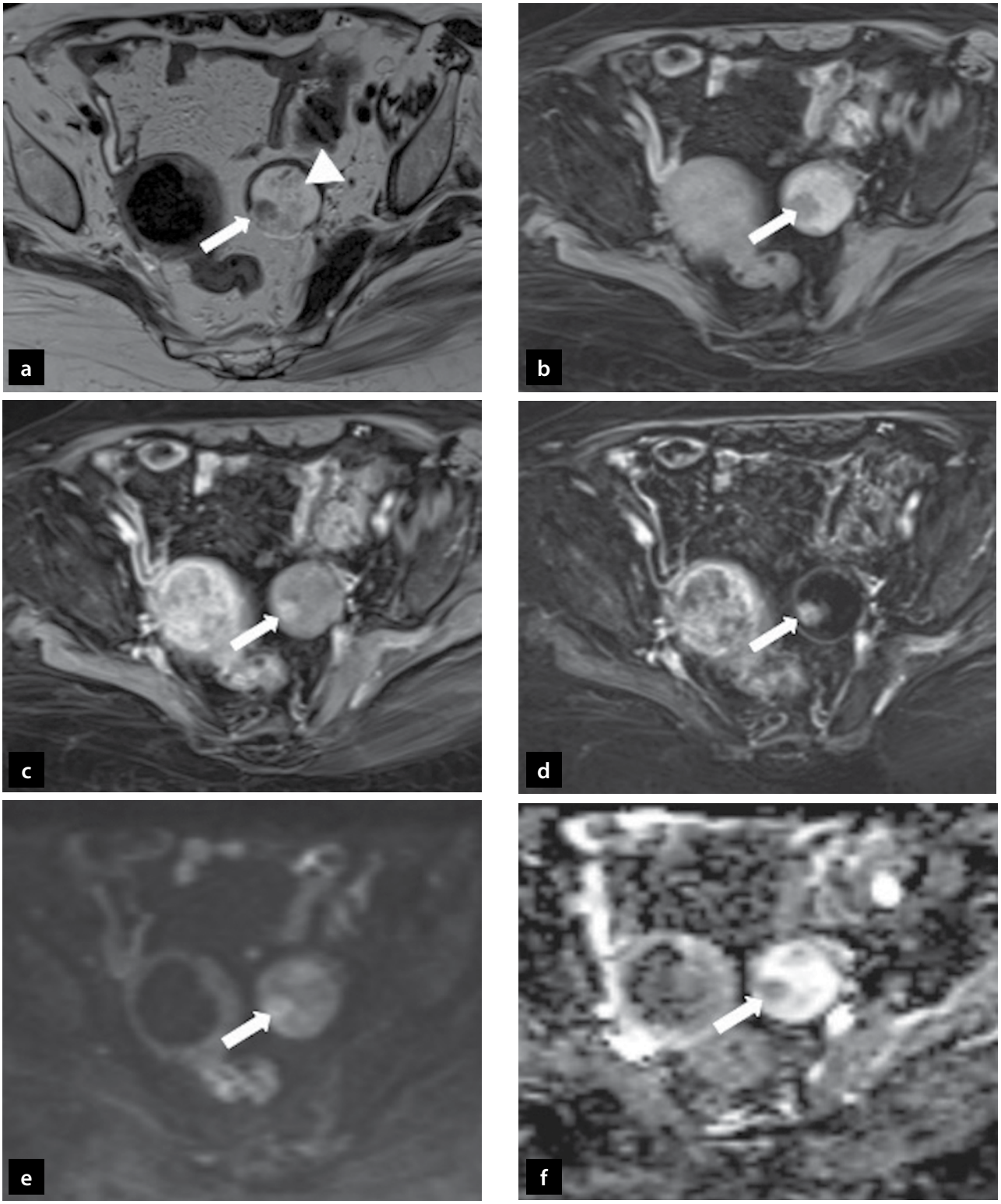

Fig. 3. *Seromucinous carcinoma within an endometriotic cyst in a 67-year-old woman. US (not shown) disclosed a small nodule within a left cystic ovarian tumour. MRI was performed for further characterisation and confirmed a left ovarian "T1-bright" lesion (arrowhead) containing a small peripheral solid nodule (arrow)* ***(a)****. On unenhanced fat-suppressed T1WI* ***(b)****, the cystic component remained bright and the nodule (arrow) showed low signal intensity. After gadolinium administration, the solid nodule enhanced (arrow in* ***c****) and this was confirmed on the subtraction images (arrow in* ***d****). On DWI, the solid nodule showed diffusion restriction with high signal intensity on high b values (b 1000)* ***(e)*** *and low signal intensity on ADC map* ***(f)****.*

