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Imaging strategy in recurrent ovarian cancer: a practical review

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Abstract

Ovarian cancer is one of the most aggressive gynaecologic malignancies in women worldwide. The lack of proper screening programs and the characteristic abdominal spreading with minimal clinical symptoms give rise of its high lethality. Most patients show advanced disease at diagnosis and have a poor prognosis. The surveillance of ovarian cancer patients after initial treatment is a challenging question in clinical practice and there is no consensus in literature about the most appropriate follow-up strategy for these women. The role of Imaging has become increasingly important, allowing to properly monitor patients, distinguishing the different relapse patterns, thus guiding the correct management and therapy. In this review, we report and analyze the scientific evidence about the role of the different imaging modalities now available in the follow-up strategy and management of Epithelial Ovarian Cancer patients with recurrent disease.

Key words: Recurrent ovarian cancer—Ovarian cancer follow-up—Recurrent ovarian cancer imaging—US—CT—MRI

Ovarian cancer (OC) is one of the most aggressive gynaecologic malignancies in women worldwide with 238.000 new cases and 151.000 cancer-related deaths per year [1]. The lack of proper screening programs and the characteristic abdominal spreading with minimal clinical symptoms give rise of its high lethality.

Standard treatment consists of complete cytoreduction, [2, 3] followed by tri-weekly paclitaxel/carboplatin with an Overall Response Rate (ORR) > 75% [4]. Despite therapies, ovarian cancer shows a high percentage of recurrences. The risk of relapse is strictly related to the surgical staging, with an overall recurrence rate in advanced disease of about 60%–80%. Recurrence often occurrs within 18 months after treatment and, even in stage I or II patients, the relapse rate is 20%–25% [1].

The surveillance of OC patients after initial treatment is a challenging question in clinical practice, and there is no consensus in literature about the most appropriate follow-up strategy for these women. Serial physical examination combined with serum Cancer Antigen 125 (CA 125) assay with the different imaging techniques now available are currently widely used for surveillance of patients with this malignancy [5].

Recurrence of OC should be considered as a chronic and lethal disease; actually, most patients experience several disease relapses during the follow-up. Although there is no clinical evidence that early relapses detection could really influence treatment outcome, it should be considered that the modality, location and the period up to the first relapse may significantly vary among patients, leading to different clinical settings (i.e. patients with an isolated recurrence treatable by surgery and/or patients with a diffuse involvement undergoing chemotherapy).

In this context, the role of imaging has become increasingly important, allowing to properly monitor patients, distinguishing the different relapse patterns,

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thus guiding the correct management and therapy, since secondary cytoreduction is only justified if resection is possible with no residual tumor.

In this review, we report and analyze the scientific evidence about the role of the different imaging modalities now available in the follow-up strategy and management of Epithelial Ovarian Cancer (EOC) patients with recurrent disease.

Ovarian cancer relapse patterns

OC relapse may present with different spreading patterns. Recurrences within the pelvis are described in about 26%–50% of relapses. The detection of local recurrent disease is challenging due to post-operative distortion of the complex pelvic anatomy. Local relapses often appear as solid and mixed solid-cystic masses in vaginal vault, cul-de-sac, bladder and pelvic wall [6].

However, the commonest pattern of recurrence is carcinomatosis. The biological behavior of OC differs markedly from the classic pattern of haematogenous metastasis of most other cancers: primarily disseminating within the peritoneal cavity and being only superficially invasive. Exfoliated tumor cells are transported throughout the peritoneum by physiological peritoneal fluid, spreading by implantation on both parietal and visceral peritoneum. Peritoneal implants may present with different patterns, such as nodular lesions, reticulonodular infiltration, serosal plaques and omental-cake (Fig. 1H–J). The commonest sites of carcinomatosis involvement are the region of hemidiaphragms (Fig. 2A–C, E), omentum (Fig. 2D, F), rectouterine pouch, right lower quadrant, sigmoid colon (Fig. 2G–J), and right paracolic gutter.

Finally, after peritoneal seeding, the tumor spreads into the lymphatics, involving the pelvic, para-aortic (Fig. 3E, F) and mediastinal lymph nodes (Fig. 3H). It should be considered that after surgery lymphatic drainage is completely modified, so metastatic spread can affect all the lymph-nodal districts including atypical sites, such as axillary or supraclavear stations (Fig. 3G). Lymph-node involvement must be suspected in presence of altered morphology (rounded instead of oval) increased dimension (short axis $>$ 1 cm), altered function (visualized through the loss of the fatty hilum) and the presence of central necrosis. The most common site of lymph-node metastases is represented by para-aortal region (in 18%–33% of cases) [7].

Haematogenous spread rarely occurs in early recurrence, while it is more commonly associated with advanced disease relapses. In his series of 112 patients with recurrent disease Kimio [8] reported distant metastasis in 17% of cases; similar results were obtained by Usami [9] al who observed distant metastasis in 22% of their 42 relapse cases.

The commonest sites of metastatic spread are liver and chest. Liver metastases have a frequency of approximately 9.4% among patients who present with recurrent ovarian carcinoma and comprise about 20% of all distant metastases of ovarian cancer. It is important to distinguish liver metastases from liver implants developing on the Glisson capsule (Fig. 4B–G) [10–12].

