High-risk endometrial carcinoma: MRI findings

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Learning objectives

To present MR imaging features of high risk rare malignant tumors of the endometrium that are clear cell and serous high grade endometrial adenocarcinomas and carcinosarcoma.

To allow radiologists a better understanding of the pathogenesis of these lesions in order to improve initial staging and follow-up.
Background

Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries, most of the time confined to the uterus at diagnosis [1]. Nonetheless, a group of high risk endometrial carcinomas including grade III endometrioid carcinoma, non-endometrioid clear cell and papillary serous histological subtypes and carcinosarcoma, although rare, is known to have a poorer prognosis, accounting for a disproportionate number of endometrial cancer deaths. Extra-uterine spread may then be present even when there is minimal uterine disease. MRI can aid the treatment planning in high risk lesions, and give additional information about the extra-uterine spread and helps define the most appropriate surgical approach.

Our purpose is to present a review of the spectrum of high risk tumors of the endometrium including grade III endometrioid carcinoma, non-endometrioid clear cell and papillary serous subtypes and carcinosarcoma illustrated with didactic cases.

Risk stratification in endometrial cancer

Factors associated with relative high risk are histological subtype, grade 3 histology, myometrial invasion # 50%, lymphovascular space invasion, lymph nodes metastases and tumor diameter >2cm [1]. Depth of myometrial invasion, cervical stroma invasion, tumor histological subtype and lymphovascular invasion are important prognostic factors correlated with the likelihood of lymph node metastases and survival. These factors allow risk stratification used for treatment planning. For patients with deep myometrial invasion and high histological grade, para-aortic lymphadenectomy is associated with improved survival. However, controversy exists regarding the benefit of systematic pelvic and para-aortic lymph node dissection in patients with low-risk and early-stage disease. MR imaging can provide an accurate assessment of the depth of myometrial invasion and prevent patients without deep myometrial invasion from undergoing an unnecessary lymphadenectomy.

MRI can aid the treatment planning in high risk lesions in showing a possible extra-uterine spread and helps define the most appropriate surgical approach. Referral for MR imaging should be preceded by preliminary results from endometrial biopsy. If lymphovascular extension is known after hysterectomy, histological subtype and tumor grade are usually available after endometrial biopsy and should be considered before reporting an MRI for endometrial carcinoma. Pre-operative histopathological sampling error rate may however reach 20% in endometrial sampling. Various grades of adenocarcinoma may coexist with papillary serous or clear cell tumor types that may not be always identified in pre-operative sampling, as well as the sarcomatous component of a carcinosarcoma.
Endometrial carcinoma histological subtypes

Because clinical staging is inaccurate, surgical staging is the reference standard to assess tumor extension according to the FIGO staging revised in 2009 (Figure 1). Surgical staging of endometrial cancer consists of an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal lavage and lymphadenectomy.

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**Fig. 1**: Endometrial carcinoma FIGO staging (2009)

**References**: Radiology department, Institut Curie - Paris/FR

Two main types of endometrial carcinoma have been recognized on the basis of clinical, biological and molecular findings. Type 1 or endometrioid adenocarcinoma is the most common endometrial cancer cell type (75-80%), composed of malignant glandular epithelial elements. Type 1 carcinoma is more commonly seen in obese patients with hyperlipidaemia, hyperestrogenism insulin resistance and infertility. Type 1 carcinoma is usually revealed by vaginal bleeding and is associated with estrogen-induced endometrial hyperplasia. Well differentiated endometrial carcinomas are composed of glands resembling those of the normal endometrium. These low grade tumors tend to occur in younger women (Fig. 2 on page 7 Fig. 3 on page 8). Grade is usually defined by the proportion of glandular and solid portions of the tumor.
Type 2 endometrial carcinomas mainly include papillary serous (10%) and clear cell (4%) carcinomas. Type 2 tumors are less frequent, high grade lesions with aggressive clinical behavior. The clinical presentation of high risk endometrial adenocarcinomas and uterine carcinosarcomas are usually similar to that of standard endometrioid adenocarcinoma, with vaginal bleeding. These aggressive cancers may however present in higher stages with ascites, omental caking and/or peritoneal carcinomatosis. They more typically arise in atrophic endometrium or endometrial polyp in older patients. Papillary serous carcinomas are high grade carcinomas. Clear cell and papillary serous carcinoma of the endometrium are tumors that are histologically similar to those noted in the ovary and the fallopian tube, and have a worse prognosis than endometrioid adenocarcinoma. They account for 50% of endometrial carcinoma related deaths. These tumors are 2-6 times more likely in patients with previous breast cancer. Grade 3 endometrioid carcinoma, undifferentiated carcinoma and carcinosarcoma are also usually included in the Type 2 tumors group.

