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ESUR guidelines: ovarian cancer staging and follow-up

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Abstract *Objective* To design clear guidelines for the staging and follow-up of patients with ovarian cancer, and to provide the radiologist with a framework for use in multidisciplinary conferences. *Methods* Guidelines for ovarian cancer staging and follow-up were defined by the female imaging subcommittee of the ESUR (European Society of Urogenital Radiology) based on the expert consensus of imaging protocols of 12 leading institutions and a critical review of the literature. *Results* Computed tomography (CT) with coverage of the base of the lungs to the inguinal region is regarded as the imaging technique of choice for preoperative staging. Critical diagnostic criteria are presented and the basis for a structured report for preoperative staging is outlined. Following primary treatment for ovarian cancer, clinical assessment and CA-125 are routinely used to monitor patients. For suspected recurrence, CT remains the imaging modality of choice, with positron emission tomography (PET)/CT emerging as the optimal imaging technique for suspected recurrence, particularly in patients with negative CT or magnetic resonance imaging (MRI). *Conclusions* CT is the imaging modality of choice for preoperative staging and detection of recurrence in patients with ovarian cancer.

Keywords Ovary cancer · Ovary neoplasm · Cancer staging · Guidelines · CT

Introduction

Ultrasound is the primary imaging technique in assessment of a suspected adnexal mass [1]. Benign adnexal masses are managed on the basis of symptoms. Staging should only be performed in patients with suspected ovarian cancer and not for indeterminate adnexal masses that may represent cancer. The latter require problem solving by pelvic magnetic resonance imaging (MRI) [2].

Staging is warranted (1) for a complex adnexal mass that is probably malignant or (2) for a non-inflammatory complex adnexal mass with associated ascites.

The goals of preoperative staging of ovarian cancer are:

- Confirmation of a malignant adnexal mass
- Assessment of tumour burden, mapping of the distribution of metastatic disease and diagnosis of possible complications, e.g. bowel obstruction, hydronephrosis or venous thrombosis
- Exclusion of a primary site in the gastrointestinal tract or pancreas whose metastatic spread might mimic primary ovarian cancer

This information will allow an individualised therapeutic strategy to be designed that is optimally the result of a

multidisciplinary consensus [3]. It is recommended that each multidisciplinary team has a clear investigation algorithm [2, 4] (Fig. 1).

CA-125, the currently most commonly used diagnostic tumour marker for ovarian cancer, provides limited information in initial staging but is crucial in monitoring the treated patient. Its interpretation depends on age, level and its dynamics. More than 80% of women with advanced epithelial ovarian cancer, but only 25-50% of women with stage I ovarian cancer, present with CA-125 elevations [5].

As 90% of false positive CA-125 measurements for ovarian cancer occur in premenopausal women, in this age group it is not useful as a single test, but its value is based upon a rise in serial measurements.

CA-125 levels may indicate the likely extent of tumour and therefore the likelihood of successful cytoreductive surgery [6].

Our guidelines were established to recommend the imaging technique of choice for staging ovarian cancer, to provide practical technical recommendations, and to present diagnostic criteria critical for treatment decisions in clinical practice.

Process

The guidelines were developed by consensus, based on expert opinion and following review of current practice among members of the female pelvis subcommittee of the European Society of Urogenital Radiology (ESUR). After reviewing the literature, two authors (R.F., J.A.S.) designed a questionnaire regarding imaging techniques used for staging ovarian cancer. Based on 12 returned forms, drafts of the guidelines for staging ovarian cancer were discussed at subcommittee meetings in 2008 and 2009, and these guidelines were presented at the ESUR meeting in 2009. The authors summarised this proposal after a further literature update.

Guidelines

Primary staging of ovarian cancer

Imaging investigations Multidetector computed tomography (CT) is currently the imaging technique of choice for staging ovarian cancer, because it provides all the required information in a short examination time and is widely available [7]. Furthermore, CT is the investigation of choice for both staging and treatment follow-up, ensuring reproducibility of the results for future comparison.

