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PET/CT Variants and Pitfalls in Gynecological Cancers

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The role of hybrid imaging with 2-[18F] flourodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) is continuously evolving and now considered standard practice in evaluation of disease stage, treatment response, recurrent disease and follow-up for numerous primary malignancies. In gynecological malignancies FDG PET/CT plays an important role, not only in the assessment of disease in the pre-and post-therapy setting, but also in radiation therapy (RT) planning by defining the metabolically active gross tumor volume (GTV. The glucose analogue radiotracer, FDG, is by far the most utilized radiotracer in PET/CT and is typically seen with high uptake in malignant cells. The radiotracer FDG has a high sensitivity but low specificity for malignancy, as benign processes with an inflammatory response for example infection, are also FDG-avid. In the evaluation of the female pelvic region an awareness of potential confounding factors in the interpretation of FDG is essential as variations of FDG uptake occur in accordance with the menstrual cycle and the menopausal state. Incidental imaging findings in the female genital can pose differential diagnostic challenges as false-positive and false-negative findings in benign and malignant processes are not uncommon. Gynecological malignancies continue to pose major public health problems with cervical cancer as the fourth most common cancer in women ranking after breast cancer, colorectal cancer and lung cancer. Familiarity with frequently encountered benign and malignant variants and pitfalls in FDG PET/CT in the female pelvic region can aid the reader in differential diagnostic considerations.
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Technical and Physiological Pitfalls

In depth technical and physiological pitfalls in wb FDG PET/CT outside the pelvic region are beyond the scope of this article and well-described elsewhere.[1] In the pelvic region, attenuation correction artifacts are commonly caused by high-attenuation structures as barium-containing contrast in the bowel, hip prosthesis and surgical clips which can potentially mimic disease.[2] Review of non-attenuation corrected images can aide in determining whether FDG uptake in relation to high-attenuating structures represents an attenuation artifact or not. Technical inherent limitations of PET/CT include the relative low spatial resolution (< 1 cm) and the acquiring of the PET and CT scan at different time-points with the possibility of misalignment due to for example patient movement or bowel motility. FDG excretion in the urine can represent potential pitfalls in the pelvic region in case of focal FDG accumulation in the ureters which potentially can mimic lymph node metastasis. Evaluation of peritoneal disease can be compromised by low-spatial resolution, misalignment due to bowel motility and intense physiological FDG uptake, predominantly in the colon, in patients with metformin treatment.[3] Careful correlation with CT can often help to overcome these potential pitfalls.

Normal Variants on FDG PET/CT in Pre-and Postmenopausal Women

An understanding of the normal metabolic and structural changes that occur in the female reproductive tract throughout the life span and periodically during the menstrual cycle

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is essential when interpreting PET/CT images of the female pelvic region. Naturally occurring physiological variations in the female reproductive are mainly due to hormonal influences or lack thereof and consequently most prominent during the reproductive and in the beginning of the post-menopausal years. On PET/CT imaging, typically occurring age-related variations are primarily visible in the uterus and ovaries. In the pre-menopausal woman, with no gynecological disorders, the pattern of FDG uptake in the uterus and ovaries can vary significantly in accordance with the menstrual cycle. The menstrual cycle consists of 4 phases; the menstrual flow phase, the proliferative phase; the ovulatory phase and the secretory phase.[4] Two peaks of potentially increased FDG uptake in the endometrium have been reported to occur in the initial days of menstruation and around ovulation.[4] A normal variation among women has been reported with most intense FDG uptake during menstruation but with lower or no FDG uptake around ovulation.[5] Physiological FDG uptake in the uterus can be intense and distinction between malignant and non-malignant uptake solely based on intensity should be avoided. Increased FDG uptake can be seen in vaginal tampons[6] (Fig. 1). Physiological uptake related to menstruation is uniformly distributed in the uterine cavity with corresponding fluid collection, while FDG uptake due to endometrial malignancy is often focal with various degrees of myometrial invasion and a visible tumor on CT (Figs. 1, 2)

In pre-menopausal women, focal and intense FDG uptake can be observed in the ovaries, usually unilaterally, around the time of ovulation in the late follicular to early luteal phase.[4,7] During the follicular phase one or more ovarian follicles are recruited but only one becomes dominant and ovulates.[8] A follicular cyst is formed if the dominant follicle fails to ovulate. The process of ovulation is thought to yield an inflammatory response which could explain increased ovarian FDG uptake around this time[9]. Physiological ovarian FDG uptake appears typically with a round or a discoid shape with smooth margins (Fig. 1). The corpus luteum is a

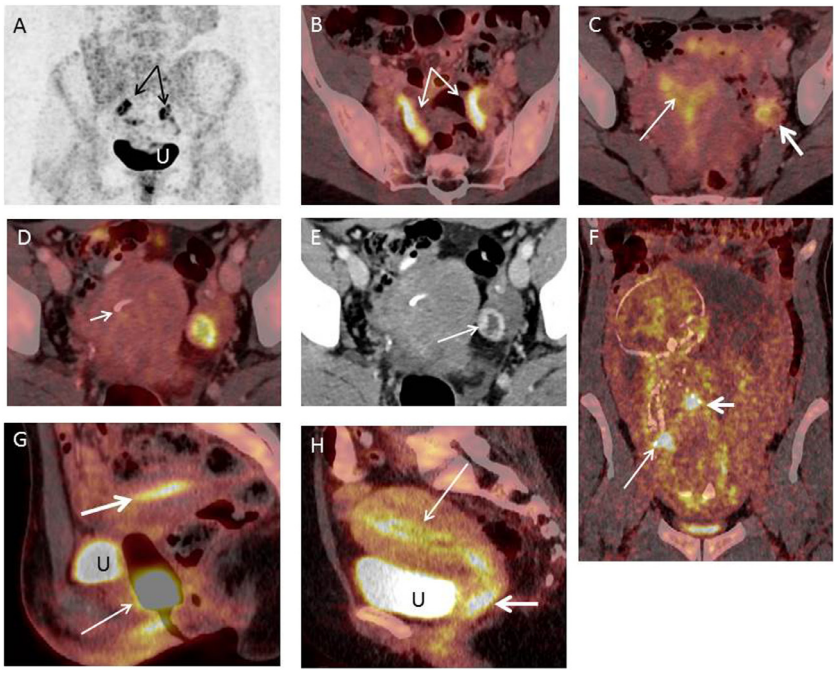

Figure 1 Typical patterns of physiological FDG uptake in the uterus and ovaries in various settings. (A) Maximum intensity projection (MIP) shows characteristic findings of physiological FDG uptake in the ovaries (arrows), the location and symmetrical FDG uptake is consistent with physiological uptake. (B) Fused axial PET/CT shows symmetrical FDG uptake in the adnexa bilaterally. Physiological FDG uptake in the adnexa is usually seen as a discoid shape with smooth margins, unilaterally or bilaterally. (C) Physiological FDG uptake in the uterus, note the uniform FDG uptake along the endometrium with a typical shape of an inverse triangle with a small corresponding fluid collection centrally (arrow). The uniform distribution and lack of focality is highly indicative of benign uptake. (D) Axial fused PET/CT and (E) axial contrast enhanced CT (ceCT) shows FDG uptake in a left sided corpus luteum cyst with peripheral rim-enhancement, "ring of fire" (E, arrow). Part of an IUD is visualized with no FDG uptake in the surrounding tissue (D, arrow). (F) Coronal fused PET/CT image in a 28 weeks pregnant patient scanned for a non-gynecological disease. Physiological high FDG uptake is seen in fetus´heart (bold arrow) and FDG accumulation in the fetus´kidneys (arrow). (G) Sagittal fused PET/CT during the menstrual phase with uniform intense FDG uptake along the endometrium (bold arrow) and FDG accumulation in a vaginal tampon which appears translucent (arrow). Note, FDG accumulation is only seen in the distal part of the tampon which is due to urine contamination. (H) Sagittal fused PET/CT in the post-partum period shows intense FDG-uptake in the uterine cavity (arrow) and cervix (bold arrow); the patient was scanned for a postpartum unrelated disease. U, urinary bladder.