Pleural effusion is the most common manifestation of thoracic involvement. Solid pleural nodules or pleural thickenings may also be present and are suggestive for pleural metastatic involvement (Fig. 4A). The increasing occurrence of unusual distant metastases from ovarian cancer possibly reflects the increased survival due to improved systemic and palliative therapy [6]. Brain involvement is rare (reported overall frequency found at autopsy of about 6%), but the incidence is increasing. The brain may be considered as a sanctuary site from systemic chemotherapy due to the blood–brain barrier

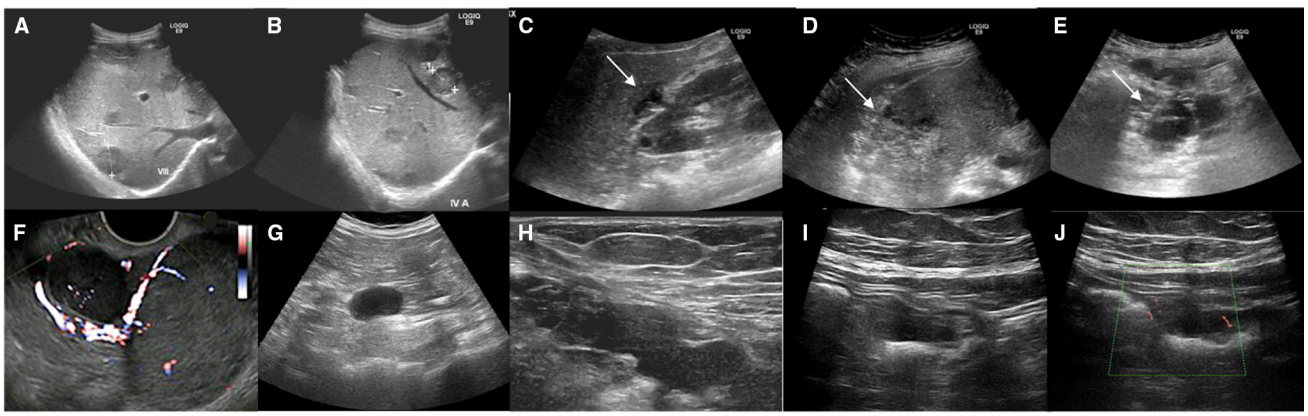

Fig. 1. Transabdominal and Endo-vaginal Ultrasound (US) examinations of OC recurrence. **A–E** show upper abdomen recurrence in a 54 years-old woman; parenchymal hepatic metastasis in VIII and IV segment are shown in **A** and **B**; white arrows show glissonian (**C**, **D**) and perisplenic (**E**) implants. **F–J** show pelvic OC recurrence in a 43 years-old woman; **F** depict endo-vaginal US of local recurrence as a solid pelvic mass showing vascularization at Color Doppler examination; a cystic implant is depicted in **G**; **H–J** show linear US findings of massive peritoneal carcinomatosis within the deep pelvic abdominal wall.

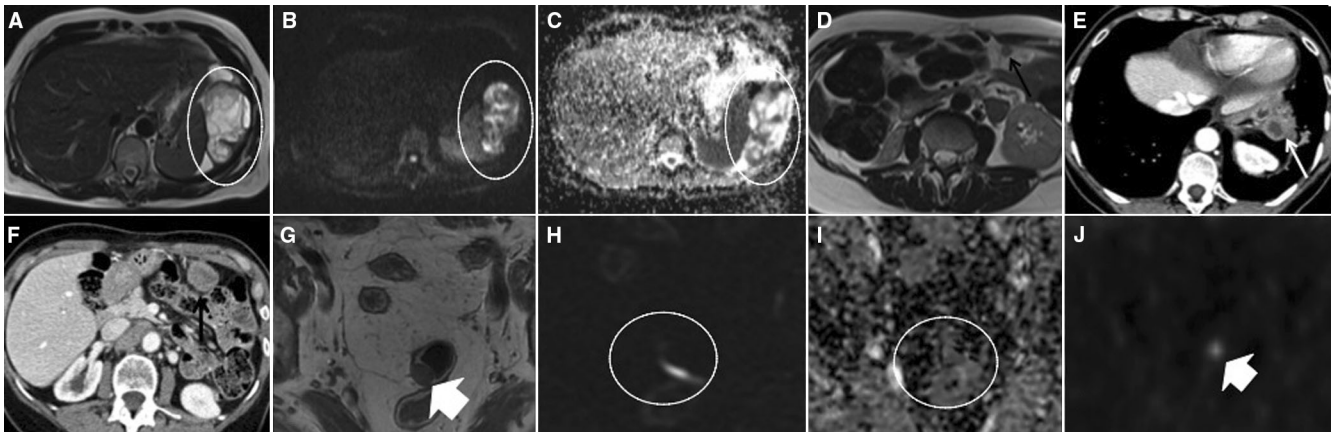

Fig. 2. Peritoneal implants in a 59 years old patient with recurrent ovarian carcinoma. An axial T2-Weighted Image (WI) shows a large lobulated implant (white circle) located under the left diaphragm, laterally to the spleen (**A**–**C**). The implant is inhomogeneously hyperintense on T2 (**A**) and shows hyperintense areas of restricted diffusion on Diffusion Weighted Imaging (**B**), which are hypointense on the Apparent Diffusion Coefficient (ADC) map (**C**). In the same patient, a hypointense implant (black arrow) has been also detected behind the anterior abdominal wall (**D**). A CT scan (**E**, **F**) performed 10 months after secondary surgery (removal of both implants and splenectomy), shows recurrence on both subdiaphragmatic (**E**; white arrow) and anterior location (**F**; black arrow). A 74 years old patient T2-weighted MR images showed a nodular thickening of the sigmoid colon serosa (**G**), but without diffusion restriction on DWI (**H**; white circle) and ADC map (**I**; white circle) images. Positron Emission Tomography/Computed Tomography (PET/CT) (**J**) revealed the presence of a nodular FluoroDeoxyGlucose (FDG) uptake at the same level, with the diagnosis of pelvic recurrence on the sigmoid colon surface.