Up to 5% of endometrial cancers are associated with Lynch syndrome type II (hereditary non-polyposis colorectal carcinoma syndrome) with a lifetime risk of developing endometrial cancers in 30-60%. Other neoplasms associated with Lynch syndrome involve colon/rectum, ovary, stomach, biliary tract, urinary tract, small bowel.

Mixed tumors composed of both type 1 and type 2 tumors account for 10% of endometrial cancers.

**Carcinosarcoma**

Previously referred as "Malignant Mixed Müllerian Tumor" (MMMT), carcinosarcoma is a biphasic tumor composed of a carcinomatous epithelial and a sarcomatous component, thought to derive from a single cell precursor [2]. Carcinosarcoma is a highly aggressive tumor, diagnosed at higher extent than endometrioid carcinoma, with a 30% overall survival in stage I disease (vs 80% in high grade other endometrial cancers) [3]. It was formerly considered the most frequent uterine sarcoma (50%) but is now regarded as an epithelial tumor with metaplastic sarcomatous component rather than a biclonal tumor (Fig. 4 on page 9). Sarcomatous component can be classified as homologous when containing mesenchymal elements normally found within the uterus, or as heterologous when containing mesenchymal elements that are not usually present in the uterus. Carcinosarcoma share same risk factors as endometrioid endometrial carcinoma such as estrogen use, obesity, pelvic radiation and tamoxifen therapy. It usually presents with post-menopausal bleeding, an abdominopelvic mass or lower abdominal pain, in the same age group as endometrioid endometrial carcinoma (mid 60's). The recent FIGO classification recommends staging these tumors like endometrial carcinomas (Fig. 1 on page 7). Preoperative Ca 125 elevation has been reported to be associated with extra-uterine spread of disease and deep myometrial invasion in carcinosarcoma and would be an independent prognostic factor for poor survival [4]
Treatment

According to the ESMO clinical practice guidelines for the management of endometrial cancer, clear cell and papillary carcinomas require complete staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, appendicectomy and peritoneal biopsies. Moreover, retrospective series show that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves progression free survival and overall survival. Platinum-based chemotherapy is recommended in patients with stage III or IV. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent papillary serous or clear cell uterine cancer. Papillary serous endometrial carcinomas are not considered to be hormone responsive.
**Fig. 1**: Endometrial carcinoma FIGO staging (2009)

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Fig. 2: Stage IA endometrial carcinoma in a 74-year-old woman who presented with post-menopausal vaginal bleeding. Sagittal (A,B) and axial (C) T2-weighted fast spin-echo, axial DW MR (E) and sagittal dynamic contrast-enhanced 3D T1-weighted gradient-recalled images (D) images show endometrial carcinoma superficially invading the myometrium.

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Fig. 3: Gross resection specimen photograph shows the endometrial mass (A). Histologic specimen shows on H&E stain a well-differentiated grade I endometrioid carcinoma (B), with a tubular architecture, invading the inner third of the myometrium.

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Fig. 4: Endometrial carcinosarcoma in a 52-year-old woman. Sagittal (A) and axial (B) T2 weighted images show a large endometrial mass distending the uterine cavity. H&E stain shows an endometrioid adenocarcinoma with intermediate differentiation (C) and a tumoral component composed of fusiform cells corresponding to a sarcomatous component. Myometrial invasion is superficial. FIGO stage IA.

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Findings and procedure details

Endometrioid adenocarcinoma grade III, clear cell and papillary serous endometrial carcinoma: MRI findings

Because of the rarity of high risk non endometrioid endometrial cancers, little data exist regarding MRI features of these lesions Fig. 5 on page 12, Fig. 6 on page 12 Fig. 7 on page 12. Nonetheless, due to their particularly aggressive nature, initial staging imaging frequently shows advanced disease at diagnosis with deep myometrial invasion, nodal dissemination and uterine serosal involvement.

Beyond the serosa, tumor dissemination is comparable to advanced epithelial ovarian cancer with omental and peritoneal invasion. When cervical stroma is involved, tumoral extension is comparable in cancers of the cervix, invading parametrium, obstructing ureters and infiltrating bladder and/or rectum. Cervical involvement should be reported since it necessitates an extended hysterectomy, not to cut through the lesion during surgery.