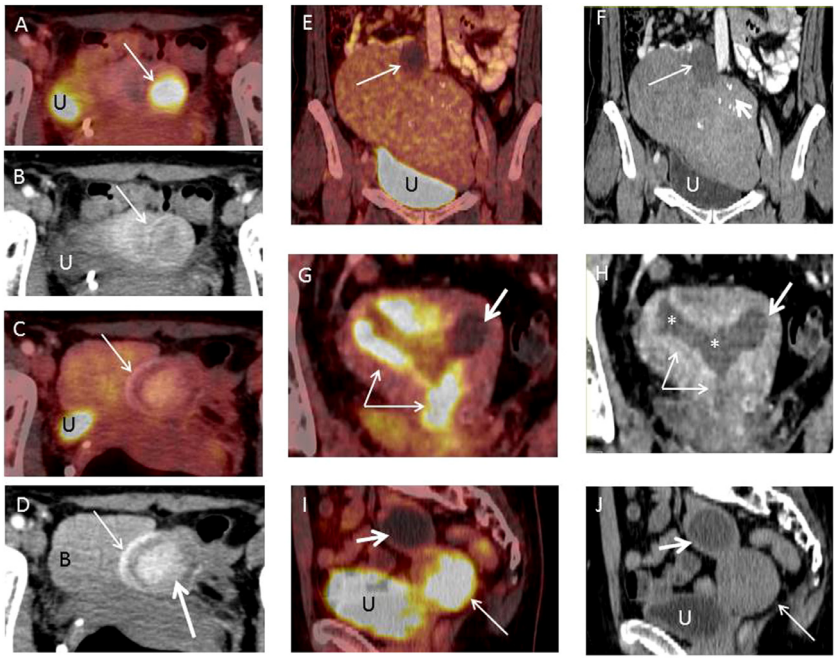

Figure 2 Axial fused PET/CT (A, C) and contrast-enhanced CT (ceCT) (B, D) in a premenopausal 44-year-old woman evaluated repeatedly with PET/CT due to a non-gynecological malignancy. Highly variable FDG uptake can be seen in a known uterine leiomyoma (A, C arrow) accompanied with variable contrast-enhancement on ceCT; with peripheral contrast-enhancement (B, D, arrow) and central contrast-enhancement (D, bold arrow). Variable FDG uptake in the uterine leiomyoma was observed continuously in this patient (not shown). Coronal fused PET/CT (E) and coronal ceCT (F) in a 58-yearl-old woman with a large uterine leiomyoma with calcifications (F, bold arrow) and cystic degeneration (F, arrow). No FDG uptake can be observed in the cystic degenerated part of the leiomyoma (E, arrow). Coronal fused PET/CT (G) and coronal ceCT (H) in a 46-year-old woman with biopsy-verified uterine serous adenocarcinoma. PET image shows intense FDG uptake in several parts of the uterus and involvement of the cervix by direct extension (G, arrows). On ceCT contrast-enhancement can been seen in the corresponding parts of the endometrium with variable degrees of myometrial invasion (H, arrows). Asterisk (*) indicates secondary uterine fluid collection due to cervical obstruction. The tumor was surgically removed. The cyst-like non FDG-avid lesion in the left side of the uterus represented a leiomyoma (G, bold arrow; H, bold arrow). Sagittal fused PET/CT (I) and ceCT (J) in a 66-year-old woman with high-grade uterine sarcoma. Intense FDG-uptake is seen in the uterine tumor (I, arrow) and ceCT shows a solid tumor (J, arrow) giving the uterus an hour-glass shape. No FDG uptake in the uterine fluid collection (I, bold arrow) seen on ceCT (J, bold arrow). B, bowel segments; U, urinary bladder.

remnant of the mature follicle that undergoes hypertrophy and vascularization and serves as a temporary gland that involutes and disappears by the end of the cycle if no pregnancy occurs.[8] The corpus luteum is thus visible during the secretory phase, if the corpus luteum fails to regress beyond this time a fluid-filled corpus luteum cyst is formed. The corpus luteum cyst can persist for several months and is recognized as a small round cyst in the adnexa with intense FDG uptake and contrast enhancement of the cystic wall, commonly called "ring of fire" (Fig. 1).

In women using an intrauterine contraceptive device (IUD) no or uniform mild FDG uptake in relation to the IUD, outside the menstrual and ovulatory phase, is likely to be of physiological origin.[7] The two most common types of IUD's, hormone-releasing and copper, are both T-shaped radiopaque devices with diverse underlying mechanisms.[10] While the hormone-releasing IUD reduces and/or stops menstrual bleeding and occasionally ovulation, the copper IUD can increase menstrual bleeding. Both IUD types trigger a local inflammatory response by releasing copper ions which is part of the contraceptive effect and the primary action of the copper IUD.[11] This local inflammatory response is believed to cause, the occasionally seen, mild FDG uptake in relation to the IUD.[12,13] The usage of oral contraceptives do not significantly alter the endometrial FDG uptake compared with pre-menopausal women not ovulating nor menstruating.[4]

The natural menopause is defined as absence of menstruation for twelve consecutive months and occurs around the age of 50 years.[14] The hormonal changes that occur in the post-menopausal age result in gradual diminishing of physiological FDG uptake, along with progressive volume reduction of the reproductive organs.[15,16] In the advanced post-menopausal years physiological FDG uptake is normally not seen in the uterus or ovaries.[4,7,17] However, during the first years of the menopause some physiological FDG uptake can still be observed in the endometrium, which supports the concept that the endometrium enters a quiescent state during this time.[4,18] Hormone replacement therapy has not been shown to affect endometrial FDG uptake in post-menopausal

women.[4] Endometrial FDG-uptake in patients with amenorrhea resemble that in postmenopausal women whilst women with oligomenorrhea have high FDG uptake, with values resembling those at mid-cycle.[4]

A limited numbers of case studies have reported the pattern of FDG uptake in pregnant women with fetus in utero.[19,20] In normal pregnancy, the uterus is usually seen with mild physiological FDG uptake and the pattern of FDG uptake in the fetus can vary inadvertently depending on the gestational age[19,20] (Fig. 1) Physiological intense FDG uptake in the uterus and cervix can be seen in patients who have recently given birth[21] (Fig. 1).

As means to minimize the possibility of misinterpretation in the female pelvic region due to physiological FDG uptake, it has been proposed to correlate imaging with the menstrual cycle. Hence, imaging should optimally be scheduled within a week before or few days after menstruation.[7] Although this could be feasible for healthy women with a regular menstrual cycle, menstrual irregularities are common among clinical patients with known or suspected malignancy, hence, such approach is not always practical in clinical practice.[4,17,22]

Uterus

Leiomyomas, or fibroids, predominantly originate from myometrial smooth muscle tissue and represent the most common benign solid uterine neoplasms with a lifetime incidence of 70 %.[23] Leiomyomas are partly hormone-dependent and most prevalent in pre-menopausal women.[23] Uterine leiomyomas are a common incidental finding on PET/CT and represent a potential pitfall in differentiating between benign and malignant FDG-uptake in the uterus.[24] FDG uptake in leiomyomas can vary considerably in pre-and postmenopausal women but abnormal FDG uptake is more frequently seen in pre-menopausal women.[25-27] Usually multiple, leiomyomas range in size from a few millimeters to 20 cm in diameter or more, often with areas of necrosis, calcification and hemorrhage.[23] FDG uptake in leiomyoma can vary during the menstrual cycle with higher FDG uptake in the proliferative phase[26] (Fig. 2). Importantly, novel focal FDG uptake or increasing FDG uptake in a pre-existing leiomyoma is commonly seen and does not necessarily signal malign transformation; still, rare cases of malign transformation to leiomyosarcoma demonstrated on PET/CT have been described.[26,28] Nonetheless, sarcomatous transformation in a preexisting leiomyoma is exceedingly rare with an estimated incidence of 0,13%-0,29%.[29] Though often asymptomatic, approximately 30 % of women with uterine leiomyoma develop at one point symptoms of vaginal bleeding, palpable pelvic mass or pain that can be suggestive of gynecological malignancy.[23] Malignancies in the uterine body include carcinomas, with endometrial carcinoma being the most common (≈90%), and different forms of very rare and often aggressive uterine sarcomas.[30,31] Uterine carcinoma and sarcoma are generally seen with intense FDG uptake; however, the highly variable FDG uptake in leiomyomas makes it particularly hard to reliably differentiate from uterine sarcoma.[24,32] Leiomyosarcoma is the most frequent uterine sarcoma but compromises only 1 % of all gynecological malignancies.[33] Leiomyosarcoma is often seen as a large heterogeneous mass with internal areas of necrosis which can resemble degenerated uterine leiomyoma, both with areas of necrosis and occasionally intense FDG uptake.[24,25,32] Uterine fluid collections in post-menopausal women can be associated with benign cervical stenosis or malignancy.[34] In pre- and postmenopausal women increased endometrial FDG-uptake has been reported in the presence of uterine fluid collection secondary to cervical stenosis, benign or malignant, but with no malignancy present in the endometrium.[4] Thus, in patients with known cervical cancer endometrial FDG uptake may be increased secondary to stenosis and uterine fluid collection and does not necessarily represent extension into the uterine body.[4]

Benign endometrial polyps are frequently encountered in clinical practice with an increased prevalence in women treated with Tamoxifen and have in a case report been described with no abnormal FDG uptake on PET/MRI.[35] Adenomyosis is a common benign gynecological disease in women of reproductive age and is characterized by the presence of diffuse or focal ectopic endometrium within the myometrium.[36] Only few case reports have described the FDG PET/CT appearance of adenomyosis with reported variable FDG uptake ranging from mild to high.[24,37]

Endometrial hyperplasia is an abnormal proliferation of endometrial stroma and one of the most frequent causes of abnormal uterine bleeding.[38] Endometrial hyperplasia is primarily seen in postmenopausal women and women at any age treated with any form of unopposed estrogen stimulation, for example Tamoxifen.[39] It can be divided in non-atypical and atypical endometrial hyperplasia with the latter acting as a potential precursor of endometrial carcinoma[38]. In one study, biopsy proven atypical endometrial hyperplasia with concurrent endometrial carcinoma was shown in as many as 42, 6% of the patients.[40] Endometrial hyperplasia has mainly been described with no or mild FDG uptake.[24,41,42] This further emphasizes that endometrial FDG-uptake in post-menopausal women or abnormal FDG uptake in women with estrogen treatment is of clinical significance and warrants further investigation.