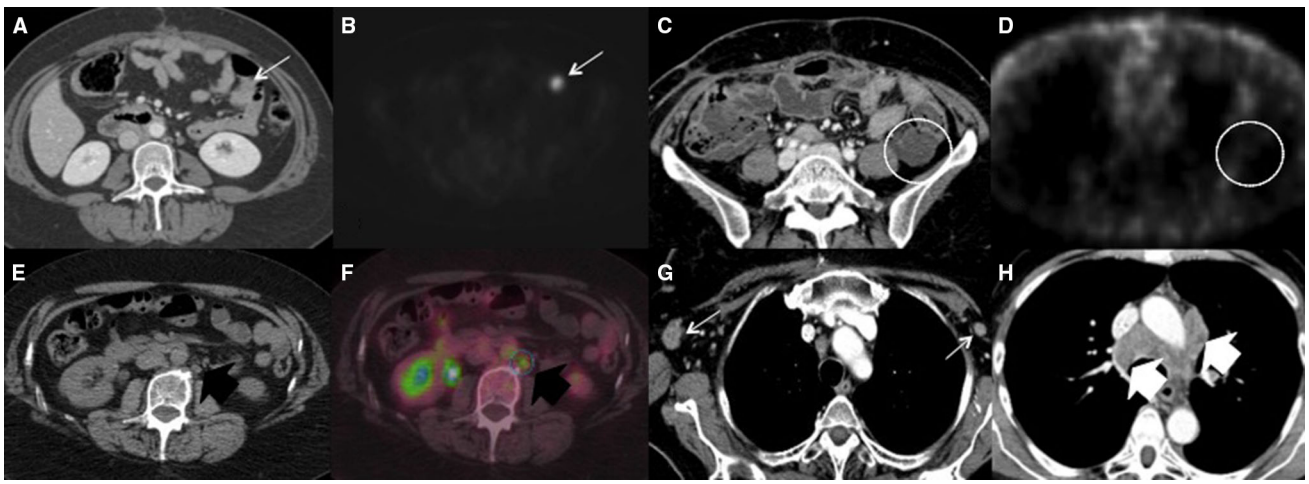

Fig. 3. In a 63 years old patient who underwent primary surgery for serous ovarian cancer, with raised CA-125 blood level but negative CT scan (**A**), PET/CT showed a small nodular area of FDG uptake on the surface of a bowel serosa (**B**; white arrow), which was not detected on the CT scan because it was misinterpreted as a bowel loop (**A**; white arrow). **C, D:** In a 48 years old patient with recurrent mucinous ovarian cancer, an axial CT image (**C**) shows a cystic, hypodense implant on the posterior surface of the colon (**C**, white circle), which does not have increased FDG uptake on PET/CT (**D**; white circle). **E, F:** An indeterminate paraortic lymph node on CT (E; black arrowhead) shows FDG uptake on PET/CT (**E, F**; black arrowhead), which suggested the diagnosis of metastatic lymph node. G, **H**: two CT images show bilateral axillary (**G**; white arrows) and mediastinal (**H**; white arrowheads) metastatic lymphadenopathies.

(Fig. 4H) [13]. From a histological standpoint, high grade primary ovarian cancer (G3) as well as advanced stage at presentation of the primary malignancy at the time of diagnosis significantly increases the likelihood of development of brain metastasis. Bone metastasis from ovarian cancer is extremely rare and occurs in approximately 1% of primary or recurrent disease with the exception of dysgerminomas. The prognosis of cases with bone metastasis is poor. It has been reported that the median survival after the clinical diagnosis of bone metastasis is only 4 months. Other rare sites of reported recurrences include the skin and subcutaneous tissues,