Papillary serous tumors tend to cause haematogenous metastases and early nodal involvement that may be bulky, mimicking lymphoma. Invasion of para-aortic nodes can occur in the absence of pelvic lymph node involvement. These clinical patterns prompt careful imaging evaluation of the chest, abdomen and pelvis to determine resectability. Fig. 8 on page 15

Clear cell carcinoma often present with extra-uterine disease, even in the absence of deep myometrial invasion Fig. 9 on page 13 Fig. 10 on page 14. Clear cell carcinoma may be associated with endometriosis and adenomyosis, which can be identified on MRI as a widening of the junctional zone. Adenomyosis may reduce the accuracy of MRI in assessing the depth of myometrial invasion on T2 weighted-images whereas diffusion-weighted images are not influenced by this potential pitfall.

If endometrial cancer and normal endometrium both appear hyperintense on diffusion-weighted images, ADC is significantly lower in endometrial cancer than in normal endometrium or benign lesions [5] Fig. 11 on page 15 Fig. 12 on page 16 Fig. 13 on page 16 . Correlation of ADC with histological grade remains controversial, no significant difference in ADC between low and high grade tumors existing according to several studies [6-8]. Another series nonetheless indicated a significantly lower ADC value in high grade disease [9]. In the study of Cao et al., quartile ADC (between the 25th and the 75th percentile voxel) representing the intra-tumor heterogeneity of water movement had a profound relationship with invasiveness of endometrial carcinomas patterns that are deep myometrial infiltration, cervical invasion, lymphovascular space invasion and lymph node metastasis [10].
Carcinosarcoma: MRI findings

Carcinosarcoma is generally centered on the uterine cavity rather than in the myometrium [Fig. 14 on page 17], appearing as a large bulky mass that distend the uterine cavity and may prolapse through the endocervical canal [7]. Fig. 16 on page 19 Fig. 16 on page 19

Signal of the tumor is mostly heterogeneous, low on T1-weighted images, high on T2-weighted images, and frequently exhibits necrosis or hemorrhage.

In a retrospective study of 17 carcinosarcomas, Tanaka et al. reported a high T2 signal intensity compared to the outer myometrium in 88% of the cases. Nine cases showed an exophytic growth with a stalk and 8 cases with a broad-based exophytic feature [11]. No invasive growth was seen. Extremely high intense area suggestive of necrosis foci was seen in only 2 cases. A majority of carcinosarcomas (81%) exhibited a strongly enhanced area. Fig. 17 on page 20 Fig. 18 on page 21

As in endometrioid carcinoma, depth of myometrial invasion is an important prognostic indicator. Carcinosarcoma shows high signal intensity on diffusion-weighted images and diffusion is restricted on ADC maps [12].

Differentiation from endometrioid carcinoma may not be possible as MRI appearances of carcinosarcoma are not pathognomonic [7]. Carcinosarcoma has been reported to appear more heterogeneous than endometrioid carcinoma with focal areas of avid enhancement [13]. After gadolinium chelates injection, CS may show areas of early and persistent enhancement, mixed with delayed gradual enhanced areas. In a small series, the avid enhancement areas have been shown to correspond to sarcomatous components with prominent vascularity [14]. Bharwani et al reported a significantly higher incidence of cervical invasion and nodal enlargement in carcinosarcoma than in endometrial adenocarcinoma [7]. Fig. 24 on page 25 Fig. 25 on page 26 Fig. 26 on page 26 Fig. 27 on page 27

Extra-uterine extension can be seen in up to 30% at presentation [15]. Local extension involves adnexa, vagina, omentum and nodal extension pelvic and para-aortic lymph nodes. Fig. 28 on page 28

Preoperative assessment with CT of the chest, abdomen and pelvis helps surgical planning. The recurrence rate is known to be 50-60% [15]. Distant metastases are more frequently seen in lung, liver and bone.
Fig. 5: A 36 year-old woman presented with persistent vaginal bleeding. Ultrasound diagnosed heterogeneous endometrial thickening. MR imaging shows on T2 weighted images on coronal (A) and sagittal (B) images a large and heterogeneous high intense endometrial mass, invading the outer half of the myometrium (white arrows).

