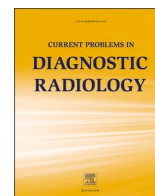


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Clear cell carcinoma of the ovary: Clues for radiologists to perform a correct diagnosis

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ABSTRACT

Ovarian clear cell carcinoma (OCCC) is an uncommon high-grade primary epithelial ovarian cancer, covering about 10-12 % of all ovarian malignancies. It has a strong association with endometriosis.

OCCC diagnosis, at advanced stages, has an aggressive biological behaviour, and the therapeutic strategies for ovarian OCCC are somehow different from other ovarian carcinomas. Therefore, early diagnosis of these tumours is of extreme importance.

As some ovarian tumours subtypes have distinguishing features, it is possible to differentiate them based on their imaging characteristics, which can guide patient management and help the clinicians and pathologists in their diagnosis.

A large mass on one side of the ovary that is mostly cystic, with a focal or multifocal irregular eccentric growing solid mural nodules or projections protruding into the cystic space, may suggest clear cell carcinoma of the ovary diagnosis. The solid nodules usually have an intermediate signal on T2-weighted images. The cystic component can be either single or multilocular, and the contents may contain protein or blood. CT scanning is still the preferred method for preoperative staging and postoperative restaging, and radiologists are crucial in identifying this type of tumour.

We reviewed the imaging files of patients with surgically proven clear cell carcinoma at the specimens, and our findings agree with previous studies. This paper aims to perform a comprehensive revision of OCCC's radiological and clinic-pathological features and assist radiologists in recognizing OCCC and narrowing down the possibilities of differential diagnosis.

Introduction

Ovarian tumours are classified based on morphologic characteristics, in which epithelial surface cell tumours are the most common type. Specific epithelial subtypes include serous carcinoma, mucinous carcinoma, endometrioid carcinoma, clear cell carcinoma, Brenner tumours, and undifferentiated carcinoma.¹ Some of those ovarian tumour subtypes have distinguishing features, according to imaging characteristics, which can guide patient management and help clinicians and pathologists in their diagnosis.

Ovarian clear cell carcinoma (OCCC) is a rare but aggressive subtype of epithelial ovarian cancer, often resistant to conventional chemotherapy, with a poorly understood pathogenesis. In recent years, there has been an increasing interest in understanding the biology of OCCC and identifying potential targeted therapies; its diagnosis has raised concerns because OCCC in advanced stages, at presentation, is associated with a poorer prognosis compared to the more prevalent epithelial type of ovarian cancer.

Imaging plays a crucial role in the diagnosis, staging, and management of the OCCC.

The authors conducted a search of the PubMed/Medline database to identify relevant articles on clear cell carcinoma. The objective of this article is to outline the spectrum of imaging features of the OCCC on different imaging techniques, highlighting the principal differential diagnoses and their pathological features in order to identify the preoperative imaging findings that could aid the radiologist in identifying clear cell carcinomas and distinguish them from other ovarian neoplasms.

Clear cell tumours

Epidemiology and clinical overview

Clear cells carcinoma is the second most common histological type of epithelial ovarian cancer. The incidence of the OCCC varies depending on its geographic distribution, and it accounts for 10–12 % of ovarian carcinomas in North America, with much higher reported prevalence

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rates in Asian countries and lower rates reported in Europe.¹⁻³ The OCCC usually appears in women with an average age of 56 years.^{1,4,5}

This tumour frequently manifests itself as a pelvic mass, presenting as an incidental finding or with bulky symptoms related to a pelvic mass, such as abdominal pain and bloating. Women with the OCCC have a greater risk of venous thromboembolic events than women with other histologic epithelial ovarian tumours.⁶ Hypercalcemia is a paraneoplastic syndrome that can become symptomatic and the OCCC is the most common ovarian tumour associated with paraneoplastic hypercalcemia.⁷

The OCCC has a strong association with endometriosis, and this is the carcinoma type most frequently associated with endometriosis. This tumour arises from endometriosis in 50–70 % of cases, mainly from endometriotic ovarian cysts, and the presence of irregular nodules lining an endometriotic cyst should be considered suspicious for malignancy.^{8,9} Endometriosis-associated ovarian neoplasms tend to occur at younger ages and present, on average, 5 to 6 years before high-grade serous carcinoma.^{3,6,10,11} The association of the OCCC with endometriosis may be helpful in the diagnosis, and it is indicative of the OCCC.^{12,13}

Clear cell carcinomas and endometrioid carcinoma are two types of epithelial ovarian cancer that share similar clinical and pathological characteristics, such as both are related to the presence of endometriosis, both are diagnosed more frequently in premenopausal patients, both are more frequently detected at early stages and, because of this, both may have a better prognosis for curative surgery compared to most other types of ovarian cancer.¹⁴ However, in most cases, the OCCC may have a worse prognosis than endometrioid carcinoma due to its chemoresistant

phenotype, so the pre-operative distinction of both is of utmost importance.^{8,15}

Diagnosis of endometriosis associated with ovarian carcinoma is outlined by the presence of ovarian malignancy in the presence of unilateral or contralateral ovarian endometriosis, pelvic endometriosis, or histopathological demonstration of transition from benign to malignant endometriosis.