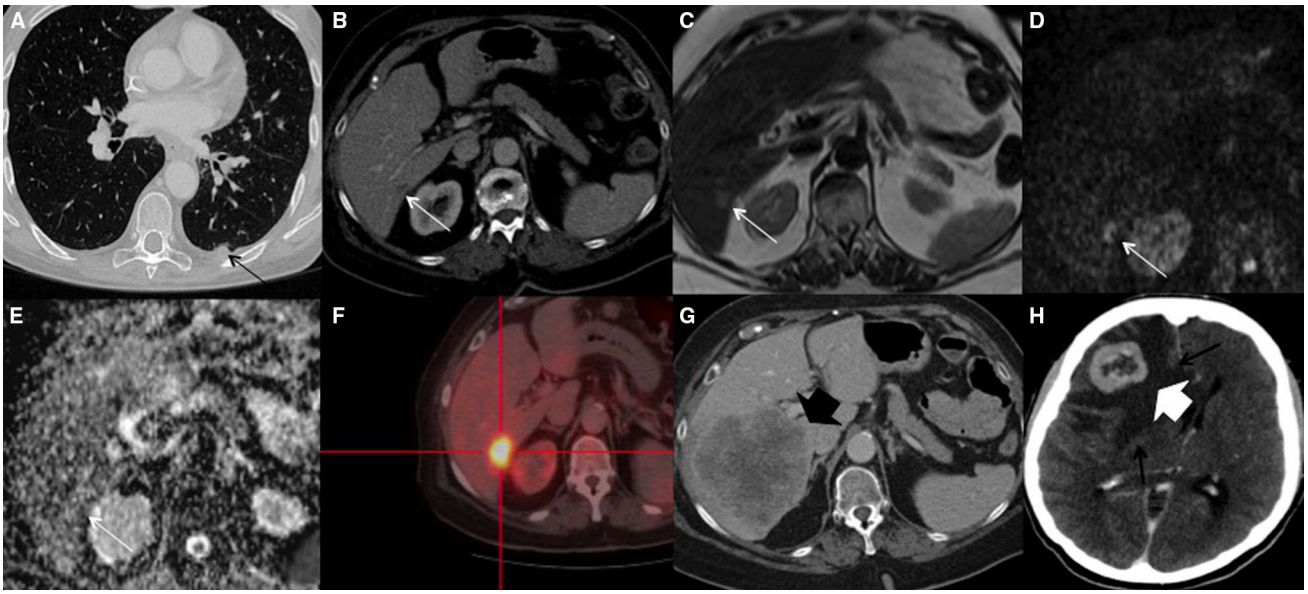

Fig. 4. In a 73 years old women with raised CA-125 after surgery for ovarian cancer, CT scan showed a small pleural metastasis (**A**; black arrow) and an indeterminate hypodense area (**B**; white arrow) on the VI liver segment; MRI (**C**–**E**) revealed a slightly hyperintense area on T2-weighted images, in the same location (**C**; white arrow), which showed restricted diffusion on DWI (**D**; white arrow) and ADC map (**E**; white arrow), suggesting the diagnosis of liver metastasis, then confirmed also by PET/CT (**F**). After 1 year, on a CT examination, the same lesion increased in size (**G**; black arrowhead); a brain metastasis (**H**; white arrowhead) with surrounding edema (**H**; black arrows) was also detected.

thymus, thyroid, breast and the urinary tract. Among these, metastases to the subcutaneous tissue are probably the most frequent, with a reported incidence of 3.5% [14].

Role of imaging in ovarian cancer relapse

Ultrasonography (US)

US with color and pulsed Doppler represents the first-line imaging method for its wide availability and low cost, playing an important role in the follow-up of ovarian cancer especially if carried out by an experienced sonographer (Table 1; Fig. 1).

Technical key points

Grey-scale and Doppler sonography with high-resolution Endo-Vaginal (EV) probe (5–7 MHz transducer) allows a detailed view of the pelvic structures, detecting relapses and providing information about morphology, mobility, and invasion of surrounding tissues.

Septated fluid collection may also be the only sonographic sign in women with pelvic OC relapse [15]. The overall sensitivity of US in local pelvic disease relapse ranges from 45% to 85% with a specificity of 60%–100% [16]. US may be also helpful in guiding tru-cut biopsy of a suspicious lesion when local recurrence is identified [17].

Transabdominal US (2–5 MHz transducer) should be systematically performed, providing information about the presence of ascites and spleen or liver metastasis.

Limits and advantages

US remains limited for the assessment of metastatic peritoneal implants or distant lymphadenopathy, two of the most common sites of recurrence in patients with ovarian cancer. The use of linear probe in selected cases may add information in the depiction of superficial

Table 1. US

	Endovaginal US	Transabnominal US	Superficial US
Probe	5–7 MHz transducer	2–5 MHz convex transducer	7–13 MHz linear transducer
Patient preparation	Empty bladder	Full Bladder	–
Anatomical regions	Pelvic loco-regional recurrence and abdeep implants	Upper and lower abdomen recurrence	Better depict deep abdominal wall implants of carcinomatosis

peritoneal implants of carcinomatosis (Table 1, Fig. 1F–L).

In addition, US is still not a standardized modality in the follow-up of ovarian cancer and in literature there is a lack of studies investigating its ability to detect recurrence [18, 19]. Operator skills in interpreting ultrasound images, equipment, and patient body habitus give rise to the high variability in diagnostic accuracy of this method, with a low reproducibility [20, 21].

Computed tomography (CT)

Currently, Contrast-Enhanced (CE)- CT is the imaging modality of choice for staging ovarian cancer but also for treatment follow-up, ensuring reproducibility of the results for future comparison.

Technical key points

The use of oral contrast media could be useful to distinguish between luminal lesions and serosal or mesenteric deposits. However, care should be taken as small, calcified deposits may be masked by oral contrast. Due to this reason, the use of oral water as a negative contrast is often preferred. It is recommended to administrate orally at least 500–750 mL of water, 15 min prior to the examination. A non-contrast sequence is useful to better depict calcific lesions and to obtain a panoramic view of the entire abdomen. A late arterial and a portal phase images should be acquired respectively at 18–23 and 60–70 s after contrast injection; a delayed phase obtained after 5 min from the start of contrast media injection is mandatory to detect small implants of carcinomatosis, especially in difficult anatomical districts [22]. Urographic post-contrast enhancement could be helpful to assess urinary involvement [23] (Table 2).

Limits and advantages

Multi-detector CT is able to acquire 1–3- mm-thick sections over large volumes in a short examination time, resulting in an improvement of the imaging quality also through reconstruction of multi-planar images [24]. Due to its low soft-tissue contrast, CT is limited in evaluating local tumor recurrence within pelvis (Fig. 5 A) and to demonstrate small volume extra-ovarian < 5 mm deposits on bowel serosa, mesentery and peritoneum especially in the absence of ascites. The sub diaphragmatic regions were historically a challenging area for CT, but with multi-planar reformatting now widely available, this limitation can be in part overcome. Despite these limitations, CT remains a valid tool in recurrent disease with a reported accuracy of about 70%–92%. In addition, CT but could be useful in certain urgent clinical setting, i.e. in evaluating patients presenting with an acute abdomen with bowel obstruction that may be due to either surgical adhesions or to recurrent disease [25].

Table 2. CT technique

Water (oral)	500–750 mL: 15 min prior examination
Non-ionic iodinated intravenous contrast	Volume: 120 mL Injection rate: 3 mL/s
Contrast-Enhanced scan delay	Arterial phase: 18–23 s Venous phase: 60–70 s
Thickness	1–3 mm
Postprocessing	Multiplanar reconstructions Volume rendering

Magnetic Resonance Imaging (MRI)

In women treated for ovarian cancer the main indications for MRI are suspicion of local pelvic recurrence and peritoneal carcinomatosis. Indeed, MRI thanks to its excellent soft-tissue high-resolution allows the discrimination between post-treatment changes and tumor recurrence [19].