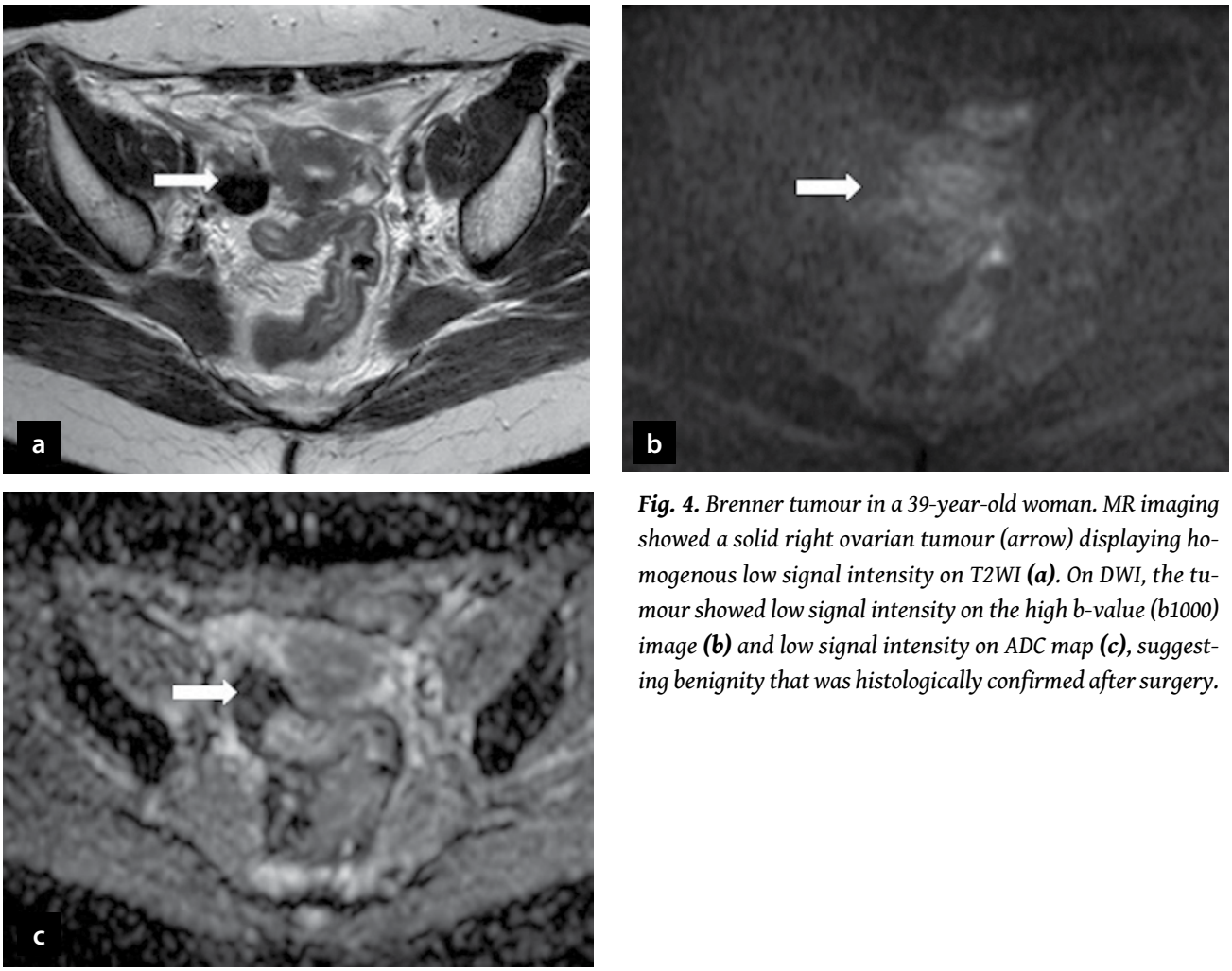

Fig. 4. *Brenner tumour in a 39-year-old woman. MR imaging showed a solid right ovarian tumour (arrow) displaying homogenous low signal intensity on T2WI* ***(a)****. On DWI, the tumour showed low signal intensity on the high b-value (b1000) image* ***(b)*** *and low signal intensity on ADC map* ***(c)****, suggesting benignity that was histologically confirmed after surgery.*

ate clinical information and consider if there is concern for inflammatory disease. Then, T2W sequences should be analysed to look for signs of tubal disease and/or malignancy signs, reminding that complex folds and mural irregularities within tubal disease may mimic malignancy [40]. CET1W imaging is recommended to look for malignant enhancement of nodular mural components, and/or to confirm if there are signs of inflammatory disease [37]. However, when available, DWI and DCE-MRI are now strongly recommended as adjunct investigations, particularly to access the solid component of the lesion [31]. On DWI, high signal using b values higher than 800 s/mm^2 with corresponding low ADC signal indicating diffusion restriction should alert for malignancy. However, T1 "bright" lesions (including mature cystic teratomas and haemorrhagic lesions), as well as some solid tumours (including fibromas, thecomas and Brenner tumours) and purulent components in tubo-ovarian inflammatory disease may also display diffusion restriction [41]. Again, the pattern of enhancement and/or TIC of the solid component will further improve characterisation of complex adnexal masses and type 3 curves on DCE-MRI should be considered as malignant (**Fig. 5**) [31].