Cervix

Cervical cancer is the fourth most common cause of cancer incidence and mortality in women worldwide and the most common gynecological malignancy in the western world.[43] Persistent human papillomavirus infection (HPV) is the main cause of cervical cancer.[44] The most common histologic type is squamous cell carcinoma that represents around 80% of cervical carcinoma followed by adenocarcinoma.[45] Other, rare histologic types include adenoma malignum,

neuroendocrine tumors and cervical sarcoma.[31] Cervical cancer, regardless of histologic subtype, is usually FDG-avid.[46,47] Benign cystic cervical lesions are common and include; endocervical hyperplasia, nabothian cysts and uterine cervicitis with retention cysts.[48] Nabothian cysts are formed by obstruction of the endocervical glands, are usually small (<1 cm), single-or multicystic lesions.[49] Herein, we present the FDG PET/CT appearance of conglomerated nabothian cysts in a patient with endometrioid carcinoma with no abnormal FDG uptake in relation to the nabothian cysts (Fig. 3). Benign cystic lesions with FDG uptake due to inflammation/infection such as uterine cervicitis can be difficult to differentiate from the very rare adenoma malignum which share similar imaging findings with high FDG uptake and multiocular cysts in the cervix.[46,50] Adenoma malignum, or minimal deviation adenocarcinoma, is a rare form of cervical cancer (< 1%) with poor prognosis due to early dissemination.[50] Benign solid masses of the cervix include endocervical polyps and cervical leiomyomas.[51] Endocervical polyps are a common cause of intermenstrual bleeding with a low prevalence of malignancy.[52] Cervical leiomyomas are rare with a reported incidence ranging from 0,6% to 10 % of all uterine leiomyomas and share similar imaging features as their counterpart in uterus.[28,48,51,53] Noteworthy, solid masses in the endocervical canal can originate from the uterine body by direct extension of malignancy or as prolapsed intracavitary masses, that is, leiomyomas.[51]

Ovary

Ovarian cancer is the third most common gynecological malignancy and the second most fatal with highest incidence in the age group 50-59 years.[54] The majority women (> 70%) have at the time of diagnosis advanced-stage disease, International Federation of Gynecology and Obstetrics (FIGO) III or IV, which contributes to the comparatively high mortality rate.[55] Ovarian cancer in an advanced stage carries a poor prognosis with a 5-year survival rate of 17,9% for stage IV disease.[55] As ovarian masses are common among pre-and postmenopausal women, reliable imaging and laboratory tools in differentiating between benign and malignant lesions are desirable in order to avoid redundant surgery. This is especially true for adnexal masses as they are frequently encountered in women with complaints of pelvic discomfort and a common incidental finding in asymptomatic women on imaging.[56] Familiarity with specific imaging features that may be present in some types of ovarian tumors is helpful when evaluating the likelihood of a tumor being benign or malignant. Importantly, CT and MRI imaging

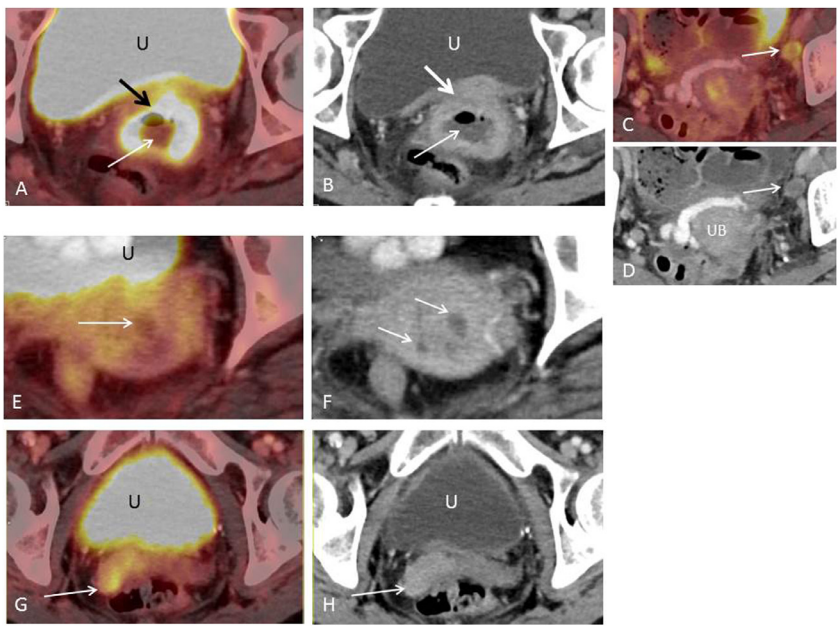

Figure 3 Axial fused PET/CT (A) and contrast-enhanced CT (B) in a 52-year-old woman with squamous cell carcinoma in the cervix. Intense FDG uptake is seen in large cervical tumor (A, bold arrow) with central photopenia as a sign of necrosis (A, arrow). There is a hyperdense tumor with contrast-enhancement (B, bold arrow) and central hypodensity (B, arrow) consistent with central necrosis. Metastasis can be seen along the iliac externa vessels on the left side with an enlarged, partly necrotic lymph node (D, arrow) with low FDG corresponding to the necrotic area (C, arrow). Necrotic primary tumors and metastasis can be a potential pitfall on FDG PET/CT due to low/none FDG uptake in the necrotic tissue. Axial fused PET/CT € and ceCT (F) in a 53-year-old with known endometrioid adenocarcinoma (not shown). The patient was treated with a complete hysterectomy and histology showed a conglomerate of nabothian cysts in the cervix (F, arrows) who appeared with no FDG uptake (E, arrow). Axial fused PET/CT (G) and ceCT (H) in a 67-year old woman with primary squamous cell carcinoma in the vagina located in right vaginal fornix. Intense FDG uptake is seen (G, arrow) in a contrast-enhanced solid tumor in the right vaginal fornix (G, arrow). UB, uterine body; U, urinary bladder.

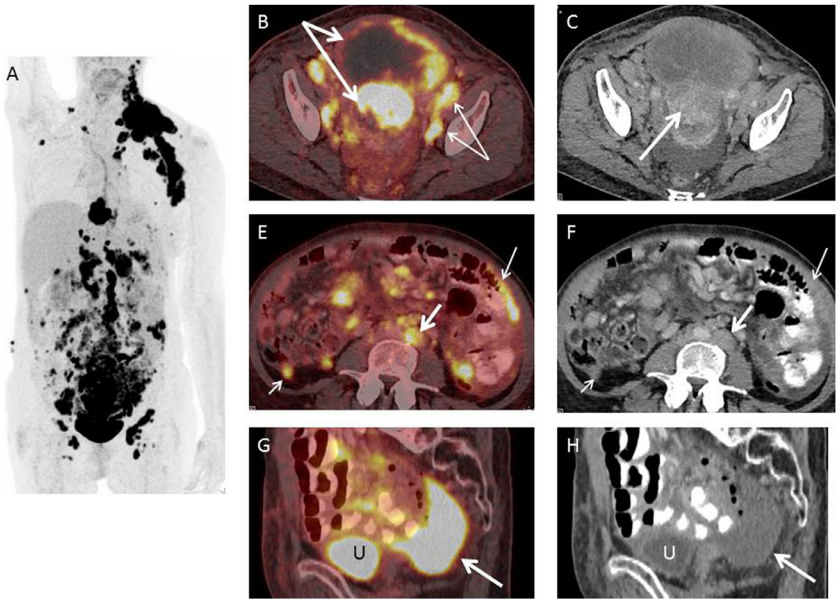

Figure 4 Imaging findings on FDG PET/CT in a 68-year−old woman with newly diagnosed high-grade serous adenocarcinoma, FIGO IV (HGSC). Maximum intensity projection (MIP) (A) shows extensive dissemination with countless foci with intense FDG uptake, corresponding to lymph nodes in all lymph nodes stations above and below the diaphragm and wide-spread dissemination in the peritoneal cavity. Axial fused PET/CT (B) and contrast-enhanced CT (ceCT) (C) shows malignant part-solid part-cystic tumour consistent with HGSC. The solid components are seen with intense FDG uptake (A, bold arrow) with contrast-enhancement on ceCT (C, bold arrow). Intense FDG uptake can be seen in lymph node metastasis in the retroperitoneum (B, arrows; E, bold arrow; F, bold arrow). Diffuse omental thickening and nodular peritoneal thickening (F, arrows) with intense FDG uptake (E, arrows). Sagittal fused PET/CT (G) and ceCT (H) in another patient with HGSC who had intense FDG uptake in the peritoneal ascites (G, bold arrow; H, bold arrow). U, urinary bladder.

features of ovarian neoplasms often overlap and lack specificity.[57-59] The diagnostic accuracy improves with the addition of the functional information obtained by FDG PET in diagnosis and staging of ovarian cancer, but not without possibility of false-positive or false-negative findings[60,61] (Fig. 5).

Epithelial Ovarian Tumors

Primary ovarian neoplasms can broadly be classified as epithelial tumors, germ cell tumors and sex cord-stromal tumors. The overwhelmingly majority of malignant ovarian neoplasms (>90) are of epithelial origin, specifically high-grade serous carcinoma (HGSC).[62] Epithelial carcinoma is nearly synonymous with the term “ovarian cancer” which is also encompasses tumors that arise from the fallopian tubes and peritoneal surfaces.[63] In fact, most ovarian cancers are thought to originate outside the ovary that is, the fallopian tubes.[64] Ovarian epithelial tumors are subdivided into benign, borderline or malignant.[62] Epithelial carcinoma arise from the epithelium surface and are classified according to cell type as; high grade serous (70%), endometrioid (10%), clear-cell (10%), mucinous (3%) and low-grade serous carcinoma (<5%).[65] Serous and mucinous tumors are often benign while endometrioid and clear-cell tumors are nearly always malignant.[65] Benign serous cystadenoma is the most common ovarian neoplasm.[66] Serous cystadenomas are usually; thin-walled (<3mm), simple unilocular cyst with no solid components, no mural nodularity or thickened septa and are frequently bilateral.[58] Benign mucinous cystadenoma share similar imaging characteristics as serous cystadenomas but tend to be larger, multiocular and unilateral[58](fig). Benign serous and mucinous cystadenomas are usually seen with no/mild FDG uptake in the interior and/or margins of the cysts with significant differences in FDG uptake measured as SUV_{MAX} between malignant and benign ovarian tumours[67] (Fig. 5).