Although MRI performs as well as CT, it is recommended as a second-line technique for the staging of ovarian cancer [8, 9], for problem solving notably in the pelvis where it has some advantages. The main reasons for only selected use of MRI are the long examination time, and the technical difficulties in covering a large field of view with adequate resolution. Expertise in interpreting abdominal MRI is limited to specialist centres, especially in the distinction of peritoneal/serosal deposits from bowel. Thus MRI is best reserved for problem solving and for staging ovarian cancer in situations where CT is contraindicated. The latter include contraindications to contrast media, renal insufficiency and pregnancy. In pregnancy and in patients at risk of nephrogenic systemic fibrosis (NSF), diffusion-weighted (DW) MRI should be added to assess peritoneal dissemination [10, 11]. In the rare cases of suspected adnexal malignancy at a young age, including adolescents, MRI should be used as the primary staging technique.

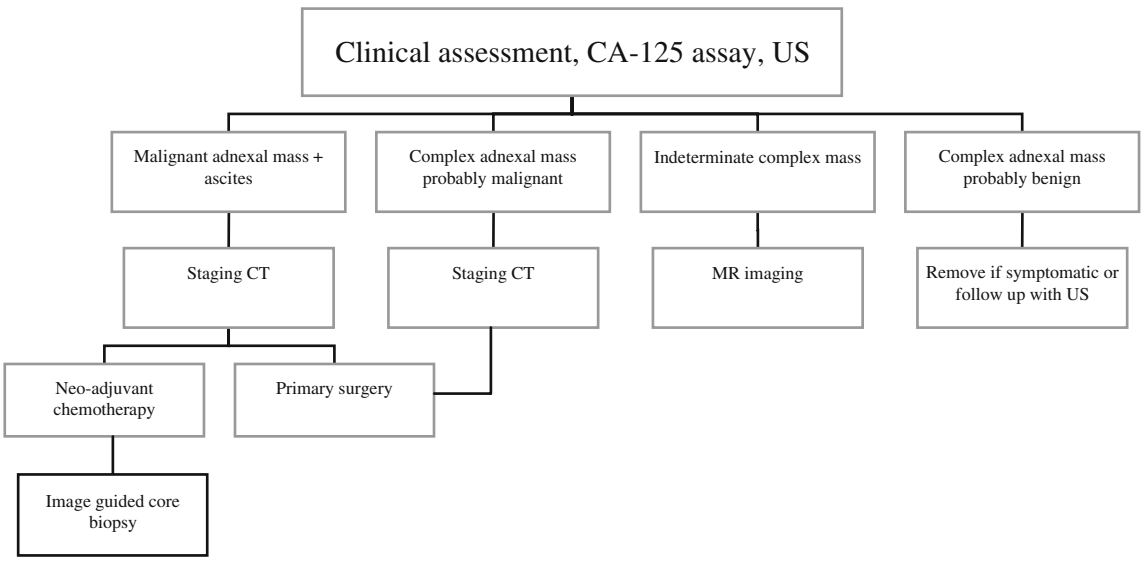

Fig. 1 Algorithm for imaging adnexal masses (modified from [4])

If an adnexal mass displays evident signs of malignancy on an MRI performed for lesion characterisation, complementary sequences of the abdomen for complete staging can be performed in the same session. However, in some institutions this will not be possible because of limited examination time (patient scheduling), and thus CT is performed as a separate staging procedure.

Ultrasound does not provide sufficient information for exact preoperative mapping, as assessment of metastatic implants in the upper abdomen and lymph nodes is inferior compared with CT or MRI [8, 9]. However, ultrasound is useful for image-guided core biopsy (IGCB) [12, 13].

Intravenous urography (IVU) and gastro-intestinal (GI) studies have been replaced by cross-sectional imaging. In the event of suspected bladder or rectosigmoid invasion, histological confirmation by cystoscopy and endoscopy, respectively, may be employed but problem-solving pelvic MRI is also helpful.

The additional benefit of positron emission tomography (PET)/CT over CT alone in the preoperative staging of ovarian cancer is not yet fully established. However, it may improve staging accuracy, particularly by detecting smaller peritoneal/serosal deposits and metastatic lesions outside the abdomen and pelvis [14, 15]. Therefore, PET/CT can be used for the staging of ovarian cancer as an alternative to MRI when there is contraindication to contrast-enhanced CT. It may also be indicated in suspected stage IV disease and in the presence of indeterminate lymph node appearance.