4. FIGO Staging and Prediction of Resectability

FIGO staging system (**Table 2**) represents the most powerful indicator of prognosis in ovarian cancer and the most commonly used worldwide [11]. Although surgically defined, preoperative assessment of ovarian cancer stage with cross-sectional imaging (CT or MRI) is essential as it guides treatment and surgical management [1]. Referral to a gynaecologic oncologist for optimal staging and debulking is the second most important determinant for survival [8, 13]. FIGO staging system was revised in 2014 according to the new concepts in ovarian cancer biology, immunohistochemical and molecular genetic analysis, histopathological features, prognostic factors and response to chemotherapy [26]. This classi-

Table 2. FIGO staging classification for cancer of the ovary, fallopian tube and peritoneum (2014)	
Stage I - Tumour confined to ovaries or fallopian tube(s)	
IA	Limited to 1 ovary (capsule intact) or fallopian tube
IB	Limited to both ovaries (capsule intact) or fallopian tubes
IC	Limited to 1 or both ovaries or fallopian tubes, with any of the following: IC1 – Surgical spill IC2 – Capsule rupture before surgery or tumour on surface IC3 – Malignant cells in the ascites or peritoneal washings
Stage II – Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	
IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB	Extension to other pelvic intraperitoneal tissues
Stage III - Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer with confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal LNs	
IIIA1	Positive retroperitoneal LNs only IIIA1(i) – Metastasis up to 10 mm in greatest dimension IIIA1(ii) – Metastasis > 10 mm in greatest dimension
IIIA2	Microscopic extrapelvic (above the brim) peritoneal involvement ± retroperitoneal LNs
IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension ± metastasis to the retroperitoneal LNs
IIIC	Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension ± metastasis to the retroperitoneal LNs (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV – Distant metastasis excluding peritoneal masses	
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastases and metastases to extra-abdominal organs (includes inguinal LNs and LNs outside the abdominal cavity)

FIGO - International Federation of Gynaecology and Obstetrics; LNs – lymph nodes

fication remains valid for both epithelial and non-epithelial ovarian cancers, although different therapeutic approaches are usually considered [1, 16]. Furthermore, according to the increasing evidence that high-grade serous ovarian cancer has the same origin as tubal cancer and primary peritoneal cancer, those cancers currently share the same FIGO staging system. In the revised staging system, tumour stage as well as histological subtypes and grade should be documented. The primary site (i.e. ovary, fallopian tube, or peritoneum) should be designated when possible [7].

Stage I ovarian cancer is relatively rare because most patients are diagnosed in higher stages. Tumour is confined to one (IA) or both (IB) ovary(ies) or fallopian tube(s). Stage I primary peritoneal cancer does not exist. With regard to time and cause of capsule rupture, stage IC is subdivided in intraoperative spill (IC1), preoperative rupture (IC2) and positive peritoneal washings or ascites (IC3). Tumours with dense adhesions often develop capsular rupture [42]. Once capsular rupture occurs, peritoneal washing and cytology studies should be performed. Tumours with dense adhesions containing histologically proven tumour cells should be upgraded to stage II [7].

Stage II ovarian cancer includes tumours that involve one or both ovaries or fallopian tubes with direct extension or implants on the surface of the uterus and/or ovaries and/or fallopian tubes (IIA), or it extends to other pelvic intraperitoneal tissues (IIB), including the bladder, the sigmoid colon or the rectum [11].

Stage III ovarian cancer involves one or both ovaries with histologically confirmed peritoneal implants out-