Patients with HGSC commonly present with advanced stage disease, FIGO stage III-IV, with intra-and/or extra abdominal dissemination[55,68] (Fig. 4). Less than 20% are diagnosed as Stage I with disease confided to one or both ovaries.[55] At the time of diagnosis the tumor has often locally advanced by direct extension, with encasement of the internal genital and neighboring organs.[69] Early peritoneal involvement with ascites and widespread dissemination within the peritoneal cavity is often seen, with high propensity for omental involvement[69] (Fig. 4). Detached tumor cells are transported within the peritoneal cavity by the circulating peritoneal fluid and implant on peritoneal surfaces, most commonly; in the pouch of Douglas, paracolic gutters, small bowel mesentery, ileocecal junction and on the diaphragmatic surface particularly in the right subphrenic space.[70] The right hemothorax can be involved due to its communication with the right subphrenic space.[70] If ascites is present, high FDG accumulation within the ascites fluid can be observed (Fig. 4). Detection of peritoneal involvement is imperative in staging and management of ovarian cancer. A

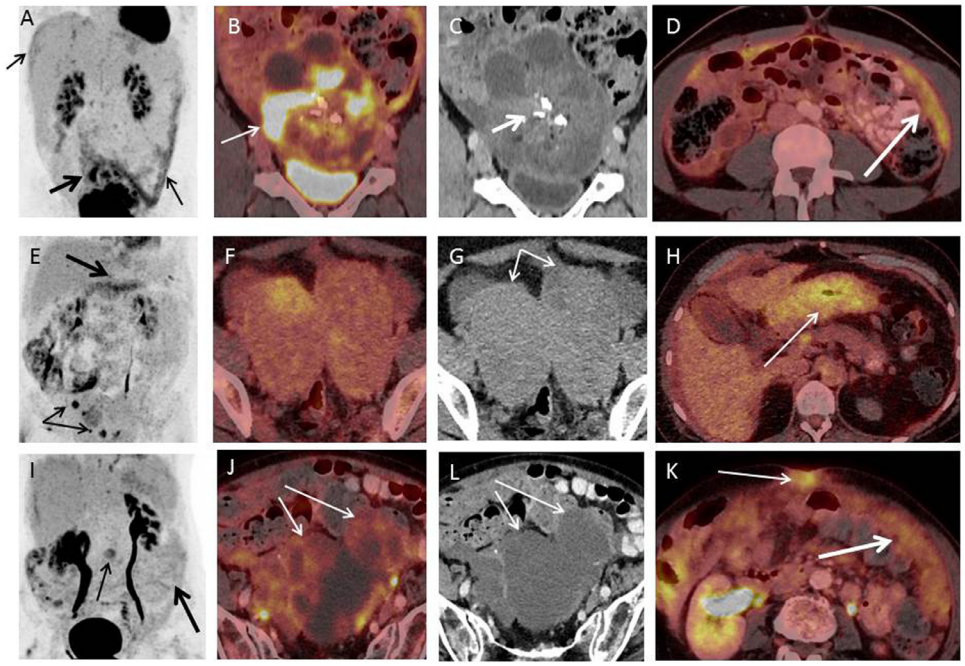

Figure 5 Maximum intensity projection (MIP(A), fused coronal PET/CT (B), coronal contrast-enhanced CT (ceCT)(C) and axial fused PET/CT (D) in 29-year-old woman referred to a PET/CT on the suspicion of disseminated ovarian carcinoma. MIP shows several foci with FDG uptake in the pelvic region (A, bold arrow) and diffusely on the liver surface and along the left paracolic gutter (A, arrows). A complex solid-cystic mass is seen with variable FDG uptake (B, arrow). Teeth formation can be seen centrally in the pelvic mass (C, bold arrow). There is thickening of the greater omentum with FDG uptake (D, bold arrow). Surgery confirmed a left sided ovarian tumor. Histologic diagnosis showed mature teratoma with small lesions of immature teratoma and containing, among other, tissue derived from the cerebellum. Histology from the peritoneum and greater omentum showed mature glia cells consistent with Gliomatosis peritonei. MIP (E), axial fused PET/CT (F), axial non-ceCT (F) and axial fused PET/CT (H) in a 52-year-old woman with disseminated stomach cancer (E, bold arrow; H, arrow). Bilateral ovarian metastasis, Krukenberg tumors (G, arrows) are seen with variable FDG with some areas of intense FDG-uptake (E, arrows). MIP (I), axial fused PET/CT (J), axial ceCT (L) and axial fused PET/CT (K) in a 60-year-old woman with high grade mucinous neoplasia of the appendix with ovarian metastasis (J, arrows). A complex predominantly cystic multiocular tumor is seen with contrast-enhancement I the periphery and thickened septa (L. arrows). Thickened greater omentum (K, bold arrow) and a periumbilical mass (K, arrow), sometimes referred as a sister Mary Joseph nodule, is seen. Imaging and surgical findings were consistent with pseudomyxoma peritonei.

recent meta-analysis reported a pooled sensitivity and specificity of 92% respectively 85% for FDG PET/CT in the detection of peritoneal disease which was comparable with the performance of MRI.[71] False-negative findings are mainly due to low spatial resolution on both CT and PET; subcentimeter lesions are not always detectable on PET even in the presence of military or diffuse peritoneal disease on CT.[72] Common sites for intra-abdominal metastasis include (by order of frequency); peritoneum, para-aortic lymph nodes, colon, pelvic lymph nodes and liver.[73] Frequent metastatic extra-abdominal sites include; lung, pleura, thoracic lymph nodes and skin.[73]

Imaging findings suggestive of HGSC include; (a) lesion diameter > 4 cm; (b) papillary projections; (c) walls and septa more than 3 mm thick; (d) a partially cystic, partially solid mass; (e) a lobulated solid mass.[59] On PET/CT the solid components are typically seen with pathological FDG-uptake[67,74,75](Fig. 4).

Mucinous neoplasms of the ovary represent 10-15% of all ovarian tumors, 80% of these are benign.[65] A characteristic feature of mucinous neoplasms is the accumulation of gelatinous fluid, mucin. At presentation these tumors are typically large (> 10 cm), multioculated and unilateral.[58,76] Mucinous cystadenocarcinoma is rare but contradictory to HGSC often diagnosed at an early stage. False negative findings on FDG-PET/CT can be attributed to tumoral low-cellularity and abundance of mucin.[77] Pseudomyxoma peritonei (PMP) is a rare entity characterized by progressive accumulation of mucinous ascites in the peritoneal cavity. PMP is associated with mucinous tumors in the gastrointestinal tract, especially the appendix, with secondary involvement of the ovaries[71] (Fig. 5). FDG PET/CT has been reported to be valuable in the pre-operative staging of high-grade PMP.[72] When presented with bilateral ovarian tumors suspicious to be of mucinous origin, one should consider the possibility of metastatic disease, especially from the gastrointestinal tract.[61] Krukenberg tumors are the most common subtype of ovarian metastasis and are histologically characterized by signet ring cell mucinous features.[73] Krukenberg tumors are frequently bilateral and predominantly affect pre-menopausal women

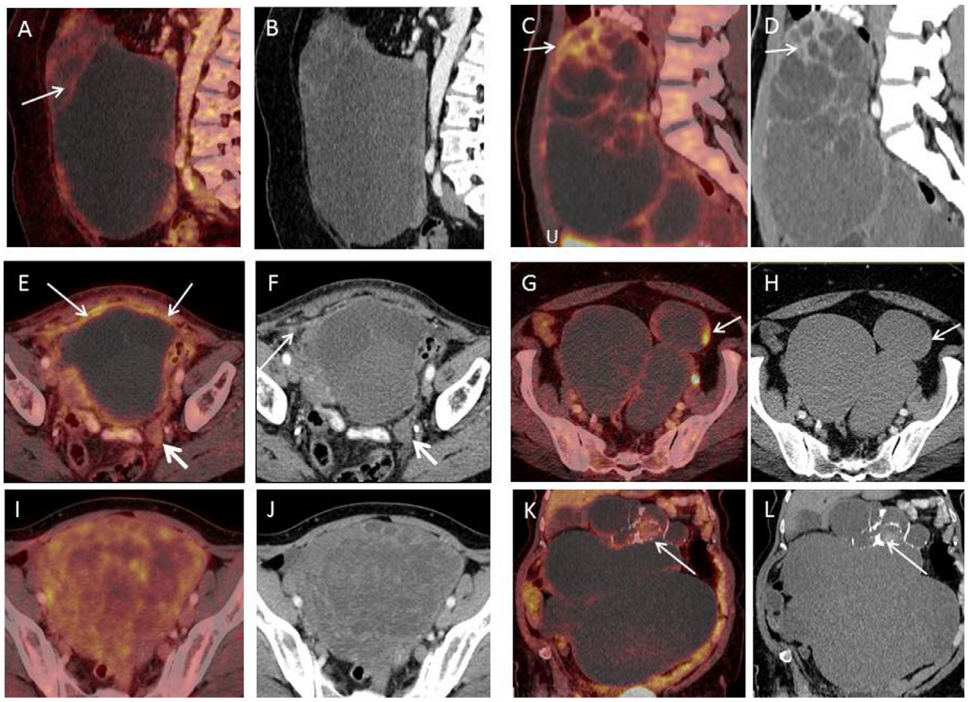

Figure 6 Sagittal fused PET/CT (A) and contrast-enhanced CT (ceCT) (B) in a 57-year-old woman with a large cystic mass on ultrasonography. PET/CT showed a multiocular cyst with mild FDG uptake in the wall of the conglomerated small cysts (A, arrow). Surgery and histology showed a unilateral mucinous borderline tumor. Sagittal fused PET/CT (C) and ceCT (D) in a 20-year-old woman with a large pelvic mass. PET/CT showed a large unilateral and multiocular cyst with intense FDG uptake (C, arrow) corresponding to contrast-enhanced and thickened cystic walls in the upper part of the tumor (D, arrow). Surgery and histology showed mucinous adenocarcinoma originating from the left ovary with no sign of dissemination. Axial fused PET/CT (E) and ceCT (F) in a 74-yeal old woman with a pelvic mass. A large cystic tumor with intense FDG uptake in the surrounding fat I seen (E, arrows). On ceCT the FDG uptake is localized to uniformly, thickened peritoneum and adjacent fat stranding (F, arrow). The findings were consistent a benign right-sided ovarian cyst with surrounded by inflammation. Histology showed torsion of benign serous cystadenoma with s hemorrhagic infarction and necrosis. Histology also showed a small benign Brenner tumor in the left ovary (E, F, bold arrow). Axial fused PET/CT (G) and ceCT (H) in a 62-year-old woman with bilateral ovarian serous borderline tumors. The tumors are predominantly cystic; however, there is a small area with intense FDG uptake in one of the cysts (G, bold arrow) which was not readily identified on ceCT (H), arrow). The tumor was reported as suspicious of malignancy. Axial fused PET/CT (I) and ceCT (J) in a 49-yeal-old woman with malignant granulosa cell tumor in the left ovary. PET shows variable FDG uptake but predominantly low (I) in a part-solid part cystic tumor (J). Coronal fused PET/CT (K) and ceCT (L) in a 86-yeal-old woman with a very large multicystic tumor that proved to be a monodermal mature teratoma composed solely of thyroid gland cells, a struma ovarii. The tumor is seen multicystic with calcifications (L, arrow). Mild FDG uptake was seen in relation to calcifications which could be due to a local inflammatory response. The tumor was reported as not suspicious of malignancy.

with dismal prognosis[73]. Depending on the primary site, ovarian metastasis is seen with variable FDG-uptake from mild to intense and can be of cystic or solid type[74] (Fig. 5). Ovarian metastasis can also ensue by direct extension of tumors in adjacent organs which can be difficult to distinguish between primary and metastatic ovarian disease (Fig. 5).