Coverage The coverage for staging ovarian cancer by CT or MRI includes imaging from the distal thorax to the inguinal region [7] (Fig. 2).

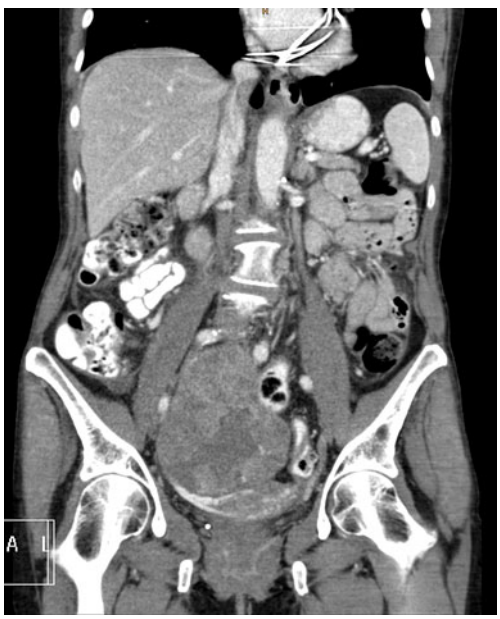

Fig. 2 For staging a patient with suspected ovarian cancer, the volume of coverage should range from the base of the lungs to the inguinal region

Inclusion of the lung bases in the field of view enables assessment of cardiophrenic lymph nodes and pleural effusion [16]. In the latter, cytology should be obtained as only positive findings indicate stage IV disease. Ultrasound-guided aspiration can be helpful in assessing pleural metastasis. In a patient presenting with suprarenal lymphadenopathy or pleural effusion, chest CT, or better still, PET/CT will enable evaluation of mediastinal or supraclavicular lymphadenopathy, if present. In all other cases, routine chest CT does not provide complementary information for staging ovarian cancer.

Radiological reporting As management of ovarian cancer is closely related to stage, comprehensive information of the primary tumour and its dissemination—including tumour burden, relevant sites of spread and details useful for surgery planning—should be provided. A consensus was established regarding the essential elements in reporting. A structured report for preoperative staging of ovarian cancer by CT or MRI is recommended and should include the description of:

- Size, morphology and uni- or bilaterality of the ovarian mass with a statement of whether the mass demonstrates features of malignancy
- Uterine endometrial thickening, bladder, bowel invasion or pelvic side-wall invasion
- Evidence of complications such as bowel obstruction, hydronephrosis or venous obstruction/thrombosis
- Ascites in the pelvis or upper abdomen, and amount of ascites
- Omental metastases
- Site and size of other peritoneal/serosal implants outside the pelvis
- Involvement of the small bowel mesentery including contraction or tethering of bowel loops
- Supracolic sites of disease including the gastrohepatic, gastrosplenic and splenocolic ligaments
- Site of lymph nodes with a short-axis diameter of >1 cm, or suspicious clusters of smaller lymph nodes
- Cardiophrenic lymph nodes with a short-axis diameter of >5 mm
- Surface, subcapsular or parenchymal liver and spleen metastases
- Invasion of the abdominal wall
- Presence and size of pleural effusion
- Stage according to the FIGO/TNM classification (Table 1)

Reporting according to the RECIST criteria is currently only warranted in the case of clinical trials [17] and is unnecessary when planning surgical intervention as the tumour burden after surgery is used as a new baseline for monitoring treatment response.