Benign and borderline clear cell adenofibromas are precursor lesions of clear cell carcinomas. They are typically present in combination and are sometimes associated with endometriosis. Clear cell borderline adenofibroma (CCBA) are adenofibromatous clear cell tumours with glandular proliferation and low-grade nuclear atypia without evidence of stromal invasion. CCBA only account for less than 1 % of borderline ovarian tumours and are seldom found as an exclusive element in an ovarian tumour. Furthermore, they are components of clear cell carcinoma. The prognosis of patients with borderline clear cell adenofibroma is more favourable than OCCC.^{1,10,16}

Morphology and histological considerations

These tumours are considered high-grade.^{1,8} Macroscopically, the OCCC appears as unilateral tumours that may be solid, solid-cystic, to predominantly cystic, with pale-yellow nodules when associated in an endometriotic cyst. They rarely occur bilaterally. The solid component may be purely carcinoma or clear cell adenofibroma. Patients with the OCCC are more likely to have a pelvic mass, with large dimensions with a mean size of 11–13cm. Microscopically, the OCCC displays different microscopic patterns, such as papillary, tubulocystic, and solid, commonly in combination, and they are composed of clear, eosinophilic

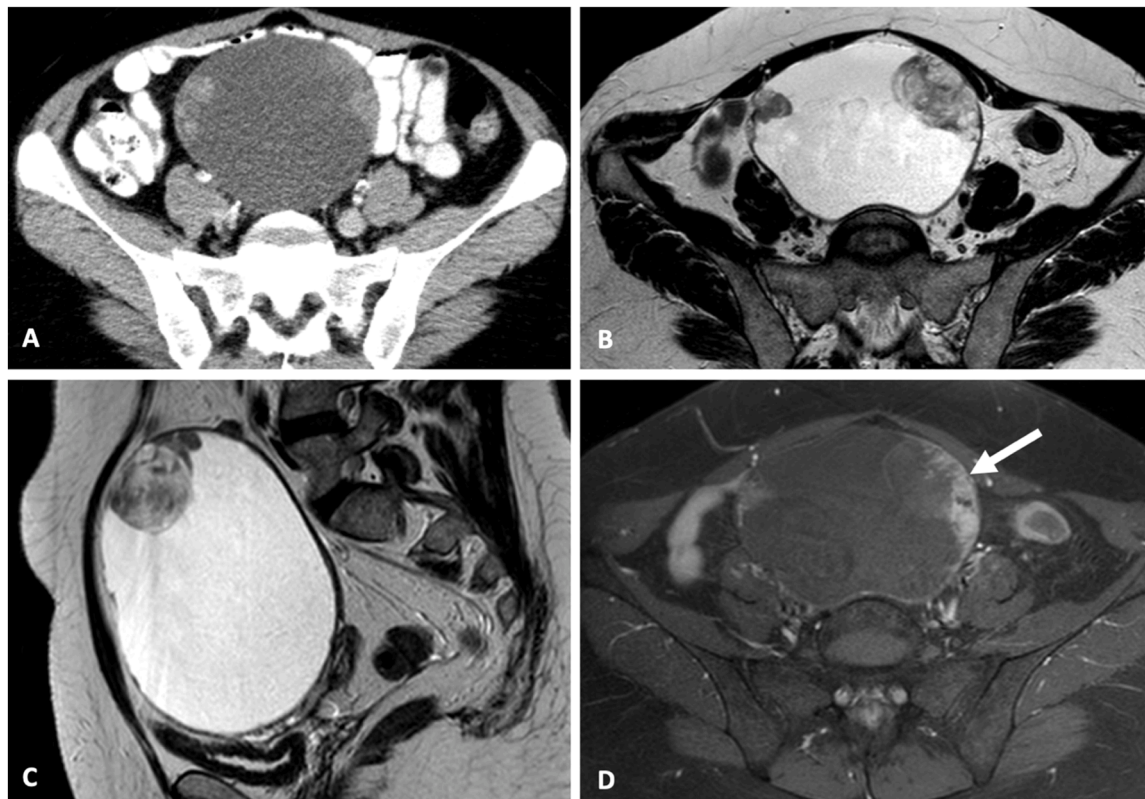


Fig. 1. A ovarian clear cell carcinoma (OCCC) in a 51-year-old woman with symptoms of pelvic bulging. A, Axial contrast-enhanced computed tomography (CT) portrays a large well-defined unilocular cystic mass with many irregular peripheral solid protrusions (arrows), suspicious. B, C, Axial (B) and sagittal (C) T2 weighted image (WI), performed after 2 months, show a large unilateral, well-defined unilocular cystic mass with heterogeneous intermediate SI multifocal eccentric mural nodules. The signal intensity (SI) of the cyst is very high on T2WI. Compared to the previous CT, there is a notice of dimensional and numerical increase of parietal solid nodules, which show a greater degree of protrusion into the lumen. D, Axial enhanced T1WI with fat suppressed (FS) describes marked enhancement of solid nodules (arrow). During surgery, the left ovary was found to be occupied by an intraovarian predominantly cystic tumour with 6cm in the largest dimension. The pathological report showed a clear cell ovarian carcinoma, pT1apN0.

cells with moderate to marked cytological atypia.⁸ They are characteristically positive for PAX8, napsin A and HNF1 β .^{1,17} These tumours are negative for oestrogens and progesterone receptors and commonly p53 wild type.