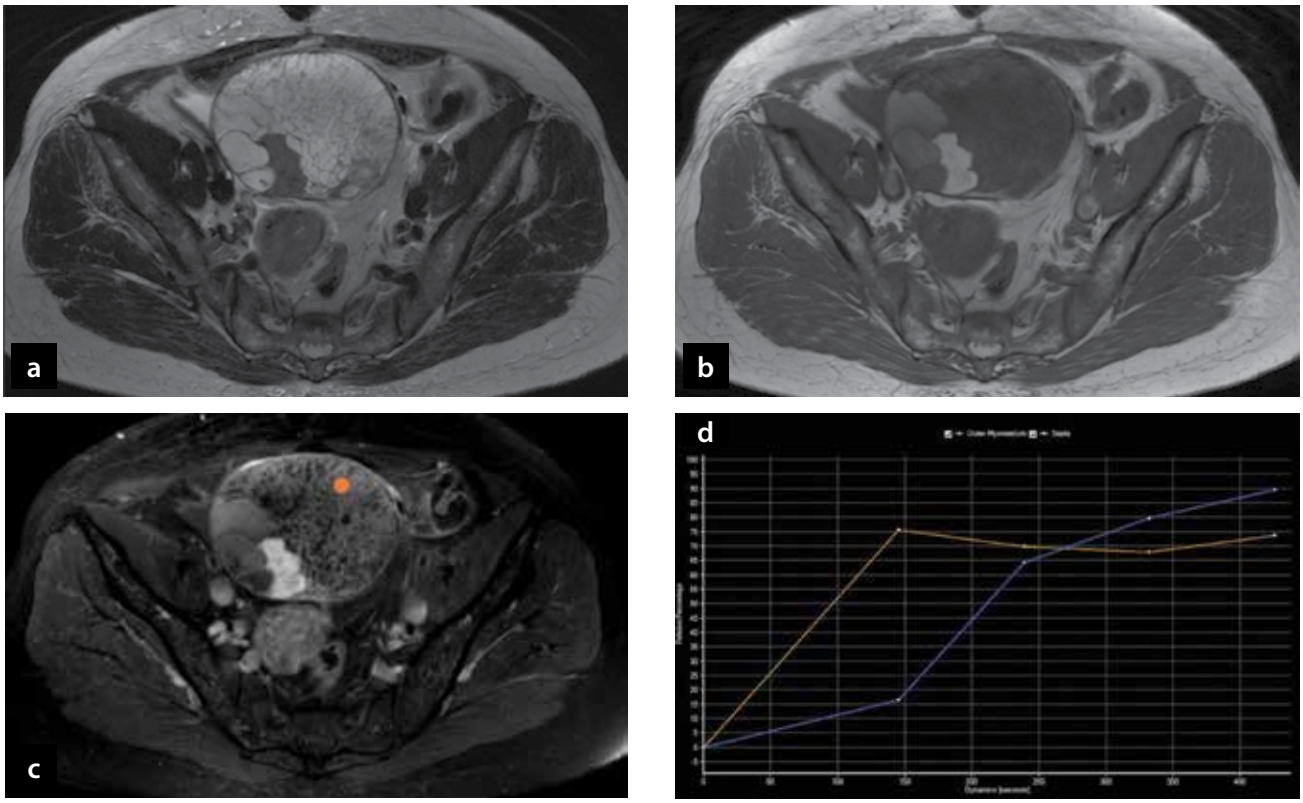

Fig. 5. *Sixty-year-old woman with left ovarian mucinous carcinoma. Transvaginal US (not shown) revealed a complex cystic-solid pelvic tumour and MRI was performed for further characterisation. MRI showed a complex cystic solid tumour of the left ovary, with multiple septa and cystic loci with different signal intensities on T2WI* ***(a)*** *and T1WI* ***(b)****. After gadolinium administration, most of the septa showed intense enhancement* ***(c)*** *with type 3 time-intensity curve on dynamic evaluation* ***(d)*** *- rapid and steeper enhancement (orange) compared to outer myometrium (blue). Surgery was performed and pathology confirmed a left ovarian mucinous carcinoma confined to the ovary (no capsule rupture, no peritoneal metastases and no ileocecal appendix disease).*

side the pelvis and/or positive regional lymph nodes. Regional lymph nodes include pelvic (internal and external iliac, obturator and common iliac), presacral, paraaortic and paracaval nodes. Some studies demonstrated that patients with exclusively retroperitoneal lymph node involvement (IIIA1) have a better prognosis than patients with abdominal peritoneal involvement. Stage IIIA1 is further subdivided into stage IIIA1(i) (metastasis ≤10 mm) and stage IIIA1(ii) (metastasis >10 mm), even with no retrospective data supporting quantification of the size of the metastasis [7]. Involvement of retroperitoneal lymph nodes must be proven cytologically or histologically. The extent of extrapelvic peritoneal involvement is a strong prognostic predictor and therefore, the presence of microscopic (IIIA2), macroscopic metastasis ≤2 cm (IIIB), and macroscopic metastasis >2 cm (IIIC) must be distinguished. Again, this 2 cm size cut-off of peritoneal metastases is subjective and not evidence-based. Stage IIIC also includes extension of tumour to the capsule of liver and spleen without parenchymal involvement of either organ [43].

Stage IV ovarian cancer is characterised by distant metastatic disease. Stage IVA includes patients with pleural metastases, proven either by cytology or biopsy. Stage IVB includes patients with parenchymal metastases in the abdomen (including hepatic or splenic parenchymal metastases and umbilical deposits), extra-abdominal metastases (including inguinal lymph nodes and other lymph nodes outside of the abdominal cavity) and/or transmural bowel infiltration (with mucosal involvement) [44].

Cytoreductive surgery is the basis of epithelial ovarian cancer treatment and one of the most important prog-