Multidisciplinary team approach The multidisciplinary team approach has substantially changed management of patients with ovarian cancer. Based on a multidisciplinary consensus, an optimised individualised treatment regimen

Table 1 Staging of ovarian cancer by CT and MRI [39, 40]

TNM	FIGO	Imaging findings	Additional findings in surgical/histopathological staging
T1	*Stage I*	*Tumour limited to the ovaries*	
T1a	IA	Limited to one ovary, no ascites	Intact capsule and no tumour on the external surface
T1b	IB	Limited to both ovaries, no ascites	Intact capsule and no tumour on the external surface
T1c	IC	Stage IA or IB with ascites	With tumour on surface or capsule ruptured, or ascites or peritoneal washings positive for malignant cells
T2	*Stage II*	*Growth involving one or both ovaries, pelvic extension*	
T2a	IIA	Extension and/or metastases to the uterus or/and fallopian tubes	
T2b	IIB	Extension to other pelvic tissues	
T2c	IIC	Tumour either IIA or IIB with ascites	Ascites or peritoneal washings positive for malignant cells
T3 and/or N1	*Stage III*	*Tumour involving one or both ovaries, peritoneal implants (including small bowel and omentum) outside the pelvis including liver surface implants and/or metastases of retroperitoneal or inguinal lymph nodes*	
T3a	IIIA	Tumour grossly limited to the true pelvis, large volumes of ascites	Microscopic implants of abdominal peritoneum
T3b	IIIB	≤2 cm implants of abdominal peritoneal surfaces, large volumes of ascites	
T3c and/or N1	IIIC	>2 cm implants of abdominal peritoneal surface and/or retroperitoneal or inguinal lymph nodes; large volumes of ascites	
M1	*Stage IV*	*Growth involving one or both ovaries, distant metastases, parenchymal liver metastases, pleural effusion with pleural abnormalities*	Pleural effusion with positive cytology

will be provided for patients with newly diagnosed ovarian cancer [3]. This includes appropriate patient selection for primary cytoreductive surgery versus neo-adjuvant chemotherapy, appropriate surgical technique and suitability for image-guided biopsy.

Non-optimally resectable ovarian cancer Cytoreductive surgery is the standard treatment for ovarian cancer. However, some patients may benefit from primary neo-adjuvant chemotherapy. This is a treatment option in patients with medical co-morbidities, stage IV disease, or extensive tumour load. Criteria for "non-optimally resectable disease" are summarised in Table 2 [18] (Fig. 3). However, it is important to realise that these criteria may vary and will depend on the aggressiveness of the surgical procedure and on the performance status of the patient. Therefore, the criteria should only be used as a basis for a multidisciplinary consensus.

Image-guided core biopsy (IGCB) Multidisciplinary discussion can also determine the need for IGCB, which is a safe, minimally invasive radiological procedure providing histology [12, 13]. It may avoid unnecessary surgery and change the treatment regimen. There is no proven risk of tumour seeding along the needle track [12, 13]. IGCB (Fig. 4) (using ultrasound or CT) should replace laparoscopic biopsy in patients with peritoneal carcinomatosis and is indicated:

- Before primary (neo-adjuvant) chemotherapy for ovarian cancer
- When there is a history of a previous cancer from the gastrointestinal (GI) tract, breast, melanoma, lymphoma or other tumours recognised to metastasise to the ovaries and peritoneum
- With an unknown primary site or with multidisciplinary uncertainty about the diagnosis

Table 2 Imaging criteria for predicting non-"optimally" resectable disease in ovarian cancer: non-resectability (modified from [18])

Retroperitoneal presacral disease
Lymph node enlargement above the renal hilum
Abdominal wall invasion
Parenchymal liver metastases and subcapsular liver metastases
Implants of >2 cm: diaphragm, lesser sac, porta hepatis, intersegmental fissure, gall bladder fossa; gastrosplenic, gastrohepatic ligament and small bowel mesentery