Serous and mucinous borderline tumors are the most common subtype of borderline epithelial neoplasm. Borderline tumors commonly affect a younger population, are relatively uncommon with excellent prognosis, though, few experience progressive disease. Generally, these tumors are regarded with low-malignant potential due to the absence of stromal invasion. Peritoneal seeding in serous borderline tumors is referred to as implants which are further divided into non-invasive or invasive. Lymph node involvement is also relatively common.[78] Borderline tumors share similar imaging findings as their malignant counterparts, serous borderline tumors more often involve both ovaries compared to mucinous borderline tumours[58,66,78] (Fig. 6). FDG PET CT has a low diagnostic value in differentiating between benign and borderline tumors as these tumors can appear with no or low FDG-uptake, yielding false-negative results.[74,75] Borderline tumors are, therefore, seldom diagnosed pre-operatively due to the lack of distinguishing imaging features.[79]

Endometrioid and clear cell carcinoma are almost always invasive and malignant.[65] These tumors are usually highly FDG-avid with non-specific imaging findings on CT, often appearing as a large complex cystic mass with solid components[58] fig). Both subtypes are also highly associated with

endometriosis.[80] Brenner tumors are uncommon epithelial −stromal neoplasms that represent 2%-3% of all ovarian neoplasms[81]. These tumors are rarely malignant, usually small (< 2cm) and often detected incidentally.[58] Imaging features include a multiocular cyst with solid components often containing calcifications and with variable FDG-uptake depending on subtype (benign, borderline, malignant) with most benign Brenner tumors displaying mild FDG-uptake[82] (Fig. 6).

Ovarian cystadenofibroma is a benign tumor of epithelial and stromal origin that can mimic a malignant lesion due to the presence of solid components. FDG PET/CT can be valuable in distinguishing various types of ovarian fibromas from malignant lesions.[74]

Nonepithelial Ovarian Tumors

Germ cell tumors are a heterogeneous group of tumors that arise from the primordial germ cells of the embryonic gonad.[83] This group includes benign mature teratoma (dermoid cyst) which is the second most encountered ovarian neoplasm, while other tumors in this group (dysgerminoma, choriocarcinoma, embryonal carcinoma) are malignant and very rare.[58,66] Mature teratomas primarily affect younger women (20-40 years of age) of whom the majority are asymptomatic at diagnosis.[83] Mature teratomas are composed of mature tissue from at least two of the three germ cell layers. These tumors are usually unilocular, filled with sebaceous material and contain various tissues such as teeth, hair follicles and bone.[83] A Rokitansky nodule, or dermoid plug, is a characteristic feature of mature teratoma which constitutes a solid intra-cavitary protuberance that typically contains hair, bone or teeth.[83] Malignant transformation is uncommon, as is primary malignant immature teratoma.[83,84] Mature cystic teratomas can be seen with variable FDG-uptake depending on the tissue present. Intense FDG-uptake can be seen in tumors containing an abundance of CNS tissue, which can represent a potential pitfall when distinguishing between mature and immature teratomas.[85] Gliomatosis peritonei is a rare condition characterized by the presence of peritoneal implants predominantly composed of mature glial tissue. Gliomatosis is often associated with immature or mature teratoma.[86] On FDG-PET/CT this condition can be easily misinterpreted as an ovarian cancer with peritoneal involvement due to the inherent high FDG-uptake in glial cells (Fig. 5). In contrast to mature teratomas, monodermal teratomas are solely composed of a single tissue type, the three main types are; struma ovarii (thyroid tissue), ovarian carcinoid tumor and tumors with neural differentiation[84](-Fig. 6). Malignant struma ovarii is exceedingly rare and extra-ovarian spread even rarer.[87]

Sex Cord-Stromal Tumors

Sex cord-stromal tumors are derived from the mesenchymal cells of the embryonic gonads or cells from the primitive sex cords and represent around 8% all ovarian neoplasm.[88] Granulosa cell tumor is the most common malignant tumor in this group and can be classified as juvenile or adult type of which the adult type represents 95% of all granulosa tumors. These tumors are derived from sex cords cells in the ovary, and as such, can produce estrogen.[88] Granulosa cells tumors have a wide spectrum of imaging findings on CT, ranging from predominantly solid to completely cystic tumors, occasionally associated with enlargement of the uterus due hyperestrogenemia.[58,89] Granulosa cell tumors are considered low-malignant and known to cause false-negative findings on FDG-PET[90,91](Fig I). However, there are case reports with reported high FDG-uptake in primary granulosa cell tumors with metastasis.[89,91]

Metastatic Ovarian Tumors and Lymphoma

Secondary tumors of the ovaries account approximately 10%-30% of all ovarian malignancies.[92] The most common primary site in the genital region is the uterine body and cervix while nongenital primaries stem predominantly from the gastrointestinal tract (colon, stomach appendix) and breast, including the aforementioned Krukenberg tumors.[92-94] Lymphoma in the ovaries is most usually part of a systemic disease rather than a primary site.[57]

In conclusion, FDG PET/CT has a high diagnostic accuracy in distinguishing between benign and malignant ovarian tumors. However, false-positive findings on FDG PET/CT have been reported in various benign ovarian lesions including cystadenomas, endometriomas and mature teratomas.[67,74,75] False negative findings include certain types of mucinous and borderline tumors. When confronted with an incidental ovarian mass in an asymptomatic pre-or postmenopausal woman one should keep in mind that the overwhelmingly majority of all detected ovarian masses are benign, unilocular cysts that spontaneously resolve over time.[56,95,96]

Malignant Peritoneal Mesothelioma

Malignant peritoneal mesothelioma (MPM) is a very rare and aggressive disease, with higher incidence in women compared to men.[97] MPM can mimic ovarian carcinoma with non-specific imaging findings, including irregular and nodular pleural thickening, omental involvement, ascites and variable tumoral FDG uptake depending on the histologic type.[98,99]

Vagina

Primary vaginal cancer is a rare entity and accounts for less than 2% of all gynecological malignancies with squamous cell carcinoma being the most common subtype.[30,100] FDG-PET/CT has been shown to detect primary carcinoma and lymph node metastasis with high diagnostic accuracy.[101] Still, when malignancy is encountered in the vagina it is more likely to be due to metastasis by contagious spread (>80%) from adjacent organs in the reproductive tract and rectum other primary sites are exceedingly rare[100,102,103](fig). Other primary vaginal

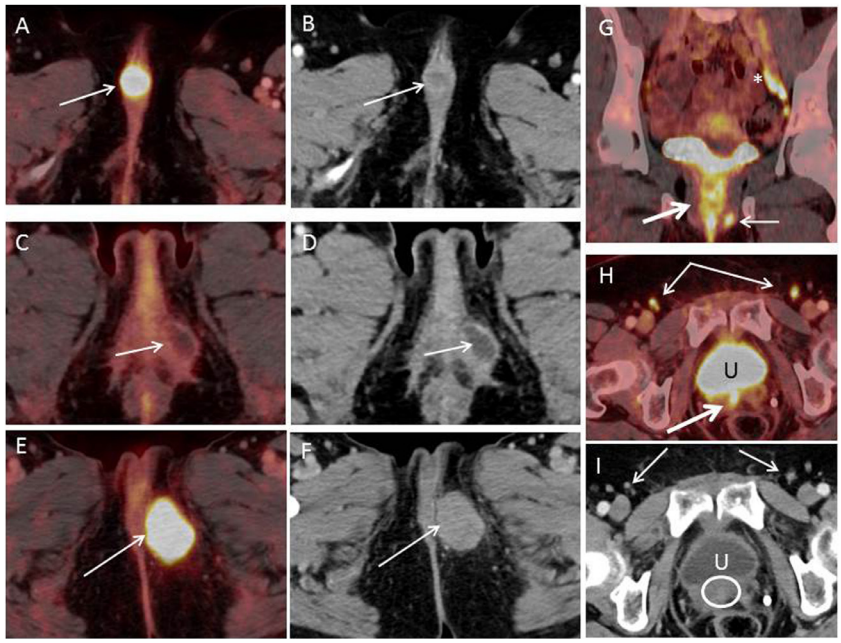

Figure 7 Axial fused PET/CT (A) and contrast-enhanced CT (ceCT) shows primary squamous cell carcinoma in the clitoris shows intense FDG uptake (A, arrow) in a tumor with central hypodensity with contrast-enhancement in the rim (B, arrow). Axial fused PET/CT (C) and axial ceCT (B) of benign Bartholin cyst with no FDG uptake (C, arrow) with mild, inhomogeneous contrast-enhancement in the circumference (D, arrow). Axial fused PET/CT (E) and axial ceCT (F) shows primary squamous cell carcinoma in a Bartholin gland with intense FDG uptake (E, arrow) in a solid tumor (F, arrow). Coronal fused PET/CT in a young woman with vulvovaginitis. Intense FDG uptake is seen in the vulva and vagina (G, bold arrow) with concurrent infection in a Bartholin gland (G, arrow). Regional lymphadenopathy along the left iliac vessels with intense FDG uptake is marked with *. Axial fused PET/CT (H) and axial ceCT (I) in a woman with biopsy confirmed recurrence of uterine serous adenocarcinoma in the vaginal cuff. The small focus with intense FDG posteriorly for the urine bladder could be overlooked and mistaken for a small urine bladder diverticulum (G, bold arrow). On corresponding ceCT image the tumor is not clearly depicted and could have easily been missed on CT alone (I, encircled). Intense FDG uptake can be seen in lymph nodes consistent with metastasis (G, arrows). The metabolically active lymph nodes are normal in size (< 1cm) and would not have necessarily been considered malignant on CT alone (I, arrows). U, urinary bladder.