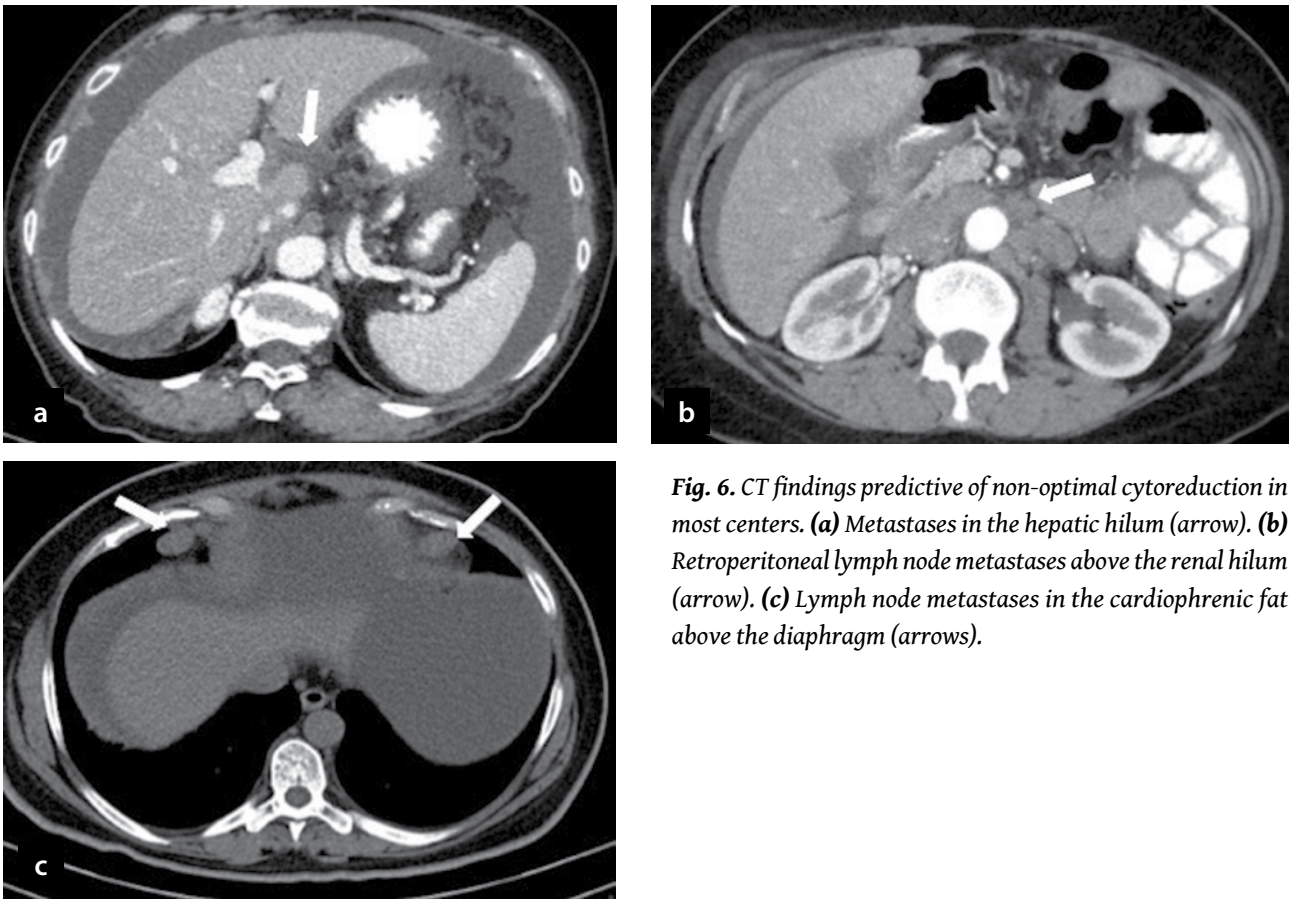

Fig. 6. *CT findings predictive of non-optimal cytoreduction in most centers.* ***(a)*** *Metastases in the hepatic hilum (arrow).* ***(b)*** *Retroperitoneal lymph node metastases above the renal hilum (arrow).* ***(c)*** *Lymph node metastases in the cardiophrenic fat above the diaphragm (arrows).*

nostic factors. The volume of residual disease after cytoreductive surgery is inversely proportional to survival. Adequate surgery for ovarian cancer should consist of peritoneal washing (preferably before tumour manipulation), bilateral salpingo-oophorectomy, hysterectomy, multiple peritoneal biopsies of all abdominal fields, at least infracolic omentectomy, appendicectomy in case of mucinous histology and pelvic and para-aortic lymph node dissection up to the renal veins. Fertility-sparing surgery could be considered in early-stage disease when young women are affected, but always after thoroughly informing the patient about the potential risks. Patients with stage IA or stage IC with unilateral ovarian involvement and favourable histology (mucinous, serous, endometrioid or mixed histology and grade 1 or 2) would be amenable to organ-preserving surgery, but only in combination with complete surgical staging, that would include a lymphadenectomy to exclude more advanced disease [1].

As expected, advanced cancer stages, with higher volume tumour and distant disease have higher volumes of residual diseases after surgery and are currently being treated with neoadjuvant chemotherapy to reduce disease and improve cytoreductive surgery (**Fig. 6**). Major determinants for debulking rates and cytoreductive surgical reduction include clinical factors (e.g. age, obesity and comorbidity), tumour markers (CA-125), and imaging features [45, 46]. The accurate mapping of tumour burden and distribution of disease by imaging plays a central role in treatment stratification and will influence patient outcome. Contrast-enhanced CT (with oral contrast) is the current imaging modality for preoperative evaluation of ovarian cancer, providing information about primary tumour, size and location of peritoneal implants, lymph nodes and visceral metastases [41]. CT is also useful for guiding biopsy, a procedure that can increase the accuracy of preoperative diagnosis if indicated [47]. Traditionally, large disease (>2 cm) in the upper abdomen around the liver and spleen, mesenteric deposits and lymph node metastases above the renal hilum were considered as sites likely to be not optimally resectable (**Fig. 7**). However, resect-