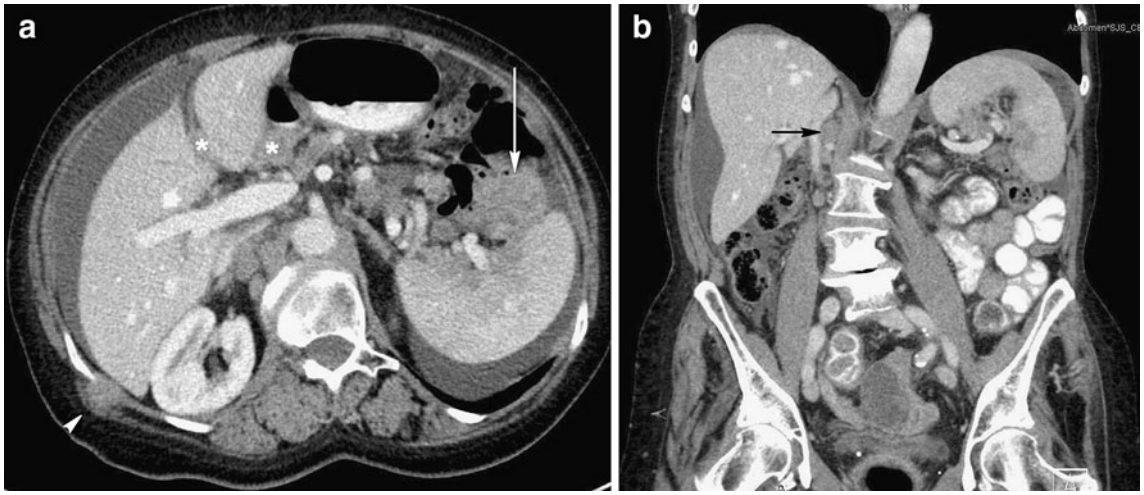

Fig. 3 Extensive peritoneal spread is demonstrated in the upper abdomen in the transaxial (**a**) and coronal planes (**b**). Lesions in the gastrosplenic ligament (with invasion of the spleen) (*arrow*), interhepatic fissure (*), lesser sac (*), and lymph nodes (*black arrow*) above the level of the renal hilum are considered as non-optimally resectable. Because of the chest wall metastases (*arrowhead*) this is stage IV ovarian cancer

Other mimics of ovarian cancer with peritoneal carcinomatosis and ascites include Meig's syndrome, Pseudo-Meig's syndrome and inflammatory conditions including actinomycosis and tuberculosis. Other diseases that occasionally present with peritoneal disease, but without or with only minimal ascites, include endometriosis, leiomyomatosis disseminata, gastrointestinal stromal tumour (GIST) and splenosis [19, 20].

Key features for staging ovarian cancer

- More than 70% of patients with ovarian cancer present with stage III disease
- In cases of suspected ovarian cancer, the presence of ascites in the upper abdomen even without visible metastatic implants is indicative of peritoneal metastasis, and large amounts of ascites are a feature of stage IIIA ovarian cancer [21]. However, a solid adnexal mass, ascites and pleural effusion may also present with a benign condition such as Meig's syndrome
- Ovarian tumours with extensive lymph node metastases at initial diagnosis include undifferentiated ovarian cancer, dysgerminoma and fallopian tube cancer [22]
- Liver parenchymal metastases are almost never present at the time of diagnosis of epithelial ovarian cancer. However, liver surface metastases (Fig. 5) are frequent, and surface metastases with (subcapsular) and without infiltrative growth into the liver (and spleen) should be differentiated as they influence the surgical management [23]
- If pleural effusion is present, cytology must be positive to diagnose stage IV ovarian cancer
- Cardiophrenic lymph nodes larger than 5 mm should be regarded as suspicious for stage IV [16]
- In patients with peritoneal carcinomatosis and elevation of CA-125 without an ovarian mass, extra-ovarian peritoneal carcinomatosis should be considered and other sites within the examination volume, such as stomach, pancreas, colon and appendix, should be scrutinised [24] and IGCB may be informative
- Primary peritoneal cancer may also present peritoneal carcinomatosis without an enlarged ovary and again IGCB should be considered
- In patients with a history of a previous primary cancer from the GI tract or breast, the differential diagnosis should include metastases to the ovaries [25]
- The role of CT staging is to confirm the clinical and ultrasound suspicion of ovarian cancer and to define disease extent in order to plan primary treatment and IGCB where appropriate