Radiological findings

General considerations

The OCCC presents commonly as a large unilateral cystic mass, more frequently as unilocular cystic mass, as illustrated in Fig. 1, whereas

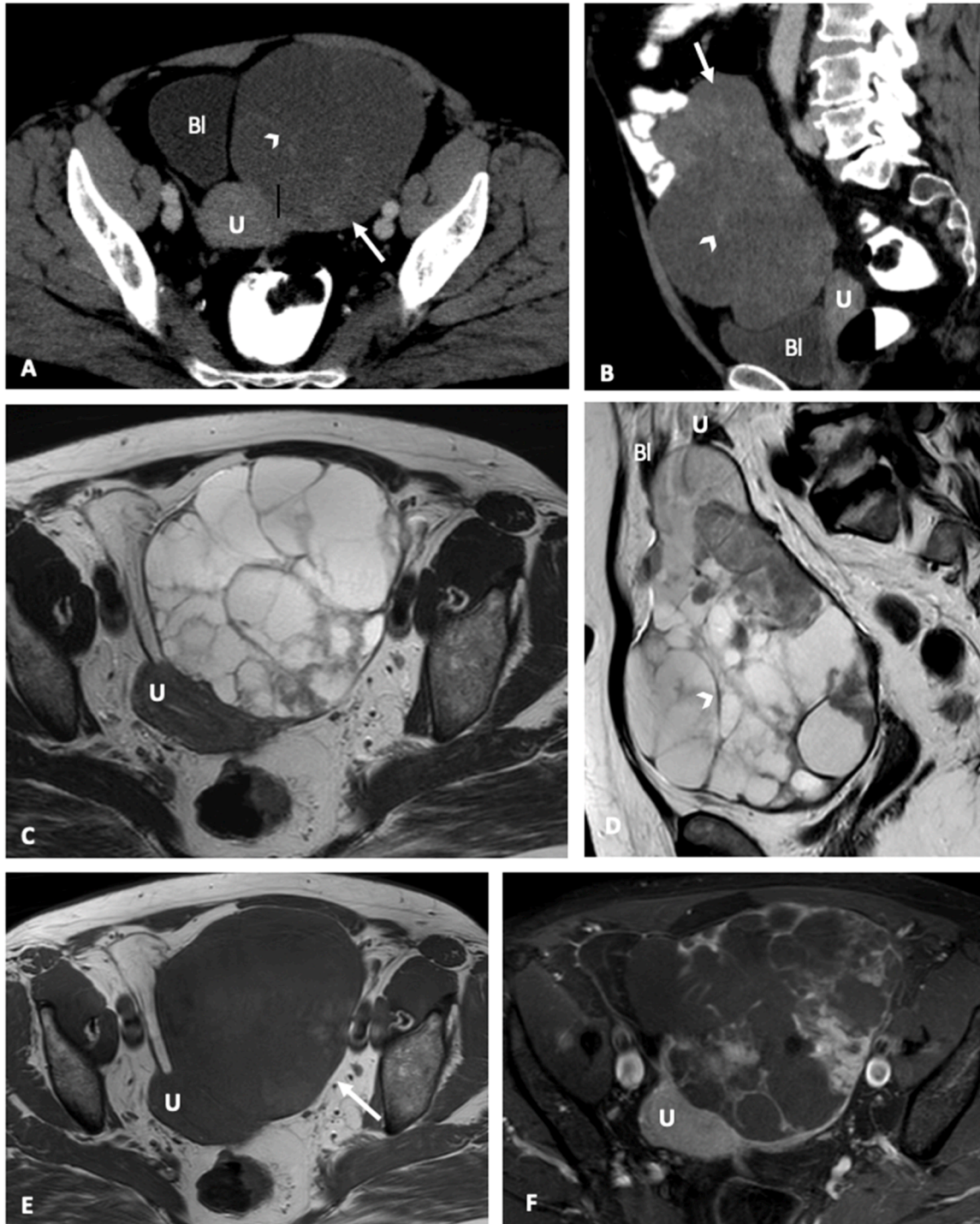


Fig. 2. OCCC in a 64 years-old woman with a pelvic mass incidentally found on a routine ultrasound examination. A, Axial (A) and sagittal (B) contrast-enhanced CT portray a large well-defined multilocular cystic mass with many irregular parietal solid protrusions (arrows) and thin septations (arrowheads), suspicious. C, D Axial (C) and sagittal (D) T2WI showing a large, well-defined multilocular cystic mass with a multifocal irregular lumen protruded intermediate SI solid nodules and many irregular and thin septations. The septations were < 3mm in thickness (arrowhead). E, Axial (E) T1-WI shows a predominantly hypointense mass. The solid portion had intermediate SI on T2WIs and hypointense SI on T1WI (arrows). The SI of the cyst was high on T2WIs and low to intermediate on T1WI. F, Axial contrast enhanced T1WI with FS exhibits a strong heterogeneous enhancement of solid mural nodules with central non-enhanced cystic areas. In surgery, the left ovary was occupied by a 12cm in the largest dimension, that was solid and cystic intraovarian tumour. U – uterus; Bl – bladder.

multilocular types are less common and are characterized by multiple cystic spaces separated by thin septa, as it is shown in Fig. 2.^{12,18} These cystic masses are associated with multifocal, broad-based mural nodules protruding into the cystic space that showed eccentric parietal growth pattern.^{14,19} The OCCC presents less frequently as cystic-solid and solid

masses, however even in predominantly cystic lesion, all tumours present a solid component.