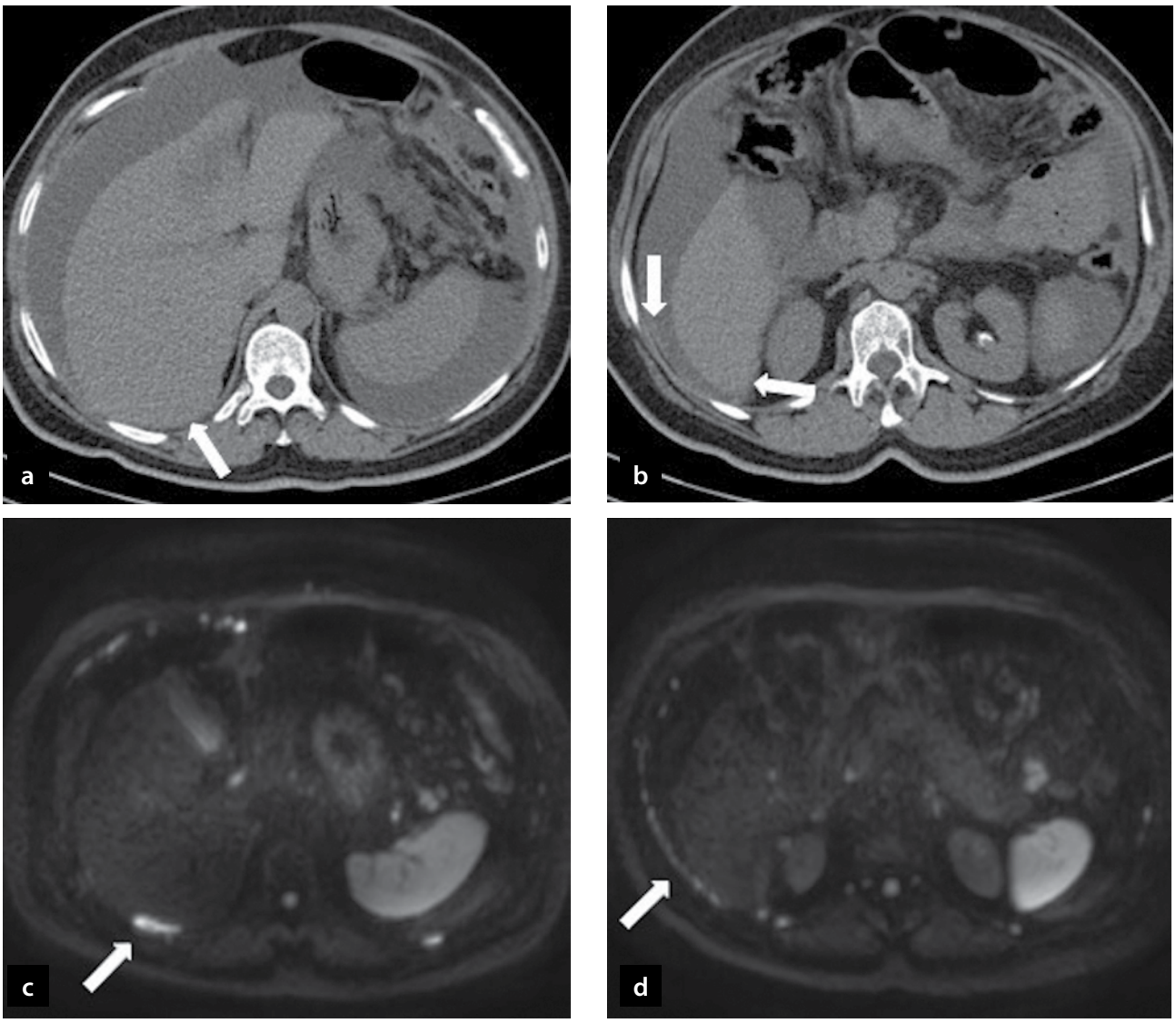

Fig. 7. *Forty eight-year-old woman with left ovarian high grade serous carcinoma.* ***(a-b)*** *CT performed without iodine contrast intravenous administration because of renal function impairment revealed a large left ovarian tumour with great omentum metastases (not shown), ascites in all abdominal quadrants and slight irregularity in lower diaphragmatic and liver surfaces (arrows in* ***a*** *and* ***b****). DWI revealed multiple small metastases (arrows in* ***c*** *and* ***d****) in the diaphragmatic and liver surfaces, presenting with high signal intensity on high b-value (b1000), that were surgically confirmed.*

ability criteria differ from centre to centre and resection rates are also different based on surgeon's experience. Individual optimal treatment should always be discussed on a multidisciplinary approach [46]. Different studies demonstrate that bowel surface and mesenteric involvement are a major limitation for optimal cytoreduction and have to be carefully analysed [48, 49]. Unfortunately, small size peritoneal deposits (<5 mm) are usually difficult to see in CT, especially in the absence of ascites [50]. There is increasing data demonstrating very good radiological-surgical correlation of MR functional techniques, DWI and DCE, in detecting subtle abdominal metastases [51, 52]. However, the role of MRI in staging is still limited because of motion artefacts. MRI is particularly recommended for patients with borderline tumours or ovarian cancers who are candidates for fertility preservation surgery. MRI can also be performed when CT findings are inconclusive or in patients with contraindication for intravenous contrast agents [53].