Technical key points

The use of a multichannel phased array coil on abdomen for pelvic and abdominal imaging and of a high-field strength magnet is recommended, in order to maximize Signal-to-Noise Ratio (SNR) and image resolution. With the aim of suppressing bowel motion artifacts, the intravenous administration of antiperistaltic drugs is recommended, helping to better visualize pelvic and adnexal region [26]. Bowel preparation could be useful in case of strong suspicion of secondary bowel wall involvement. MRI should include dedicated sequences on the pelvis (in order to study local recurrence) and the abdomen (to depict peritoneal carcinomatosis and/or upper superior abdomen metastasis). Fast Spin-Echo (FSE) T2-Weighted Imaging (WI) is the sequence of choice to show pelvic anatomy. Pre- and post-contrast T1-WI of the pelvis and abdomen with Fat Suppression (FS) and breath-hold is recommended. The diagnostic performance of MR imaging may be improved adding dynamic contrast-enhanced sequences and Diffusion Weighted Imaging (DWI) in the routine protocol for pelvic MR imaging, increasing diagnostic confidence and tissue characterization. Contrast-enhanced FS T1-WI allows the detection of free peritoneal surface and bowel serosa implants [19]. Ascites enhancement may appear 15–20 min after administration of contrast in patient with peritoneal carcinomatosis [27] (Table 3).

Limits and advantages

MRI is the most sensitive technique in detecting local pelvic disease recurrence [28, 29] showing a high sensitivity, specificity and accuracy in detecting local recurrences respectively 91%, 86%, and 89% [28]. MRI is able to confirm or exclude the infiltration of adjacent tissues,

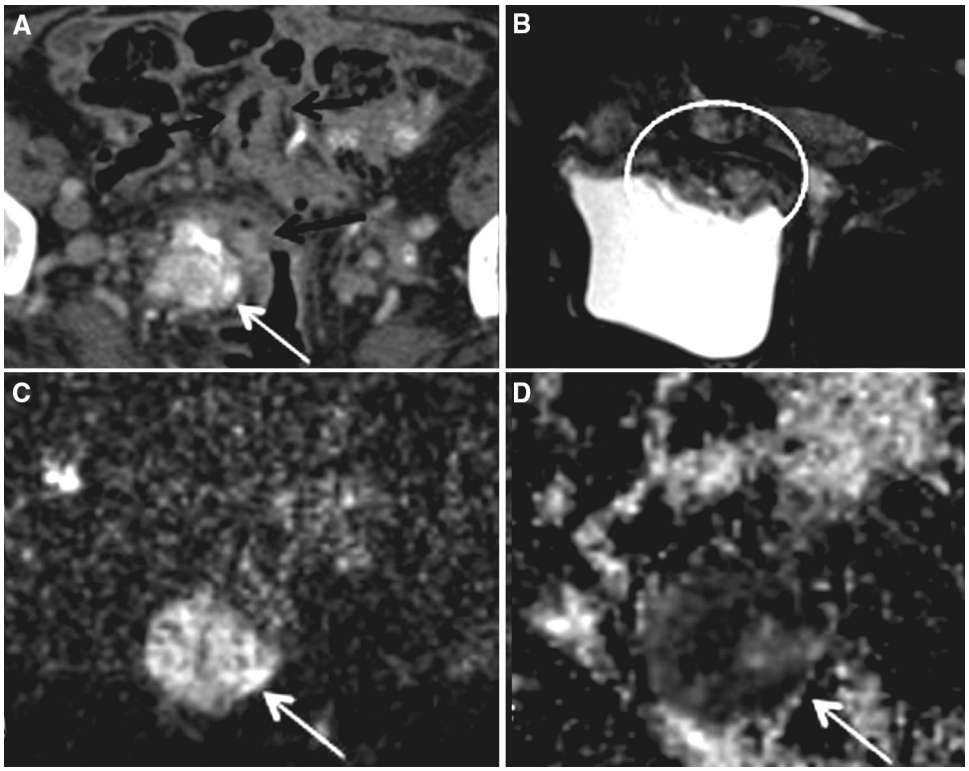

Fig. 5. EOC recurrence within the pelvis. In 81 years old patient who underwent surgery for EOC, a 2 years follow-up CT scan showed local recurrence as a pelvic solid enhancing mass (**A**; white arrow) and diffuse sigmoid colon walls thickening (**A**; black arrows). MRI also revealed a hypointense superior bladder wall thickening (**B**; white circle) on T2-weighted FS MR image. DWI (**C**; white arrow) and ADC map (**D**; white arrow) images showed restricted diffusion within the mass.

depicting the presence of fatty cleavage planes between the neoplastic tissue and the neighboring structures. Pelvic recurrence usually appears as a solid lesion with inhomogeneous signal intensity on T1 and T2-WI and it may be prevalently cystic with only some peripheral mural thickening. The lack of visualization of physiological T2 hypointensity of bladder or bowel wall has to be considered a suspicion of infiltration (Fig. 5B). Ureteral involvement should be suspected if the upstream ureter appears dilated [19].

MRI is able to better recognize the presence of fistulae between vagina, bladder, and rectum.

The dynamic study and DWI sequences help to find loco-regional recurrence and improve the detection of peritoneal and omental carcinomatosis. Low et al. showed that Dynamic Contrast-Enhanced (DCE)-MRI was comparable (sensitivity 90% and specificity 88%) to laparotomy (sensitivity 88% and specificity 100%) for the detection of recurrent pelvic disease spread in women who have been treated for ovarian cancer, with a positive predictive value respectively of 98% and 100% [29].