Imaging findings of ovarian tumours are often nonspecific; however, some ovarian tumour subtypes have distinctive features, and differentiating these types based on their characteristics can guide patient

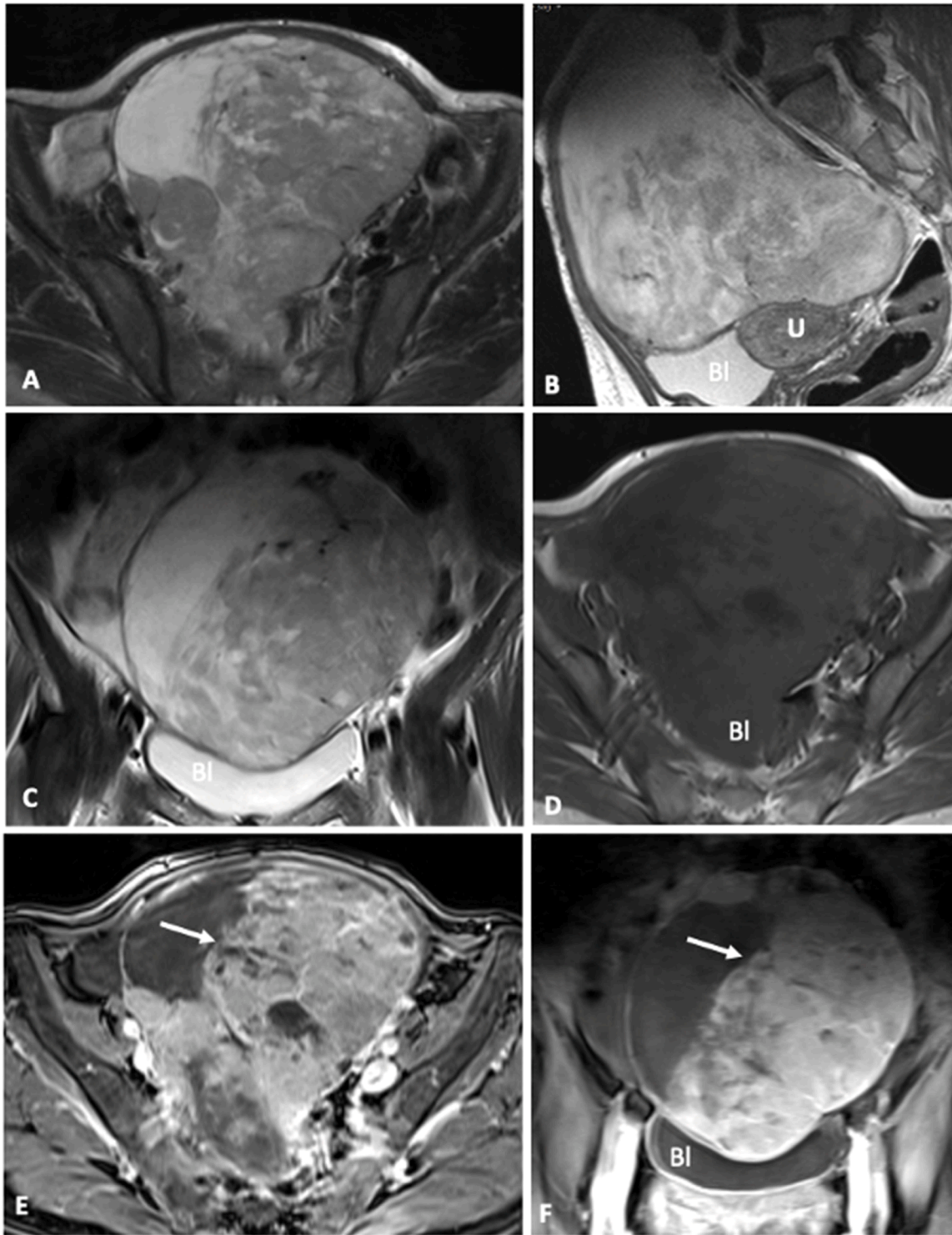


Fig. 3. A 55-year-old woman with histologically proven diagnosis of OCCC who had a pelvic mass incidentally discovered on ultrasound examination. A–D Axial T2WI (A), sagittal T2WI (B) coronal T2WI (C), and axial T1WI describing a well-defined solid and cystic mass, with irregular solid protrusions. The solid component had intermediate SI on both T2WIs and T1WI. The SI of the cyst was very high on T2WIs and low on T1WI. E, F Axial (E) and coronal (F) contrast enhanced T1WI with FS showing brisk and heterogeneous enhancement of solid components. Notice that the solid parietal nodules show eccentric pattern growth, with protrusion into the cyst lumen, which demonstrates central confluence (arrow). In surgery, the left ovary was 19cm in size and it was occupied by a solid and multicystic tumour. U – uterus; Bl – bladder.

management and aid the pathologists in establishing the diagnosis.^{20,21} Ultrasonography, CT, and MRI are useful tools in detecting, differentiating, and diagnosing ovarian tumours. Although a specific histological type cannot be confidently diagnosed with MRI findings, some imaging features are more characteristic in some histological tumour types. Therefore, the imaging outcomes may be a clue for the specific tumour type.