5. Conclusion

Ovarian cancer remains a major challenge. Advances in histopathological and molecular genetic studies introduced new concepts in the pathogenesis of ovarian cancer that are related with primary presentation and metastatic dissemination. Radiologists play a central role both in the characterisation of complex adnexal masses as well as in the preoperative assessment of ovarian cancer, providing a roadmap for cytoreductive surgery or selecting patients who may benefit from neoadjuvant chemotherapy. R

Conflict of interest

The authors declared no conflicts of interest.

References

1. Ledermann JA, Raja FA, Fotopoulou C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; 24 Suppl 6: vi 24-32.
2. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. *Lancet* 2014; 384: 1376-1388.
3. Spencer JA, Forstner R, Cunha TM, et al. ESUR guidelines for MR imaging of the sonographically indeterminate adnexal mass: an algorithmic approach. *Eur Radiol* 2010; 20(1): 25-35.
4. Kurman RJ, Carcangiu ML, Herrington CS, et al. Classification of tumours of the ovary. In: WHO classification of tumours, Vol. 6. 4th ed. Lyon: IARC Press 2014.
5. Cannistra SA, Gershenson DM, Recht A. Ovarian cancer, fallopian tube carcinoma, and peritoneal carcinoma. In: DeVita VT, Lawrence TS, Rosenberg SA (eds). DeVita, Hellman, and Rosenberg's cancer: principles and practice of oncology. Lippincott, Williams & Wilkins, Philadelphia, PA 2011: pp 1368-1391.
6. Rendi MH. Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: histopathology. Available via www.uptodate.com. Published 2016. Updated June 26, 2017; *Accessed* January 19, 2018.
7. Prat J. FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet* 2014; 124(1): 1-5.
8. Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol* 2000; 19: 3-10.
9. Hartge P, Whittemore A, Itnyre J, et al. Rates and risks of ovarian cancer in subgroups of white women in the United States. *Obstet Gynecol* 1994; 84: 760-764.
10. Weiderpass E, Tyczynscki JE. Epidemiology of patients with ovarian cancer with and without a BRCA1/2 Mutation. *Mol Diagn Ther* 2015; 19(6): 351-364.
11. Javadi S, Ganeshan DM, Qayyum A, et al. Ovarian cancer, the revised figo staging system, and the role of imaging. *AJR Am J Roentgenol* 2016; 206(6): 1351-1360.
12. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. *Lancet* 2014; 384(9951): 1376-1388.
13. Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res* 2013; 19(5): 961-968.
14. Lalwani N, Prassad SR, Vikram R, et al. Histologic, molecular, and cytogenetic features of ovarian cancers: implication for diagnosis and treatment. *Radiographics* 2011; 31(3): 625-646.
15. Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol* 2010; 34: 433-443.
16. Colombo N, Peiretti M, Garbi A, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; Suppl 7: vii20–vii26.
17. Tewari K, Cappuccini F, Disaia PJ, et al. Malignant germ cell tumours of the ovary. *Obstet Gynecol* 2000; 95(1): 128-133.
18. Horta M, Cunha TM. Sex cord-stromal tumors of the ovary: a comprehensive review and update for radiologists. *Diagn Interv Radiol* 2015; 21: 277-286.
19. Chen VW, Ruiz B, Killeen JL, et al. Pathology and classification of ovarian tumours. Cancer 2003; 97(10): 2631-2642.