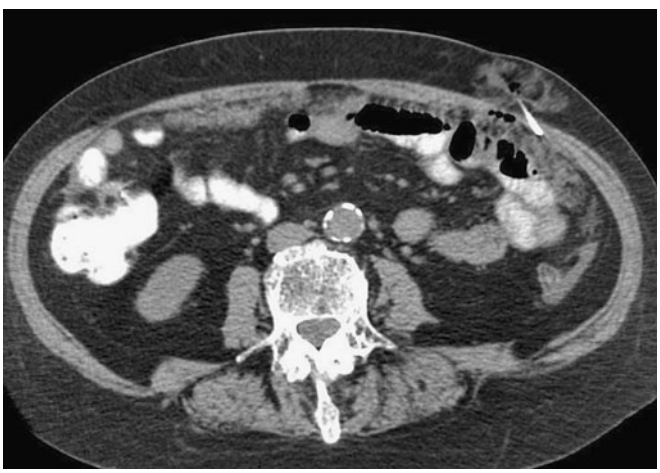

Fig. 4 CT-guided core biopsy of the omentum in a patient with suspected ovarian cancer, peritoneal carcinomatosis, and in poor medical condition. Based upon the histological result of serous papillary ovarian cancer, primary chemotherapy was performed

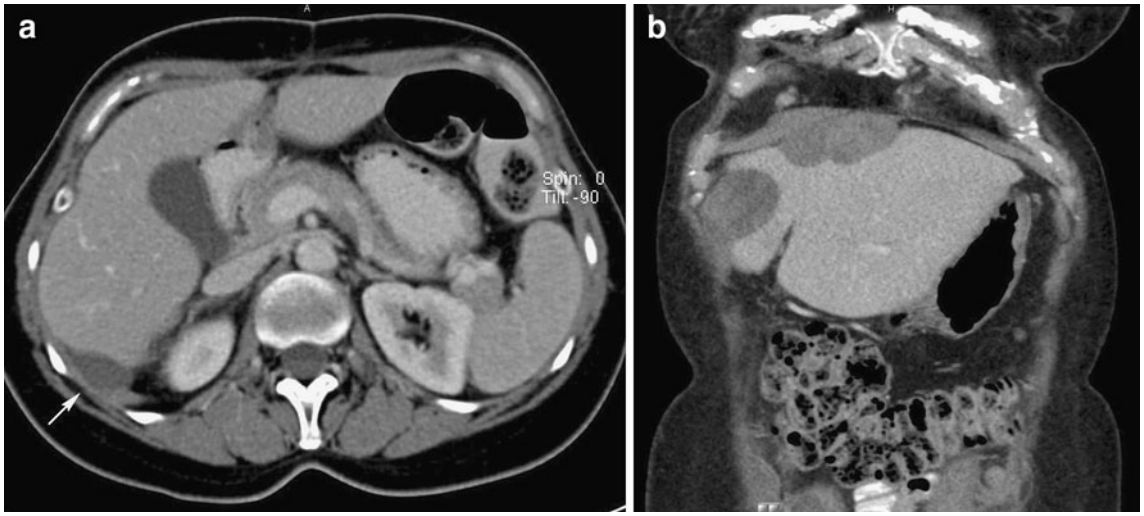

Fig. 5 Perihepatic peritoneal deposits in two different patients with ovarian cancer. **a** A cystic surface lesion impressing the liver surface (*arrow*) with a smooth liver–lesion interface. **b** On the other hand, perihepatic lesions protrude into the liver parenchyma and display ill-defined margins, indicative of infiltrative growth with a subcapsular peritoneal deposit

Staging the treated patient The combination of clinical assessment and CA-125 measurement is routinely used to monitor patients treated for ovarian cancer in many institutions [26]. In this setting, CT is used to evaluate treatment response and to assess suspected relapse with rising CA-125 levels or clinically suspicious symptoms. Rising CA-125 levels may, however, precede clinical recurrence with a median lead time of 3-5 months [26].

CT is reproducible, widely available and well understood. Ultrasound is often used as the initial examination to investigate new symptoms. MRI is reserved as a problem-solving technique to clarify the nature of indeterminate masses on CT. MRI is also particularly useful if there is suspicion of pelvic side-wall invasion or surgical resection of a pelvic recurrence is planned [27].

There are emerging data that PET/CT may help in the assessment of patients with elevated CA-125 but negative imaging findings. PET/CT is useful in assessing persisting ovarian cancer and serves as a complementary imaging technique when CT or MRI findings are inconclusive or negative [28]. Unlike in primary ovarian cancer, in recurrent disease ascites is a less common finding, and more often an indicator of extensive peritoneal recurrence [29].