Ultrasound

Ultrasound is a widely used imaging modality for the evaluation of ovarian masses and is the first line of investigation in determining the benign or malignant potential of an adnexal lesion. On ultrasound, the OCCC typically appears as predominantly anechogenic cystic mass with irregular eccentric hyperechogenic mural nodules. Colour Doppler imaging may show increased vascularity within the mass and typically

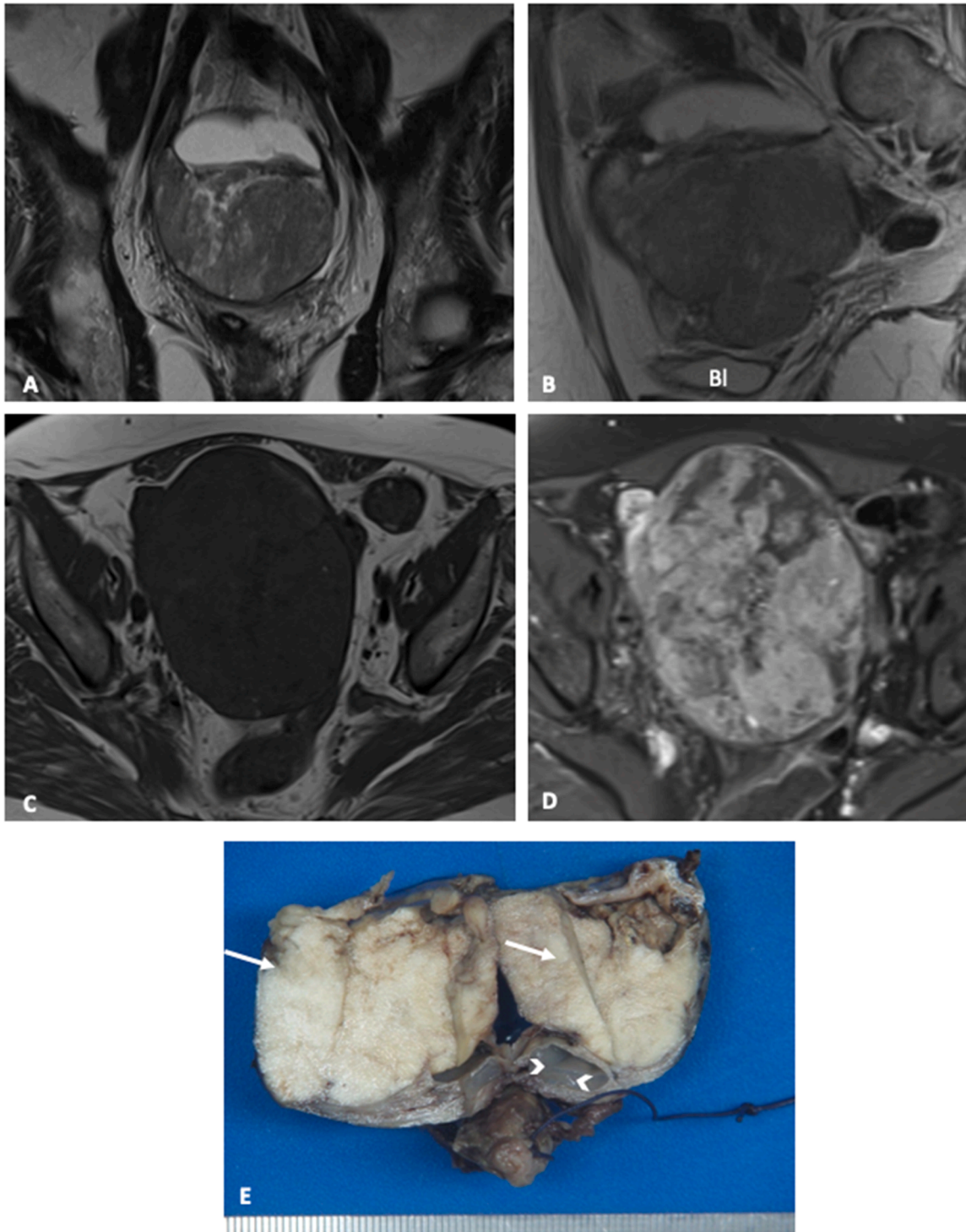


Fig. 4. The OCCC in a 65-year-old woman with discomfort symptoms in the pelvic area. A–C, Coronal T2WI (A), sagittal T2WI (B) and axial T1WI (C) display a well-defined and predominantly solid mass, appearing with intermediate SI on T2WI and iso-intensity on T1WI. D, Axial (D) contrast enhanced T1WI with FS show a heterogeneous enhancement of solid mass. E, In surgery, the left ovary weighed 48g and measured $6.5 \times 4.5 \times 4$ cm and it was totally occupied by a solid (arrowheads) and cystic tumour (arrows). Bl – bladder.

exhibits a moderate to high degree of vascularity, with blood flow seen within the solid component of the mass.¹⁴

Computed tomography

Computed Tomography (CT) is a useful tool for the staging of the

OCCC and it is suboptimal for ovarian tumours characterization. At CT, OCCC typically appears as a predominantly low attenuation cystic mass on non-contrast CT hypodense with enhancing parietal nodules after administration of iodinated contrast medium, as exemplified in Fig. 1. The presence of solid or nodular components within the cystic areas is