Ovarian recurrence shows variable degrees of enhancement after contrast administration, particularly more evident in the peripheral region and/or in cyst walls and mural thickenings. DWI combined with conventional anatomical MR sequences, improves accuracy to 84%–88% (MRI alone accuracy 52%–72% and DWI alone 71%–81%) in detecting local pelvic relapse, appearing hyperintense on high b-value (1000) images due to the high cellularity, which corresponds to hypointensity on Apparent Diffusion Coefficient (ADC) maps (Fig. 5C, D). Furthermore, DWI combined with T2-WI

Table 3. MRI protocol

Sequence	TR (m/s)	TE (m/s)	FOV (mm)	Matrix	Thickness (mm)	Distant factor	B (s/mm^2)
T2 TSE	3000	68	240 × 200	128 × 256	5	30	
T1 TSE with and without FS	500	Min	320 × 280	192 × 256	5	30	
Non-CE and CE Spoiled 3D GRE	150	Min	320 × 280	256 × 256	4	0	
DWI	5000	50	340 × 260	128 × 128	5	0	0, 500, 1000
Whole-body DWI	6789	68	320 × 480	88 × 132	5	0	0, 1000

DWI diffusion-weighted imaging, *FOV* field of view, *TSE* turbo spin echo, *TE* echo time, *TR* repetition time, *CE* contrast enhanced, *VIBE* volumetric interpolated breath-hold examination, *WB-DWI* whole body *DWI* from neck to pelvic floor

can facilitate differentiation of post-treatment fibrosis, which show low signal intensity on both T2 and DWI, from disease recurrence, characterized by persistent restricted diffusion with intermediate T2 signal intensity [30].

Dynamic multiphase contrast-enhanced MR imaging is an excellent imaging tool for detection of peritoneal deposits (per-lesion sensitivity 95% and specificity 80%). The inclusion of DWI sequences may improve the accuracy of MRI in detecting small implants [31].

The appearance of peritoneal carcinomatosis on MRI depends on the growth pattern: solid, cystic, or mixed. Solid nodules appear slightly hypointense on T2-weighted images and show a significant restriction of diffusion coefficient while cystic and mixed nodules show no or minimal restriction of diffusion coefficient. Radiologist should evaluate both morphological and diffusion images at different b values and ADC maps in order to avoid pitfall related to T2 shine-through effect. Markedly hypointense spots on T2-weighted images correspond to calcifications. Peritoneal implants and omental-cake are best seen on delayed (5-min) images [32].

However, as for CT, MR per-lesion sensitivity is considerably lower for implants smaller than 1 cm, and in anatomic sites where small tumor implants are adjacent to tissues with similar signal intensity, such as the right sub diaphragmatic space, omentum, root of the mesentery and serosal surface of the small bowel and bladder [27]. According to recent literature, the usefulness of Whole-Body MRI is actively debated; Michielsen et al. [33, 34] showed higher accuracy for DWI/MRI compared with CT (94% vs. 78%) in recognizing tumor recurrence in difficult surgical locations and in detecting subcentimetric serosal tumoral deposits (Fig. 2A–C, H–J).

Ricke et al. [31] obtained very low values of MRI sensitivity for pelvic lymph nodes (28%), accuracy was only 58.3% for retroperitoneal and pelvic lymph nodes overall. Introducing DWI sequences in MRI protocol, and qualitatively evaluating signal intensity at b1000 for DWI, MRI performs better to diagnose lymph-node involvement [35, 36]. In particular, DWI/MRI improved detection of nodal metastases by 17% and 21%, compared to conventional MRI [33, 35, 37]. Although Nakai et al. [38] reported no significant improvement in differentiating between benign and metastatic lymph nodes in gynecological tumors using ADC measurements, other Authors showed significantly lower ADC and relative ADC (rADC) values of positive lymph nodes (ADC: 0.7483–0.7651 $\times$ 10^{-3} mm^2/s; rADC: 0.06–0.3832 $\times$ 10^{-3} mm^2/s) compared to negative lymph nodes (ADC: 0.9960–1.0021 $\times$ 10^{-3} mm^2/s; rADC: 0.21–0.5383 $\times$ 10^{-3} mm^2/s) [39–42].

Positron emission tomography combined with CT (PET-CT)

PET-CT with FluDeoxyGlucose (PET-FDG) is a diagnostic imaging study that combines the best features of Positron Emission Tomography (PET) and Computed Tomography (CT) allowing anatomical and functional imaging of tissues thus providing qualitative and quantitative metabolic information (Table 4). PET-CT is an accurate technique in Patients with suspected tumor recurrence (i.e. with rising CA125), particularly in cases with inconclusive or doubt CT and/or MR imaging findings.

Technical key points

FDG accumulation in biological tissue depends on the amount of glucose utilization. Neoplastic tissues overexpress the GLUT membrane transporters and have an increased hexokinase activity [43]. PET examination is performed 1 h after the administration of a glucose analog, the 2-[fluorine-18]fluoro-2-deoxy-D-glucose , after checking blood glucose levels to exclude diabetes. The combination of PET with intravenous contrast injection and high-resolution CT has proven useful for increasing the accuracy of detecting recurrences in women with previous ovarian cancer [44].

The overall impact on changing the clinical and therapeutic approach is between 25% and 58% but the relationship between prognosis and FDG-PET/CT remains indeterminate [44]. PET/CT may have limited accuracy in the detection of microscopic disease: in pathological positive lymph nodes the sensitivity of PET to detect small foci of recurrent tumor is lower than that of second-look laparotomy [45].

Recent studies have suggested the possible role of standardized uptake value (SUV) as a imaging biomarker in predicting recurrence in patients with advanced EOC [46].

Limits and advantages

PET/CT has been shown to have better diagnostic performance than CT or MR imaging for the evaluation of recurrent disease. In a meta-analysis of 34 studies, Gu et al. [47] found the pooled sensitivity and specificity for the detection of recurrent ovarian cancer was 79% and 84%, respectively, for CT, 75% and 78%, respectively, for MR imaging, and 91% and 88%, respectively, for PET/CT.