20. Vernooij F, Heintz P, Witteveen E, et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. *Gynecol Oncol* 2007; 105: 801-812.
21. Levine D, Asch E, Mehta TS, et al. Assessment of factors that affect the quality of performance and interpretation of sonography of adnexal masses. *J Ultrasound Med* 2008; 27: 721-728.
22. Nunes N, Ambler G, Foo X, et al. Use of IOTA simple rules for diagnosis of ovarian cancer: meta-analysis. *Ultrasound Obstet Gynecol* 2014; 44: 503-514.
23. Brown DL, Doubilet PM, Miller FH, et al. Benign and malignant ovarian masses: selection of the most discriminating gray-scale and Doppler sonographic features. *Radiology* 1998; 208: 103-110.
24. Kinkel K, Lu Y, Mehdizade A, et al. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization-meta-analysis and Bayesian analysis. *Radiology* 2005; 236(1): 85-94.
25. Van Calster B, Timmerman D, Valentin L, et al. Triaging women with ovarian masses for surgery: observational diagnostic study to compare RCOG guidelines with an International Ovarian Tumour Analysis (IOTA) group protocol. *BJOG* 2012; 119: 662-671.
26. Forstner R, Meissnitzer M, Cunha TM. Update on imaging of ovarian Cancer. *Curr Radiol Rep* 2016; 4: 31.
27. Anthoulakis C, Nikoloudis N. Pelvic MRI as the "gold standard" in the subsequent evaluation of US-indeterminate adnexal lesions: a systematic review. *Gynecol Oncol* 2014; 132(3): 661-668.
28. Forstner R, Thomassin-Naggara I, Cunha TM, et al. ESUR recommendations for MR imaging of the sonographically indeterminate adnexal mass: an update. *Eur Radiol* 2017; 27(6): 2248-2257.
29. Namimoto T, Awai K, Nakaura T, et al. Role of diffusion-weighted imaging in the diagnosis of gynecological diseases. *Eur Radiol* 2009; 19(3): 745-760.
30. Thomassin-Naggara I, Daraï E, Cuenod CA, et al. Contribution of diffusion-weighted MR imaging for predicting benignity of complex adnexal masses. *Eur Radiol* 2009; 19(6): 1544-1552.
31. Thomassin-Naggara I, Toussaint I, Perrot N, et al. Characterization of complex adnexal masses: value of adding perfusion- and diffusion-weighted MR imaging to conventional MR imaging. *Radiology* 2011; 258(3): 793-803.
32. Johnson W, Taylor MB, Carrington BM, et al. The value of hyoscine butyl-bromide in pelvic MRI. *Clin Radiol* 2007; 62: 1087-1093.
33. Li HM, Qiang JW, Ma FH, et al. The value of dynamic contrast-enhanced MRI in characterizing complex ovarian tumours. *J Ovarian Res* 2017; 10(1): 4.
34. Dias JL, Gomes FV, Lucas R, et al. The shading sign: is it exclusive of endometriomas? *Abdom Imaging* 2015; 40(7): 2566-2572.
35. Corwin MT, Gersovich EO, Lamb R, et al. Differentiation of Ovarian endometriomas from haemorrhagic cysts at MR imaging: Utility of the T2 dark spot sign. *Radiology* 2014; 271(1): 126-132.
36. Oh SN, Rha SE, Byun JY, et al. MRI features of ovarian fibromas: emphasis on their relationship to the ovary. *Clin Radiol* 2008; 63(5): 529-535.
37. Thomassin-Naggara I, Daraï E, Nassar-Slaba J, et al. Value of dynamic enhanced magnetic resonance imaging for distinguishing between ovarian fibroma and subserous uterine leiomyoma. *J Comput Assist Tomogr* 2007; 31: 236-242.
38. Foti PV, Attina G, Spadola S, et al. MR imaging of ovarian masses: classification and differential diagnosis. *Insights Imaging* 2016; 7(1): 21-41.
39. Hricak H, Chen M, Coakley FV, et al. Complex adnexal masses: detection and characterization with MR imaging-multivariate analysis. *Radiology* 2000; 214(1): 39-46.
40. Ghattamaneni S, Bhuskute N, Weston MJ, et al. Discriminative MRI features of fallopian tube masses. *Clin Radiol* 2009; 64(8): 815-831.
41. Mitchell DG, Javitt MC, Glanc P, et al. ACR Appropriateness criteria staging and follow-up of ovarian cancer. *J Am Coll Radiol* 2013; 10(11): 822-827.
42. Tognon G, Carnazza M, Ragnoli M, et al. Prognostic factors in early-stage ovarian cancer. *Ecancermedicalscience* 2013; 7: 325.
43. Kandukuri SR, Rao J. FIGO 2013 staging system for ovarian cancer: what is new in comparison to the 1988 staging system? *Curr Opin Obstet Gynecol* 2015; 27(1): 48-52.
44. Zeppernick F, Meinhold-Heerlein I. The new FIGO staging system for ovarian, fallopian tube, and primary peritoneal cancer. *Arch Gynecol Obstet* 2014; 290(5): 839-842.

45. Suidan RS, Ramirez PT, Sarasohn DM, et al. A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer. *Gynecol Oncol* 2014; 134(3): 455-461.
46. Borley J, Wilhelm-Benartzi C, Williamson R, et al. Radiological predictors of cytoreductive outcomes in patients with advanced ovarian cancer. *BJOG* 2015; 122(6): 843-849.
47. Spencer JA, Weston MJ, Saidi SA, et al. Clinical utility of image-guided peritoneal and omental biopsy. *Nat Rev Clin Oncol* 2010; 7(11): 623-631.
48. Rockall A. Diffusion weighted MRI in ovarian cancer. *Curr Opin Oncol* 2014; 26: 529-535.
49. Suidan RS, Ramirez PT, Sarasohn DM, et al. A multicenter prospective trial evaluating the ability of preoperative computed tomography scan and serum CA-125 to predict suboptimal cytoreduction at primary debulking surgery for advanced ovarian, fallopian tube, and peritoneal cancer. *Gynecol Oncol* 2014; 34: 455-461.
50. Borley J, Wilhelm-Benartzi C, Williamson R, et al. Radiological predictors of cytoreductive outcomes in patients with advanced ovarian cancer. *BJOG* 2015; 122(6): 843-849.
51. Gomez-Hildago NR, Martinez-Cannon BA, et al. Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: time to incorporate laparoscopic assessment into the standard of care. *Gynecol Oncol* 2015; 137: 553-558.
52. Low RN, Barone RM, Lucero J. Comparison of MRI and CT for predicting the peritoneal cancer index (PCI) preoperatively in patients being considered for cytoreductive surgical procedures. *Ann Surg Oncol* 2015; 22: 1708-1715.
53. Kang SK, Reinhold C, Atri M, et al. ACR appropriateness criteria staging and follow-up of ovarian cancer. J Am Coll Radiol 2018; S198-S207.

READY - MADE CITATION

Gil RT, Cunha TM, Horta M. Imaging of ovarian cancer: Current concepts. *Hell J Radiol* 2018; 3(4): 43-57.