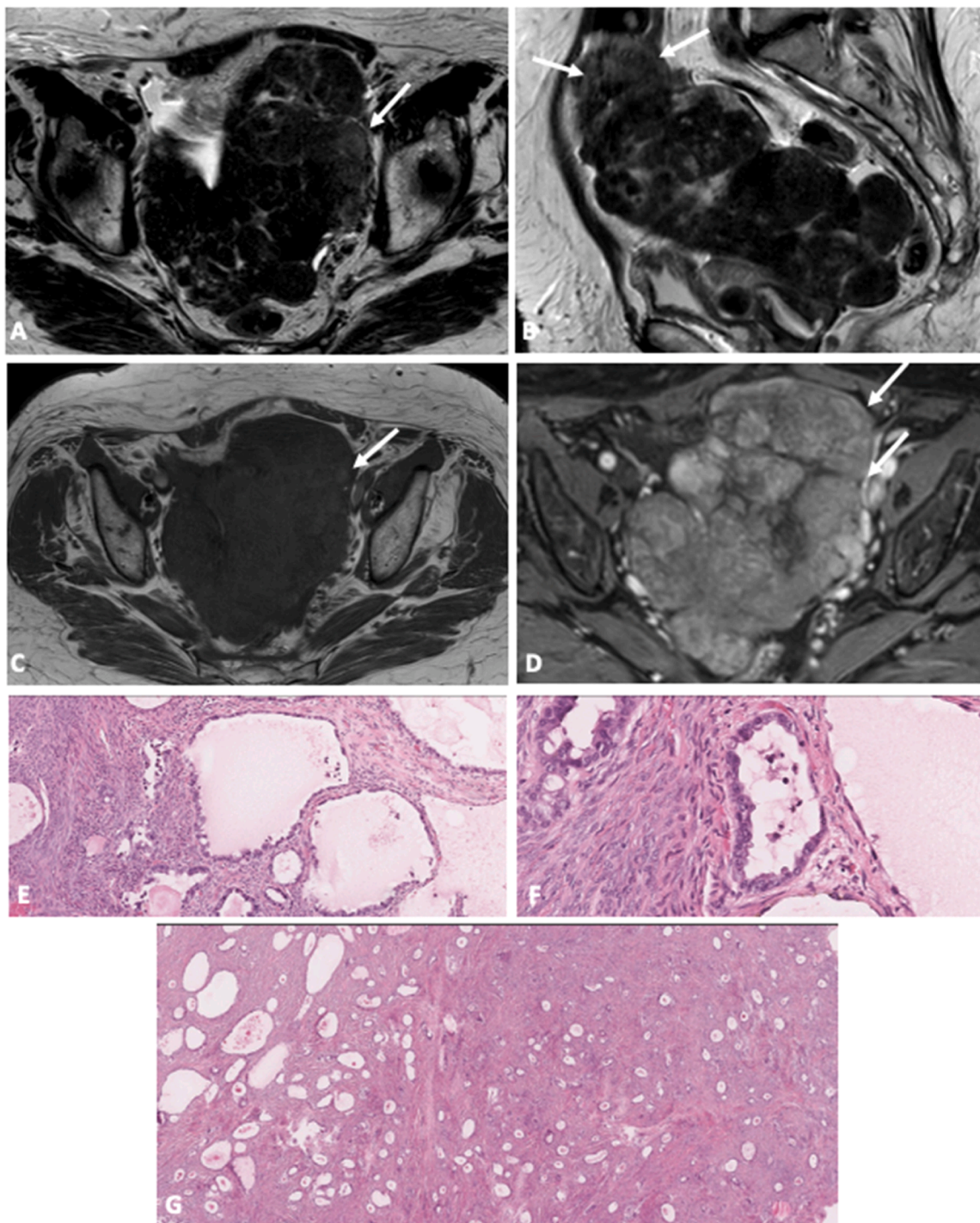


Fig. 5. Histopathological analysis compatible with bilateral borderline adenofibroma with intra-tumoral focus of the OCCC in a 91-year-old woman presenting with abdominal distension for 7 months. A, B axial (A) and sagittal T2-weighted imaging (B) show a left-side large, well-defined predominantly solid mass, and similar MRI features of a right-side smaller solid mass. C, Axial T1-WI shows a bilateral well-defined predominantly solid mass. The solid mass had heterogeneous hypointense and intermediate signal intensity on both T2WIs and it is predominantly hypointense on T1WI. Mild ascites was detected. The intermediate SI areas may correspond to clear cells carcinoma (arrow). D, axial contrast enhanced T1WI with FS depicts markedly heterogeneous enhancement of solid components (arrow). Surgery shown that the left ovary grossly was occupied by a 679g tumour, measuring 17cm in the largest dimension, that was yellow whitish multinodular tumour in the surface section. Right ovary weighed 3,2cm and in the section surface was similar to the left ovary. This case was bilateral intraovarian borderline clear cell adenofibroma (G) with bilateral focus of clear cells carcinoma (E and F) at pathology examination.

worrisome for malignancy.^{22,23} The presence of lymphadenopathy may also suggest malignancy. CT has a crucial role in assessing the extent of disease and evaluating for metastatic spread.