Particularly, PET-CT has proved to be more accurate over other imaging methods in detecting small carcinomatosis implants (Fig. 6A, B). Satoh and colleagues compared PET/CT, diffusion-weighted MRI (DWI), and contrast- enhanced multi-detector CT in the diagnosis of peritoneal dissemination of malignant tumors and demonstrated that the sensitivity of PET/CT (94%) was

Table 4. PET/CT technique

FDG dose	3.7–7.4 MBq/kg (min 185 MBq)
Anatomical regions	Skull-midthigh
Preparation	Fasting (at least 8 h) Basal glicaemia < 200 mg/dL
Timing of imaging	First scan: 60 min post-FDG injection Delayed scan: 180 min post-FDG injection
Patient care after injection	Hydration (500–750 mL post-injection)
Postprocessing	Multiplanar 3D reconstructions

significantly higher than that of MRI without DWI (70%), whereas the specificities of the modalities were not significantly different [48]. Further, the PPV of PET/CT (94%) was significantly higher than that of the other three modalities (contrast-enhanced multi-detector CT, 73%; MRI without DWI, 70%; MRI with DWI, 72%) [48]. Suppiah et al., in a systematic review about the detection accuracy of peritoneal recurrence in OC involving 426 patients, reported a pooled sensitivity and specificity of 93.94% and 93.80%, respectively [49]. Similar results were obtained by Limei et al. in their meta-analysis including 29 studies about patients with recurrent EOC, reporting sensitivity of 88.6% and specificity of 90.3% for PET-CT in relapses detection [50].

Regarding lymph-node involvement, FDG-PET/CT may still accurately depict metastatic disease on the basis of significantly increased metabolic activity, even in normal-sized nodes (Fig. 3 F) [50]. However, even if PET or PET/CT performed better (Se 73% and Sp 96%) compared with CT (Se 42% and Sp 95%) and MRI (Se 54% and Sp 88%), it has been reported the presence of false-negative cases, probably due to the low FDG uptake of lymph nodes with low-grade metastastic EOC [51].

PET–CT performs better than CT alone in detecting chest metastatic OC recurrence with a reported sensitivity respectively of 100% and 75%, Specificity 96% and 91%, Accuracy 96% and 89% [52].

Osseous metastases may manifest as destructive lesions on conventional radiographs; they are associated with a soft-tissue mass on CT and MRI. PET/CT show increased activity at sites of osseous metastases [53].

Although the impact of PET/CT on patient management varies across studies in the literature, PET/CT has been shown to influence clinical management in about 44% to 60% of patients [54–56]. Furthermore, the impact varies depending on clinical setting. In fact, Han et al. found PET/CT able to exclude disease or recurrence in 17% of patients with clinical suspicion and to change management in approximately 11% of cases [57].

Major limits of PET/CT are miliary peritoneal involvement, cystic or necrotic lesions or lesions with copious mucinous collections, low-grade tumors, and clear cell OC thus leading to false-negative cases (Fig. 3C, D). In case of mucinous tumors, DWI should improve the detection rate of implants; Schwenzer et al. demonstrated the additional value of DWI in case of slight or no FDG uptake in PET [58].

FDG-PET has not been found to be as sensitive as MRI in the evaluation of brain metastases [19]. Cerebral cortex is highly FDG avid, and metastases often appear as focal areas of hypometabolism, which may also be seen in non-neoplastic entities such as infarction. Some

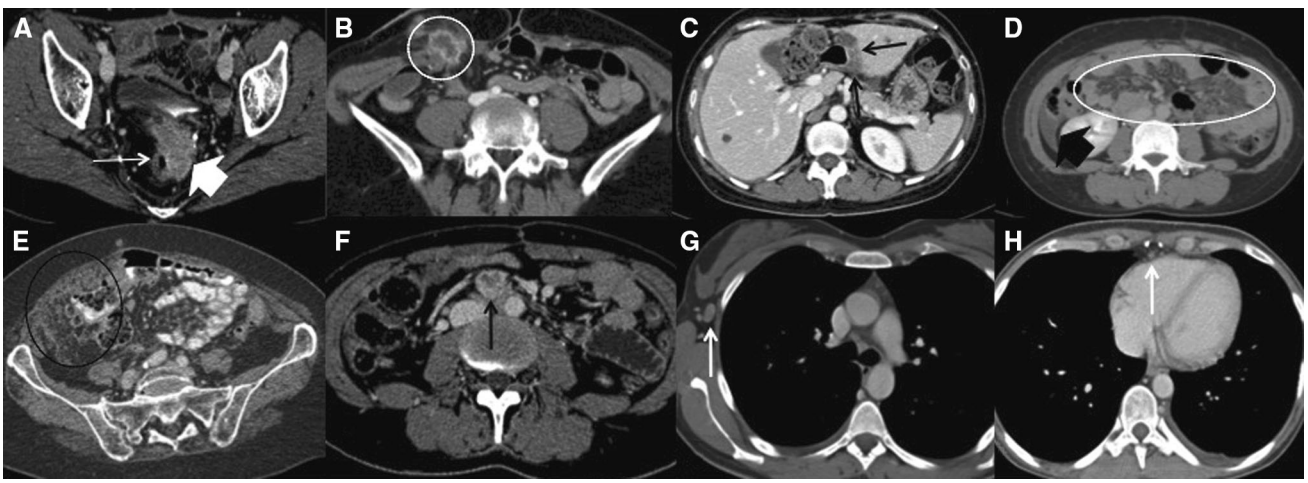

Fig. 6. CT scan detection of ovarian cancer recurrence. An axial post-contrast CT image (**A**) shows pelvic recurrence (white arrowhead) after primary surgery on the vaginal vault, with infiltration of the sigmoid colon (white arrow). Other post-contrast CT images show recurrent implants on the ileostomia (**B**; white circle) and on the liver serosa (**C**; black arrow). A typical pattern of ovarian cancer recurrence is also diffuse peritoneal carcinomatosis seen as straining of the mesenteric (**D**; white circle) and omental (**E**; black circle) fat tissue. CT scan can also detect abdominal (**F**; black arrow), cardiophrenic (**H**; white arrow) and more rarely axillary (**G**; white arrow) metastatic lymph nodes.