tumours include malignant melanoma, leiomyosarcoma and adenocarcinoma[103] (fig). The vaginal cuff, located between the urinary bladder and rectum, is a common site for recurrent gynecological malignancy especially cervical carcinoma[104] (fig). Benign lesions such as leiomyomas, polyps, and endometriosis are likewise rare but a potential pitfall for misinterpretation.[102] In women using vaginal tampon high FDG-uptake can be seen in the vagina which is attributed to urine contamination of the tampon that appears radiolucent on CT[105](fig). Other foreign bodies that can be normally seen in the vagina such as menstrual cups and vaginal pessary are radiopaque and can easily be identified by their characteristic shape.[106]

Vulva

Vulvar carcinoma accounts for around 3% of all gynecological malignancies with squamous cell carcinoma being by far the most common subtype (> 80%).[30] Carcinoma of the vulva primarily affects older women (> 70 years) but incidence of HPV-associated carcinoma in younger women is rising.[30,81] The vulva constitutes the external part of the female genital tracts and consists of the mons pubis, labia major and minor, clitoris, Bartholin glands (vestibular glands) and the vestibule of the vagina. Evaluation of vulvar malignancy with FDG PET/CT can be challenging due to inherent imaging limitations with poor soft tissue resolution of anatomical structures on CT and contamination with urine FDG-activity in the vulva region which could potentially mask small lesions. The labia major is the primary site in two thirds or more of vulvar carcinoma.[30] Bartholin cysts are common in women of reproductive age and arise as a result of duct obstruction of the mucin secreting Bartholin glands that are located bilaterally at the posterolateral vaginal introitus.[107] Simple Bartholin cysts are normally seen with no FDG-uptake but can appear with intense FDG-uptake if infected or in case of abscess formation (Fig. 7). Primary malignancy or metastasis in the Bartholin glands are rare but in case reports described with intense FDG-uptake[108] (Fig. 7). Noteworthy, in women over the age of 40 years the Bartholin glands have undergone natural involution and FDG-uptake in a Bartholin gland in these women should be not be dismissed as a benign finding without further clinical examination.[107,109] Infectious or chemically induced vulvovaginitis is a common condition and can appear with intense FDG-uptake in the vulvar vaginal region potentially masking

additional pathological lesions or misinterpreted as malignancy (Fig. 7).

Endometriosis

Endometriosis is a relatively common benign gynecological disorder that almost exclusively affects women in the reproductive age with a peak incidence at 25-29 years of age.[110] In women of reproductive age the prevalence of endometriosis is estimated at around 10% in the general population[111]. Endometriosis is defined as presence of functional endometrial glands and stroma outside the uterine cavity and is a distinct clinical entity from adenomyosis.[112] Endometriosis can present with a wide spectrum of symptoms depending on the site of involvement and remains a diagnostic and therapeutic challenge. Signs and symptoms are caused by endometriotic cyclic bleeding eliciting an inflammatory response that ultimately leads to fibrosis and adhesions with pelvic pain and infertility as frequent symptoms. The most common sites affected by endometriosis are the ovaries, fallopian tubes, pelvic ligaments and pelvic peritoneum followed by the gastrointestinal tract with the rectosigmoid colon as the most common site.[113,114] However, endometriotic implants can appear anywhere in the body and potentially mimic malignancy on FDG PET/CT in unexpected locations such as the lungs.[115]

A limited number of studies have described the pattern of FDG-uptake in endometriosis showing that, although, endometriosis can occasionally be seen with abnormal FDG uptake most endometriotic lesions have no clear FDG uptake.[67,115-118] FDG PET/CT is therefore not suited for diagnosis or staging in endometriosis but, nevertheless, represents a potential pitfall.[74,75] Endometriosis affecting the ovaries is referred to as endometriomas that can be unilocular or multiocular.[114] Endometriomas can display, depending on the severity, a wide plethora of imaging findings and occasionally be indistinguishable from ovarian cancer, as there is a considerable overlap in imaging characteristics of endometriomas with other adnexal masses[114,117] (Fig. 8). Accompanying endometriotic

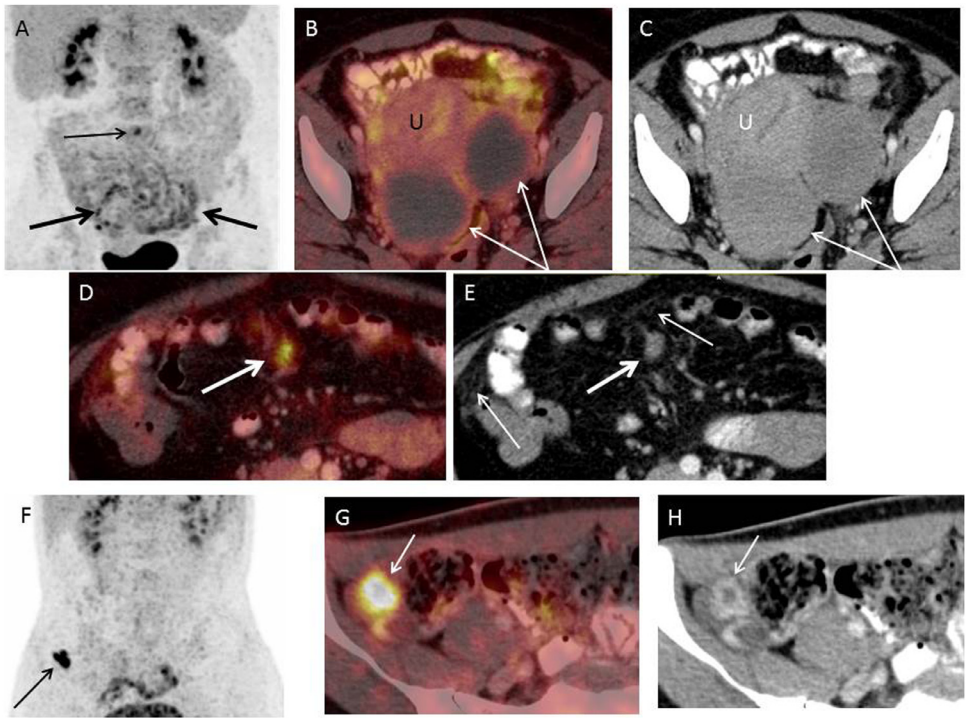

Figure 8 Maximum intensity projection (MIP) (A), axial fused PET/CT, and contrast-enhanced CT (ceCT) (C) in 46-year old woman with known endometriosis referred for a PET/CT due to elevating CA-125. MIP shows FDG uptake in a circular, inhomogeneous pattern in the pelvis (bold arrows) and focal FDG uptake in the middle of the abdomen (arrow). Only mild FDG uptake can be observed in the wall of two cystic lesions in the adnexa bilaterally (B, C arrows). Intense FDG uptake is seen in the mesentery fat corresponding to a solid mass on ceCT, note there is some misalignment between the PET and CT scan (D, E bold arrow). Fat stranding is observed in the omentum and right paracolic gutter (E, arrows). The findings were consistent with bilateral endometriomas, "kissing ovaries" with endometriotic implants in the mesenteric fat and spread fat stranding due to inflammation/small endometriotic implants. MIP (F), axial fused PET/CT (G), and axial ceCT (H) in a 30-year old woman who was referred for a follow-up PET/CT 3 months after completing radiation therapy (RT) for cervical carcinoma. The right ovary had prior to RT been transposed out of the radiation field for preservation of ovarian function. Intense FDG uptake is seen in the lower right abdominal quadrant (F, arrow). Intense FDG uptake in the right transposed ovary (G, arrow) consistent with a corpus luteum cyst on CT (H, arrow). Identification of a transposed ovary can be simplified if there is a surgical clip marking (not shown).

implants in the peritoneal cavity can further distort imaging evaluation by mimicking peritoneal carcinomatosis.[117] In severe endometriosis, discharged blood products may cause adhesions between the ovaries and fallopian tubes resulting in, what is often referred to as, "kissing ovaries."[119] "Kissing ovaries" are formed when the ovaries and fallopian tubes are pulled by adhesions towards the midline and occasional encasement of the ovaries resembling a complex pelvic solid mass[119] (Fig. 8). Dilatation by blood products of the fallopian tubes can result in hematosalpinx. The cancer antigen CA-125 can be elevated in endometrioses but 49% of women with endometriosis will have a serum CA-125 within the normal range.[120] Importantly, endometriosis can serve as a precursor lesion to certain histological subtypes of ovarian cancer such as endometrial carcinoma and clear cell carcinoma.[80] It is therefore important to note that definite diagnosis of endometriosis can only be made with histological confirmation.[114]

Pelvic Imaging With FDG PET/CT Following Surgery, Chemotherapy and Radiation Therapy

Treatment options for gynecologic malignancies include surgery, chemotherapy and radiation therapy (RT), often in combination depending on primary site and stage. Posttreatment imaging plays a crucial role in therapy assessment and in follow-up for recurrence but can be challenging due to