Magnetic resonance

Magnetic Resonance Imaging (MRI) is a valuable imaging modality for the evaluation of ovarian masses. Due to its multiplanar imaging and its superior soft tissue contrast resolution, MRI has greater accuracy than ultrasound and CT in characterizing complex ovarian neoplasms, with more reliable measurements, better inter-observer agreement in ovarian tumours depiction, and could contribute to the correct identification of OCCC.^{23,24} Therefore, MRI is the modality of choice for evaluating an ovarian mass.⁸

On MRI, the OCCC appears as a predominantly high signal intensity cystic mass on T2-weighted image (WI) with enhancing solid and irregular nodules. The growth pattern of the solid components was usually eccentric along the inner surface of the cyst, as demonstrated in Fig. 1.^{21,25} As they grow, these nodules protrude into the lumen of the cyst, tending to converge, and may appear as mixed cystic and solid masses, as showed in Fig. 3, or even as a predominantly solid mass. The OCCC are rarely solid masses, as it is displayed in Fig. 4. Identifying solid mural nodules on MRI is critical because they are the best predictors of an epithelial tumour and can be correlated with the tumour's aggressiveness;^{17,23} however, they are non-specific for the OCCC. The mural nodules often demonstrated intermediate T2 signal intensity and rarely showed low signal intensity on T2-weighted images.^{21,24,25} On the other hand, clear cell carcinomas that present as solid tumours with low signal on T2-WI should raise the suspicion of association with clear cell

adenofibroma,²¹ as it is shown in Fig. 5. Mural nodules typically exhibit enhancement after administration of gadolinium. However, the enhancement of solid components after intravenous contrast-enhanced MRI and CT do not aid in distinguishing between OCCC and other epithelial tumours.¹²

At MRI, the signal of cystic component is very high on T2-weighted image. Sometimes, the signal of cystic components exhibited variable signal intensity on T1-weighted imaging, from low to very high, but mostly exhibit hyperintense content when compared to pelvic muscle, as illustrated in Fig. 6.^{12,26} The cystic components may show heterogeneous attenuation on CT scans, with spontaneously hyperdense areas corresponding to the high-intensity areas of the cystic components on T1-weighted images. These imaging findings may occur due to intracystic haemorrhage and the association of the OCCC with endometriosis.^{12,22,27}

MRI can help identify the presence of lymph node involvement and distant metastases. MRI may also show signs of capsule rupture or irregularity of the ovarian mass contour, which are valuable findings in predicting distant dissemination. In most patients with OCCC who are in the early stages of the disease, the presence of enlarged lymph nodes, ascites, and peritoneal metastases is less common, which may also be an important clue in distinguishing clear cell carcinoma from other epithelial tumours. Massive ascites and peritoneal metastases are more indicative of high-grade serous epithelial carcinoma.^{12,24,28}

The radiologist plays a significant part in ovarian tumour characterization and diagnosis, namely in suggesting ovarian origin, predicting benign, borderline, and malignant behaviour, as well as in evaluating the extent of the disease. Although imaging features may be highly