Table 5. MR multiplanar protocol in PET/MRI

Sequence	TR (m/s)	TE (m/s)	FOV (mm)	Matrix	Thickness (mm)	Gap	B (s/mm^2)
SS-TSE with and without FS	750	76	240 × 200	128 × 256	4	30	
T2 TSE with and without FS	3000	68	240 × 200	128 × 256	5	30	
DWI	5000	50	340 × 260	128 × 128	8	0	0, 1000
T1 TSE	500	Min	320 × 280	192 × 256	5	30	
Spoiled 3D GRE (chest)	110	190	320 × 280	256 × 256	3	0	
FLAIR (head)	12,000	94	240 × 200	256 × 256	4	30	

lesions do manifest as focal areas of hyper-metabolism, although this can be difficult to detect in the setting of normal physiologic grey matter metabolism [59].

In addition, radiologist should be aware about prior surgeries and their complications in order to properly interpret PET images. Asymmetric FDG uptake along the surgical bed is common and may mimic malignancy; caution should be exercised when studies are interpreted within 6 months of surgery [59].

PET/CT in asymptomatic patients with increasing levels of CA125

In the last few years, a multimodal approach combining imaging techniques with clinical and laboratory parameters, has been used to improve management and follow-up of patients previously treated for OC.

The serial evaluation of CA125 is widely recommended to non-invasively detect OC relapses. Indeed, CA 125 levels often rise at least 3 months before there is any clinical or radiological evidence of recurrence and a level of twice the upper normal limit is supportive of disease progression [60].

The sensitivity of CA 125 for recurrence is 62%–94% and the specificity is 91%–100% [61] but normal CA 125 levels cannot exclude disease relapse; indeed, about 50% of patients with normal CA 125 after primary therapy have microscopic disease at second-look surgery [10].

However, if CA125 levels are increasing and patient is asymptomatic, additional imaging studies such as a CT scan or MRI should be performed. If these exams result inconclusive a PET/CT will offer additional insights (Fig. 2G–J). Zimny et al. [62] reported that PET has a sensitivity of 96% in localizing recurrent disease in patients with rising CA-125 levels, preceding CT findings by 6 months. Other studies confirmed these results, reporting a sensitivity of 94%–98% combining FDG-PET and CA-125 levels, whereas conventional imaging results are negative or equivocal [63, 64].

Positron emission tomography combined with MRI (PET-MRI)

Technical key points PET-MRI is a brand new hybrid modality [65, 66], less used in clinical practice than FDG-PET/CT (to date the most helpful imaging tool to study recurrence). However, early evidences show that PET/MR may add information in patients with a suspicion ovarian cancer recurrence through the use of a whole-body and loco-regional study [67], overcoming the limitations of conventional MR imaging and providing metabolic information to better distinguish between post-treatment changes and recurrence.

During the PET acquisition, whole-body Dixon images, single-shot turbo spin-echo images, fluid-sensitive inversion recovery images and DWI are co-acquired in simultaneous PET/MR scanners (Table 5).

A dedicated pelvic MR imaging examination follows including dynamic intravenous gadolinium administration. On the current scanners the examination time is about 1.0–1.5 h.

Limits and advantages

The post-operative distortion of the pelvic anatomy may lead to several difficulties in relapses detection: in this setting PET/MRI, combining functional information with high contrast soft-tissue resolution, may be the key to solve doubt cases. Grueneisen J et al. compared PET/MRI and PET/CT in OC recurrence detection obtaining comparable results for sensitivity and specificity, i.e. 85% and 87% vs. 82%, and 91%, respectively with the advantage to reduce radiation exposure by removing the CT component of PET/CT, especially in patients undergoing serial examinations. Disadvantages of PET/MRI include the high purchase and maintenance costs, and its limited availability. In any case, current evidence strongly supports the use of hybrid imaging with PET/MRI or alternatively with PET/CT instead of conventional imaging for women with suspected recurrence of pelvic cancer [68].

Best imaging strategies according to current guidelines

The primary objective in the appropriate surveillance of OC patients is to provide clinical and cost-effective modalities able to detect recurrence through clear recommendations [69].

In literature, there is a great debate regarding the best strategy to correctly follow-up patients treated for ovarian cancer. A careful collection of history, new and

potentially tumor-related symptoms and clinical examination is essential during follow-up. The evaluation of biological tumor marker (CA125) is also recommended.

Major gynecological and oncological guidelines such as the Society of Gynecologic Oncologists (SGO) [69] and the National Comprehensive Cancer Network (NCCN) [70] suggest the employ of imaging methods only in suspected clinical recurrence and not for surveillance, based on the lack of data to support their routine use.

MR is recommended when a local recurrence is suspected, especially in low-grade tumors and for patients whose CT is contraindicated or when findings are inconclusive. Furthermore, recent studies highlight the feasibility of Whole-Body MRI to improve the depiction of mesenteric/serosal metastatic spreading, compared with CT and FDG-PET/CT.

However, in clinical practice CT and PET–CT remain the best option to follow-up these patients, showing high reproducibility and accuracy according to the American College of Radiology (ACR) [11] and the European Society of Urogenital Radiology (ESUR) [25] guidelines for OC follow-up.

Conclusion

The chronic nature of relapsed ovarian cancer has important implications in the assessment of follow-up strategies and treatment planning for both oncologist and radiologist.

Nowadays, a multimodal approach including clinical examination, serum tumor biomarkers evaluation combined with imaging techniques, seems to be the best strategy to evaluate tumor relapses.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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