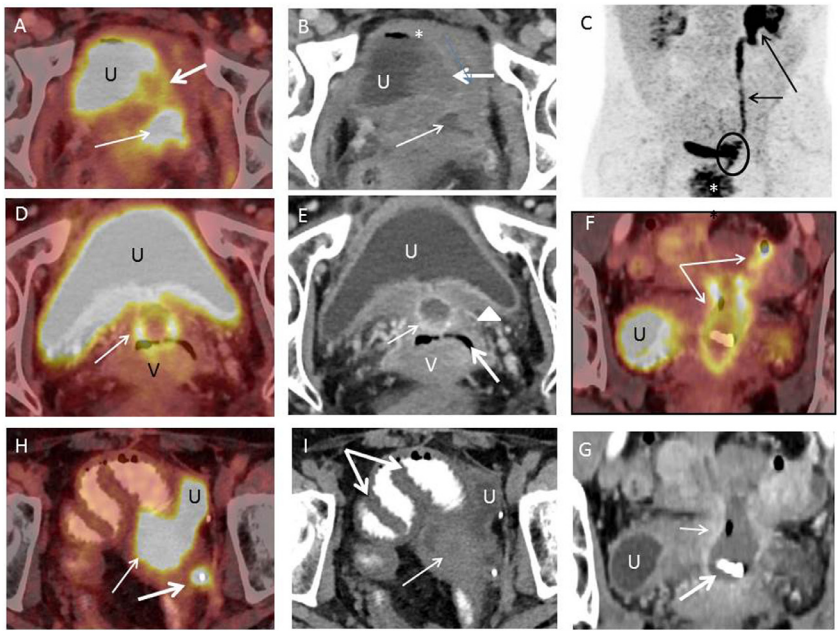

Figure 9 Axial fused PET/CT (A), axial contrast-enhanced CT (ceCT) (B) and maximum intensity projection (MIP) (C) in a 44-year old woman who five months prior to scanning had received intracavitary brachytherapy for stage IV, squamous cell carcinoma in the uterine cervix. Within 5 months following radiation therapy (RT), the patient had developed continuous urine incontinence and vaginal bleeding. Routine follow-up renogram showed left-sided partial obstruction. PET/CT was performed to exclude parametrial recurrent disease. A vesicovaginal fistula is seen with intense FDG accumulation due to FDG excretion in the urine (A, arrow). During surgery, the urinary bladder was seen encased in radiation induced fibrosis with distal ureter obstruction (A, B, bold arrow). MIP shows left-sided hydroureter and hydronephrosis (arrows, * indicates extracorporeal urine contamination, the vesicovaginal fistula is encircled). Axial fused PET/CT (D), axial ceCT (E), coronal fused PET/CT (F) and coronal ceCT (F) in a 50-year old woman with stage IV, squamous cell carcinoma who two years prior had prematurely completed intracavitary brachytherapy due to severe RT induced injury of the colon sigmodieum requiring a transverse loop colostomy. MRI had shown complex fistula formation with several fistula tracts between the colon sigmodieum and vagina, PET/CT was performed to evaluate presumed distant metastasis in the lungs. Intense FDG uptake and contrast-enhancement is seen at the border of the enterovaginal fistula (D, F, arrow; E, G, arrow). Air in the vagina is present as sign of communication between colon and vagina (E, bold arrow); there is substantial thickening of the urinary bladder wall following RT (E, arrowhead). A displaced sterilization clip is seen in the fistula, originating from the left side (G, bold arrow), the right sterilization clip was in situ (not shown). Axial fused PET/CT (H) and axial non-ceCT (I) in a 55-year old woman with stage IIIc, ovarian cancer with recurrent disease, 10 years post primary diagnosis, located between the bladder and vagina. Palliative RT was given. Due to clinical suspicion of residual disease a PET/CT was performed. Intense FDG uptake is seen in the residual tumor located posteriorly for the urinary bladder (H, arrow) and a new recurrence in relation to surgical clip along the left pelvic wall (H, bold arrow). Note radiation-induced wall-thickening of the small intestine (I, bold arrows). U, urinary bladder; V, vagina.

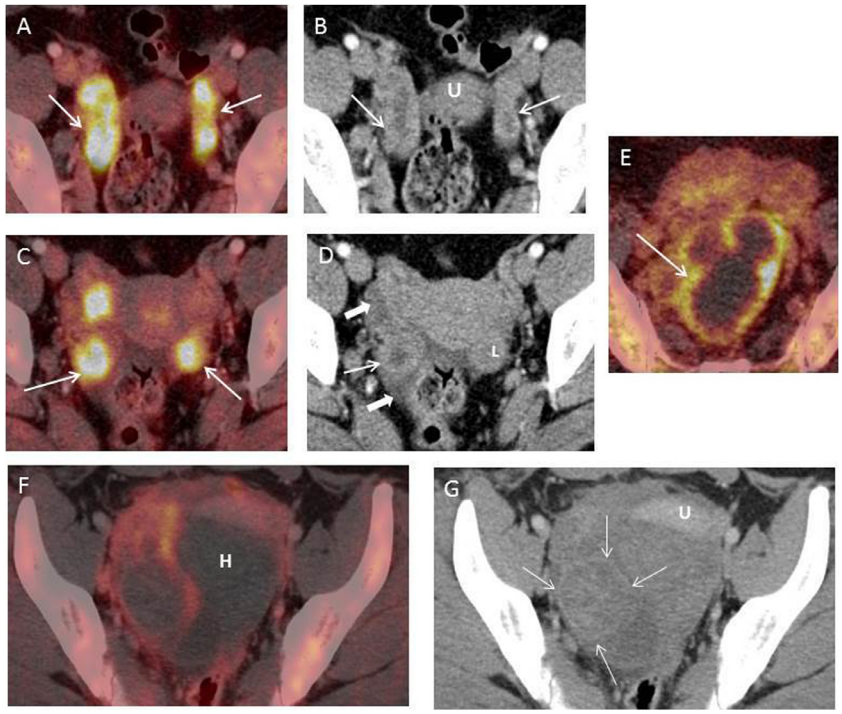

Figure 10 Axial fused PET/CT (A) and contrast enhanced CT (ceCT) (B) shows intense FDG uptake in the fallopian tube bilaterally (A) which on ceCT appear as wall-thickened filled fluid-filled structures (B, arrows). Imaging findings were suggestive of pyosalpinges. (C) Axial fused PET/CT and (D) ceCT in the same patient shows bilateral involvement of the ovary (arrow) with surrounding free-fluid (D, bold arrows). The 22-year- old patient was subsequently diagnosed with PID due to Chlamydia trachomatis infection. (E) Axial PET/CT (E) with low-dose CT shows a complex cystic mass in the right adnexal region with unidentifiable adnexal structures and with central photopenic regions and intense FDG uptake in the peripheral rims suggestive of abscess formation (arrow). The adnexal mass was surgically removed and showed a right-sided tubo-ovarian abscess. PET/CT was performed in a 25-year-old woman who presented with abdominal pains, hypotensive episodes and an adnexal mass on ultrasonography with positive β-HCG. (F) Axial fused PET/CT and axial ceCT (G) show a right-sided tubal ectopic pregnancy with mild FDG uptake, surrounded by hemoperitoneum (H) with variable contrast enhancement on CT (G, bold arrows). Surrounded by bloody ascites (confirmed at surgery), a sac-like structure is seen with low peripheral enhancement consistent with an extra-uterine gestational sac (G, arrows). Final diagnosis was ruptured right-sided tubal ectopic pregnancy. As β-HCG can be elevated in certain ovarian malignancies, uncertainties in diagnosis arose since the patient used contraceptives. H, hemoperitoneum; U, uterus; L, left ovary.

alterations of the normal anatomy with loss off tissue planes.[121] Familiarity with expected FDG PET/CT imaging findings depending on the type of therapy given, as well as potential post therapy complications is crucial.[122] Surgical procedures and RT elicit FDG avid inflammatory responses in the surgical bed and, in case of RT, in the tumor and adjacent structures within the radiation field.[122,123] Therefore, it is generally recommended that FDG PET/CT should be delayed for 8 weeks post-surgery and 12 weeks following RT, to reduce the possibility of false-positive findings in the early post-therapy setting.[122] Complications following RT are dived in acute and chronic, of which, chronic complication can appear several years' post-RT and cause confounding imaging features which can be misread as recurrent disease. For instance, RT induced damage to the distal part of the ureters and subsequent stricture formation, resulting in hydroureter and hydronephosis, can occur several years after RT imaging and mimic recurrent parametrial disease.[124] In pelvic RT the organs at risk for RT induced sequela include the urinary bladder, colon-and small bowel, pelvic bones and genital tract causing a plethora of symptoms and potential pitfalls on imaging.[122,124] In premenopausal women receiving pelvic RT, preservation of ovarian function and avoidance of premature menopause and infertility is vital for quality of life preservation.[125,126] In ovarian transposition the ovary is surgically moved out of the radiation field and repositioned laterally within the pelvis, in the lower paracolic gutters or anterior for the psoas musculature.[125,127] If ovarian function is preserved, it may exhibit physiological variations in FDG uptake in accordance with the menstrual cycle[128](Fig. 8). Benign cystic formation, especially of follicular cysts are common.[127] Fistula formation is a late, debilitating complication following pelvic RT or surgery that frequently occurs between the bladder or rectum and the vagina.[129,130] Fistula formation poses diagnostic challenges on PET/CT as the fistula tracts can be difficult to differentiate on CT and abnormal FDG uptake is usually observed in surrounding tissue due to inflammation and, in case of vesicovaginal fistula, further complicated by contamination due to urinary FDG excretion[2,130] (Fig 9). Furthermore, fistula formation can be

caused by primary tumor or recurrent disease.[130] Recently performed cervical conization is seen with diffuse FDG uptake which can potentially mask or mimic disease.