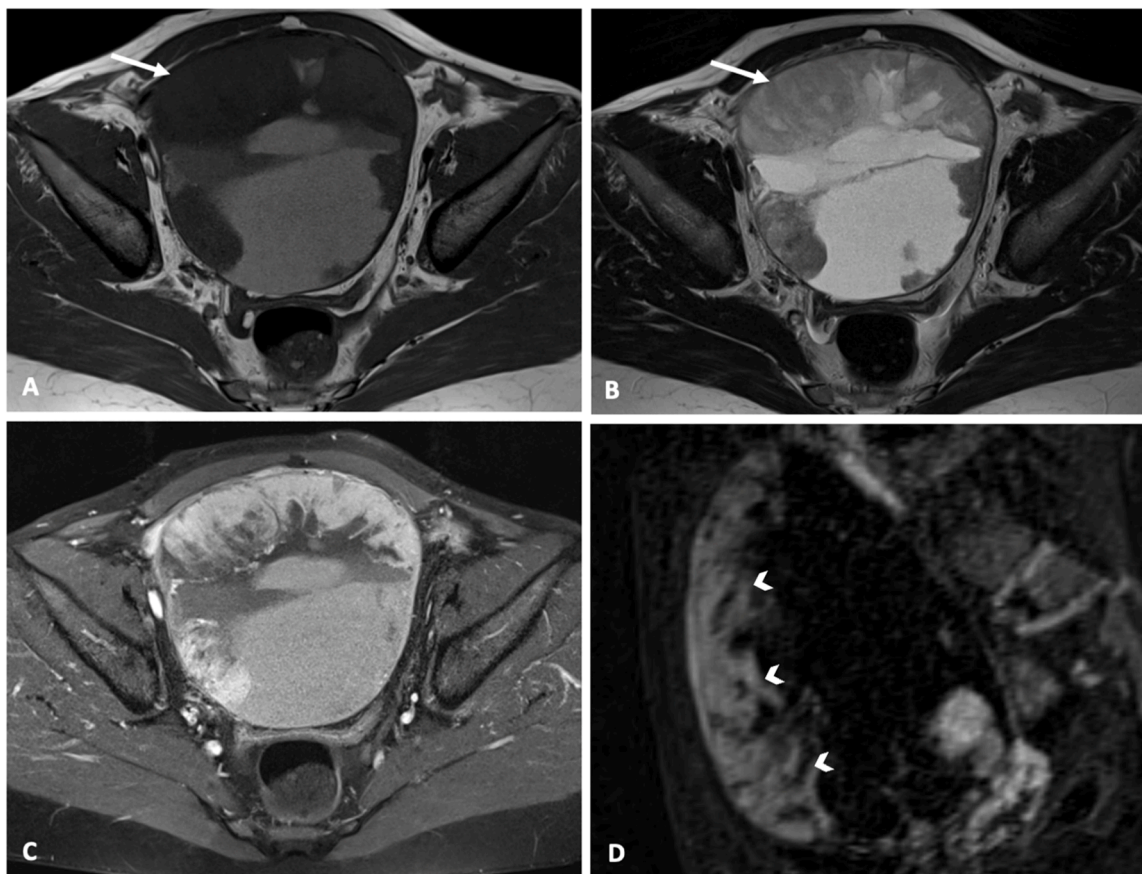


Fig. 6. A 53-year-old woman with frequent and urgent micturition and pelvic bulging. A, B, Axial T1WI (A) and axial T2WI (B) presenting a large, well-defined unilocular cystic mass with a multifocal irregular solid luminal protrusion and some irregular thin septations (< 3mm). The solid portion had intermediate SI on T2WIs and hypointense SI on T1WI (arrows). The SI of the cyst was heterogeneously intermediate to high on both T2WIs and T1WI. D, Enhanced and subtracted T1WI with FS exhibits a strong heterogeneous enhancement of solid mass (arrowheads) with central non-enhanced cystic areas.

suggestive of clear cell carcinoma, particularly when integrated into a specific clinical setting and a particular demographic presentation, the OCCC imaging-based diagnosis remains challenging. Thus, the final diagnosis is determined by pathological microscopic examination of surgical specimens.

In summary, the OCCC must be suspected in younger patients, with mean age of 56 years, with a unilateral large cystic and solid mass in the early stage of the disease. There should exist one of the two types of MRI features, namely a multilocular or unilocular T2-weighted image high signal intensity thick-walled cystic ovarian mass with mural nodular projections that outline intermediate signal intensity at T2-weighted images and heterogeneous enhanced irregular solid components; or this tumour may be presented as a heterogeneous enhancing predominantly solid ovarian mass with cystic areas.²⁵

Staging

The OCCC is staged according to the FIGO staging system and the TNM classification. Prognosis depends above all on the stage of diagnosis, and most OCCCs are limited to the ovary and confined to the pelvis, with a higher incidence of stage I disease.^{7,29} The 5-year survival rate of the OCCC has a significantly poorer outcome and more aggressive biological behaviour at advanced stages than other epithelial tumours, based on its platinum chemoresistant phenotype.³⁰

Treatment

Despite its biological and clinical features, the therapeutic strategies for ovarian OCCC are different from others ovarian carcinomas. The main treatment for OCCC is surgical and the standard surgical conduct includes hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy with peritoneal sampling and lymphadenectomy, with or without adjuvant chemotherapy or radiotherapy, approaches that are common to other epithelial ovarian tumours. Postoperative observation is an option for select patients with stage I clear cell carcinoma, and surveillance should only be considered in patients who have had a complete surgical resection and who have undergone exhaustive surgical staging to exclude the possibility of clinically occult disease.^{12,30,31} Despite its more aggressive outcome, some studies have shown that fertility-sparing surgery, different from other epithelial ovarian approaches, is a viable option. Fertility-sparing surgery does not increase the risk of recurrence or shorten survival compared with radical surgery patients with stage I disease.^{32,33} It is worth noting that the OCCC is relatively resistant to conventional platinum-based chemotherapy when compared to other epithelial ovarian tumours chemotherapy responses. Therefore, early detection and accurate preoperative diagnosis of ovarian OCCC are critical for an optimal therapeutic strategy since their management requires completely different surgical approaches and chemotherapy modalities.³⁴⁻³⁶

Clear cell carcinoma of the ovary is a rare and aggressive form of ovarian cancer. It is important to recognize the distinctive imaging features to make an early diagnosis. Imaging plays a crucial role in the diagnosis and management of OCCC. It is also fundamental in predicting treatment response and postoperative outcome and it is extremely important in monitoring surveillance. MRI is effective for the diagnosis and accurate characterization of a wide spectrum of ovarian masses, and large unilocular cystic mass with one or more nodules protruding into the lumen may be indicative of the OCCC. These possible features may aid radiologists in making a proper early diagnosis, which is of great importance for oncologic and surgical treatments insofar as the OCCC is less sensitive to conventional platinum-based chemotherapy. Furthermore, the OCCC may have a better prognosis than most types of ovarian cancer given that is more likely to be diagnosed at earlier stages, despite its aggressive behaviour and increased risk of poor outcome.³¹ Thus, some characteristic imaging features may allow a prompt and early diagnosis, leading to a potential better surgical results and general survival rate.

Conclusions

Understanding the radiologic and pathologic features of the multiple subtypes of ovarian neoplasms can help radiologists differentiate benign from borderline or malignant tumours. MRI is the modality of choice for evaluating an ovarian mass. Clear cell carcinoma of the ovary has distinctive characteristics and behaviour among ovarian cancers, such as has a well-known strong association with endometriosis. This tumour frequently presented as a large unilateral mass, mainly cystic with eccentric solid mural nodules or papillary projections protruding into the cystic space. The solid mural nodules most frequently presented an intermediate signal on T2-WI. The cystic component can be unilocular or multilocular and its content can appear proteinaceous/haemorrhagic. CT remains the recommended modality for preoperative staging and restaging after surgery. Thus, although the described imaging characteristics are common to general epithelial ovarian cancers and are not specific to the OCCC, some features may allow the radiologist to recognize this tumour and narrow preoperatively the differential diagnosis.

Ethics statements

The authors declare no conflict of interest.

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