Preliminary findings of the combined EORTC 55955 and MRC UK OV05 studies have reported no advantage in the treatment of women with raised CA-125 without confirmation of recurrence by standard imaging (CT) and this challenges the need to use sophisticated imaging such as PET/CT to assess such women. Indeed the MRC has already recommended that routine CA-125 assessment in follow-up be viewed as discretionary and subject to informed patient choice [30, 31].

CT should be used in treated patients to:

- Assess the presence of residual tumour following surgery
- Monitor treatment response to chemotherapy, including those patients treated with neoadjuvant therapy before interval debulking surgery (IDS)
- Evaluate the complications of treatment
- Assess the presence of any residual disease at the completion of chemotherapy
- Confirm disease remission
- Assess suspected disease progression or relapse
- Evaluate patients presenting with an acute abdomen, e. g. with bowel obstruction that may be due to either surgical adhesions or to recurrent disease

Coverage Routine chest CT is not indicated, but the lung bases should be included in the CT of the abdomen and pelvis to evaluate for the presence of pleural effusions [32].

Chest CT may be indicated in a patient with unexplained elevation of CA-125, but usually the cause is an abdomino-pelvic tumour beyond the resolution of CT rather than unsuspected bulk disease in the chest and in patients with lymph node metastases [33]. Lung metastases are rare and mediastinal lymphadenopathy without retrocrural, paracardiac or retroperitoneal disease is also unusual.

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Appendix 1

CT imaging technique

Ideally, patients fast for 4 h.

Bowel opacification, usually applied orally with 1,000ml of diluted contrast media or alternatively water 1 h before the CT study, is generally recommended. Water facilitates differentiation of bowel loops from tiny calcifications, but small peritoneal implants may be better visualised with positive opacified bowel loops [34]. Rectal opacification aids in assessing local invasion, particularly in large tumours but is reserved for problem solving. Alternatively, an aliquot of oral contrast medium may be given at 6-8 h before examination to aid colonic opacification. It is taken at bedtime for a morning examination and on rising for an afternoon examination.

The use of intravenous contrast medium is mandatory for staging. A portal venous phase examination (at 70-90s) is suggested, as solid enhancing components and papillary projections in adnexal masses and in implants may be missed in an early phase. The value of a dual-phase (arterial and portal venous) protocol has not been assessed. It may, however, be useful for large adnexal masses [35].

Reformatted images, using 3- to 5-mm slice thickness at 3- to 4-mm intervals in transaxial, coronal and sagittal planes allow assessment of morphology and local extent of ovarian cancer and of peritoneal carcinomatosis. As radiation protection is a concern, techniques with tube modulation and automatic current settings are recommended in imaging of the pelvis in general, and particularly in women with extensive subcutaneous fat [36].

Appendix 2

MRI technique

The use of antiperistaltic agents is recommended to optimise image quality, particularly in assessing peritoneal implants and for diffusion-weighted imaging [37]. Bowel preparation with diluted barium sulphate may be performed, however at the expense of increased imaging time [11]. Imaging sequences include a T1W sequence, T2-weighted (W) sequences of the pelvis in axial, sagittal and coronal planes, and T2W with fat saturation (FS) and T1W with gadolinium and FS for the whole examination field, the latter at least in two planes. Slice thickness should not exceed 6mm in the pelvis and 10mm in the upper abdomen.

DW-MRI seems a new promising technique as it provides a new contrast mechanism in assessing peritoneal carcinomatosis [11]. The optimal *b* value is not yet established and reported *b* values for diagnosing peritoneal implants range from 400-500 to 800-1,000s/mm^2 [38]. DW-MRI combined with conventional imaging sequences seems most accurate for the depiction of peritoneal metastases [11].

Contrast-enhanced MRI should be performed not longer than 10 min after contrast medium application, because contrast medium diffusion into ascites may occur. In patients with renal insufficiency, the use of gadolinium-based contrast media has to be cautiously estimated [10]. In these patients, thin-slice T2W imaging with FS and transaxial DWI will provide depiction of implants at least of more than 1-2cm in size.

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