Pelvic Inflammatory Disease and Pelvic Infections

It is well known that infectious and inflammatory conditions may display intense FDG uptake which potentially can mimic or be indistinguishable from malignant disease. Infectious processes can further confound imaging interpretation by abnormal FDG uptake in regional lymphadenopathy or nearby structures, suggestive of disseminated malignancy. Pelvic inflammatory disease (PID) of the upper genital tract (the endometrium, fallopian tubes, ovaries, or pelvic peritoneum) is typically caused by ascending microbes from the lower genital tract. Sexual transmitted pathogens account for approximately 85% of acute PID cases with Chlamydia Trachomatis and Neisseria gonorrhea being the two most common pathogens.[131] Salpingitis, inflammation of one or both fallopian tubes, is the most common manifestation of acute PID frequently involving the ipsilateral ovary.[132] In salpingitis, the fallopian tubes are edematous and congested with high FDG uptake in the inflamed structures[132] (Fig. 10). A serious and late complication of PID is inflammatory progression with subsequent formation of a tubo-ovarian abscess. Typical imaging findings of a tubo-ovarian abscess include a complex cystic and solid mass lacking any identifiable normal adnexal features[132](Fig. 10). PID can result in long-term disability with infertility, ectopic pregnancy and chronic pelvic pain as common symptoms.[131] Ectopic pregnancy is in 95% tubal, on contrast-enhanced CT the gestational sac can be identified as an extra-uterine cystic structure with some degree of peripheral contrast enhancement.[133] We present a case of ectopic tubal pregnancy with no FDG uptake in relation to the gestational sac (Fig. 10). Chronic PID (> 30 days) is defined as a chronic infection with mycobacterium tuberculosis or actinomyces species.[131] Female genital tuberculosis (FGT) is rare and usually secondary to other primary sites.[134] Diagnosis is difficult due to non-specific symptoms including ascites, menstrual irregularities and palpable pelvic masses.[135] In FGT the fallopian tube is always involved, usually bilaterally, followed by the endometrium, cervix and ovaries, the vagina and vulva are very rarely involved.[136] On imaging FGT can be misdiagnosed for metastatic ovarian carcinoma especially if peritoneal involvement is present.[135] Tuberculosis infection yields a granulomatous inflammatory response with high FDG avidity which can be helpful in disease assessment and follow-up of FGT[137] (Fig. 11) Pelvic actinomycosis infection is a rare and often associated in women with an IUD.[138] Due to its slow-growing nature, rarity and potential to mimic malignancy, pelvic actinomyces is seldom diagnosed pre-operatively.[139] Imaging findings are often non-specific but pelvic actinomycosis infection should be considered when confronted on imaging with a infiltrative mass that invades across tissue planes and boundaries.[140] Like, tuberculosis, actinomycosis yields a highly FDG avid granulomatous inflammation[138](Fig. 11).

Infection and inflammation from non-gynecological sources in the pelvic region can originate from appendix, colon and the urinary tract. Common imaging features of pelvic abscess include; thick or thin walls, simple or complex fluid collections, adjacent fat stranding and free fluid accompanied

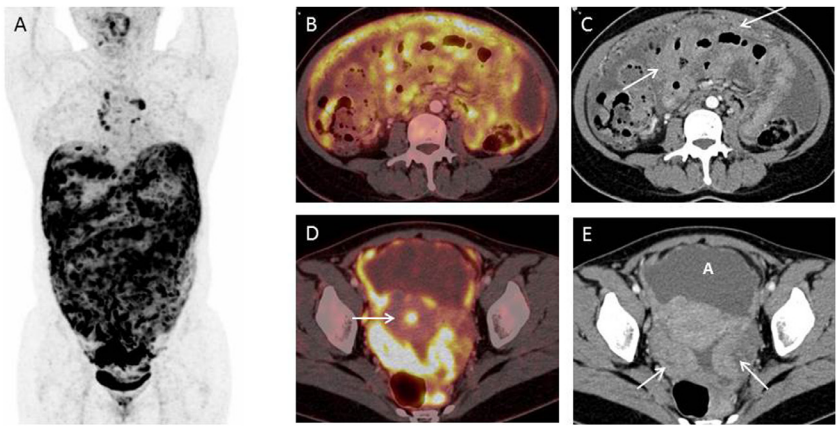

Figure 11 A young patient that was referred to a FDG PET/CT under the suspicion of disseminated ovarian carcinoma due to imaging findings on ultrasonography. CA-125 was elevated to 170 (reference interval). The patient was subsequently diagnosed with female genital tuberculosis (FGT). (A) Maximum intensity projection shows intense FDG uptake in wide-spread peritoneal involvement that apparently involves all abdominal peritoneal surfaces. Pathological uptake is seen in mediastinal and hilar lymph nodes (arrows). (B) Axial fused PET/CT and (C) contrast enhanced CT (ceCT)show intense FDG uptake in thickened omentum majus (C, bold arrow) and peritoneum extending into the mesentery (C, arrow). (D) Axial fused PET/CT and (E) ceCT in the pelvic region shows intense FDG uptake in bilateral, predominantly solid, adnexal masses with various degrees of contrast enhancement (E, arrows). Intense FDG uptake is seen in the uterine cavity suggestive of uterine involvement (D, arrow). Large amount of ascites is also present (A=ascites). Note the absence of FDG positive foci in the lungs (A). Diagnosis based on FDG PET/CT findings was not possible and disseminated ovarian carcinoma could not be ruled out.

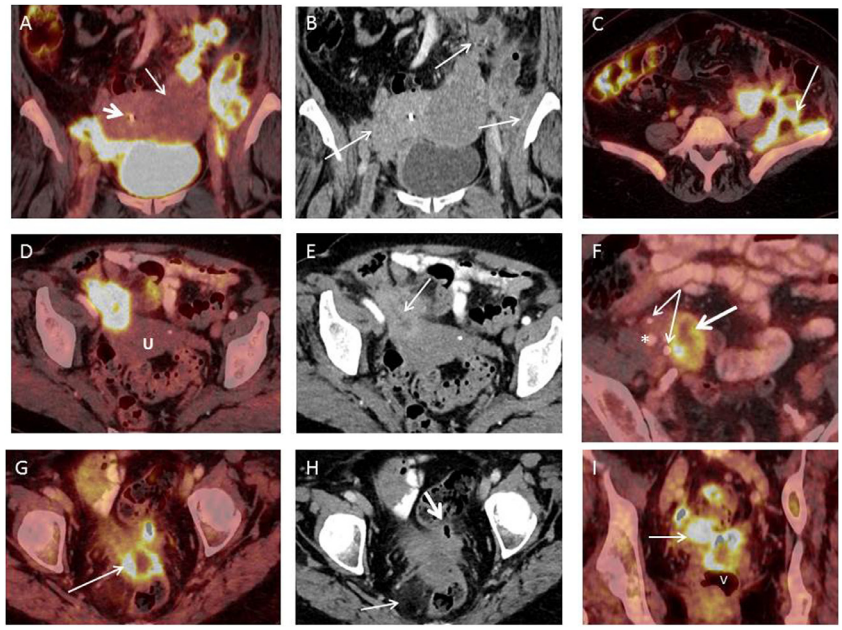

Figure 12 (A) Coronal fused PET/CT, coronal contrast-enhanced CT (B), and axial fused PET/CT show imaging findings in a 56-years old woman diagnosed with pelvic actinomycosis on endometrial histology. There is an IUD in situ, with notably, no FDG uptake in the uterine cavity (A, bold arrow). A cyst-like tumour is seen adjacent to the uterus with no marked FDG-uptake, precise etiology is unknown but leiomyoma was suggested. Due to the lack of FDG-uptake in the structure it was presumed not to be associated with the on-going infection (A, arrow). Intense FDG uptake is seen bilateral pelvic infiltrative masses surrounding the internal genital tract extending intra-abdominally with infiltration of adjacent tissue, intestines and psoas musculature, with contagious crossing over tissue boundaries (A, B, arrows, C). Axial PET/CT (A), axial ceCT and axial fused PET/CT in a 73-year old woman with acute appendicitis. PET shows intense FDG uptake in appendix (D) that is seen with thickened walls and intra-luminal fluid along the right pelvic wall fusing with the right adnexal region in close proximity to the uterus (E, arrow). More proximally, a mass is seen with peripheral intense FDG and central photopenic region suggestive of abscess formation (F, bold arrow). Appendicolithiasis, calcified deposits in the appendix, often associated with perforated appendicitis is seen (C, arrows). Axial fused PET/CT (G), axial ceCT (H) and coronal fused PET/CT (I) shows perforated diverticulitis with extensive FDG avid inflammatory response with abscess formation (A, arrow) surrounding the wall-thickened colon sigmodieum w diverticula (H, bold arrow). Pericolonic fat stranding is observed (H, arrow). Air trapped within the vagina signals communication between colon sigmodieum and the vagina, indeed the patient had vaginal, pus containing, discharge (H, v).

with intense FDG uptake.[141,142] Appendicitis and diverticulitis can be difficult to distinguish from PID in case of adnexal involvement and abscess formation.[132] Diverticulosis has a high a high prevalence in the general population and the presence of diverticula in involved segments is indicative of diverticulitis[143](Fig. 12).

Concluding Remarks

The pattern of FDG-uptake in the female reproductive tract should be correlated with the patient́s menopausal status and if possible, menstrual cycle. FDG uptake in the ovaries or uterus in post-menopausal women should be evaluated further to exclude malignancy. Gynecological malignancies are mostly FDG avid but false-negative findings in certain histologic subtypes and in the presence of necrosis occur. False-positive findings in benign tumors, infections and in the post-therapy setting are not uncommon. Subcentimeter lesions can be missed due to low-spatial resolution of PET/CT especially in the evaluation of potential peritoneal disease. Post-radiation complications can become appareant several years after completed RT, a thorough review of patients´ previous medical history is therefore essential.

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