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Fig. 6: Axial T2 weighted image (C) and corresponding diffusion weighted (D) and ADC map images (E) show the mass exhibits high signal intensity on diffusion weighted images and restriction on ADC map. Resection specimen histological analysis shows a poorly differentiated grade III endometrioid adenocarcinoma with clear cell and squamous components. Tumor invades more than half of the myometrium. Lymphovascular invasion is also seen. FIGO stage IB

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Fig. 7: Sagittal dynamic acquisition after gadolinium chelates injection shows heterogeneous enhancement with foci of avid enhancement on early acquisition (F). Delayed phase images (G) show diffuse myometrial enhancement, greater than that of the tumor.

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Fig. 9: Endometrial mass exhibits a heterogeneous pattern on sagittal T2 weighted images (A), with areas of avid enhancement (B) high signal intensity on diffusion weighted images and restriction on ADC map (C, D).

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**Fig. 10:** H&E stain shows a grade III papillary serous adenocarcinoma (E) with cervical stroma invasion on a few millimeters and superficial myometrial invasion, extensive lymphovascular invasion (F) in the myometrium of the uterine body, isthmus, cervix and right fallopian tube wall. Extensive pelvic and paraaortic lymph node metastatic involvement. FIGO stage IIIC2

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**Fig. 8:** Clear cell adenocarcinoma, grade III. Thoracic CT shows bilateral lung metastases (A). Pelvic MRI shows endometrial mass on sagittal T2 weighed images (B). Depth of myometrial invasion is difficult to assess on T2 images due to a poor tumor-to-myometrium signal contrast. On contrast-enhanced sagittal TSE T1 weighted fat-suppressed images, endometrial mass boundary is more easily delineated (C). FIGO stage IVB

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**Fig. 11:** An endometrioid adenocarcinoma with clear cell component exhibits an intermediate signal intensity on coronal (A) and sagittal (B) T2-weighted images and an infiltrative pattern. Tumor invades the outer half of the myometrium (white arrows).

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**Fig. 12:** The endometrial mass has high signal intensity on diffusion weighted axial images (C, D). Note a pathologically enlarged left external iliac lymph node metastasis (arrowhead) with comparable signal intensity to the endometrial mass on both T2 and diffusion weighted images (A, C). FIGO Stage III C1

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**Fig. 13:** On sagittal dynamic images performed after contrast media injection, the endometrial mass shows early enhancement, equal to subendometrial early enhancement. On late acquisition phase, adjacent myometrium shows greater enhancement than endometrial tumor.

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Fig. 14: Endometrial carcinosarcoma in a 73 year-old woman. Sagittal (A) and axial (B), T2-weighted images show a large bulky mass distending the endometrial cavity, with a high T2 signal intensity and a heterogeneous pattern. Resection specimen (C) and H&E stain (D, E) show a tumoral proliferation containing both malignant epithelial and spindle cell components. Myometrial infiltration was superficial. FIGO stage IA

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**Fig. 15:** 62 year-old woman. Vaginal bleeding. Pelvic ultrasound showed an enlarged uterus. Speculum examination showed a mass protruding through a distended endocervical canal. Endometrial sampling showed an endometrial carcinosarcoma with a heterologous chondrosarcoma sarcomatous component. Myometrial invasion was inferior to 50%, no cervical stroma invasion was seen. FIGO stage IA

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Fig. 16: 79 year-old woman previously treated for breast cancer, with vaginal bleeding. Speculum examination showed a mass protruding through the external os into the vagina. Sagittal T1 weighted and Sagittal T2 weighted images show a large carcinosarcoma (asterisk) invading the deep myometrium and the cervical stroma (white arrow), protruding into the vaginal lumen. Histological analysis shows a carcinosarcoma with a predominant clear cell sarcomatous component, invading the full thickness of the myometrium. Tumor extended to the uterine cornua and parametria. Histological analysis showed a large carcinosarcoma infiltrating the uterine corpus and the cervix. Tumor infiltrates the entire myometrium up to the serosa and the parametria. Lymphovascular extension was seen in adnexae. FIGO stage IIIB

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Fig. 17: 63-year old woman previously treated for breast cancer, presenting for post-menopausal bleeding. Sagittal (A) and axial (B) T2-weighted images show a slightly hyperintense, large bulky mass enlarging the uterine cavity with a broad-based to the anterior uterine inner wall. Tumor exhibits high signal intensity on diffusion weighted images and restriction on ADC map (C, D)

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Fig. 18: Sagittal dynamic acquisition after gadolinium chelates injection shows areas of avid enhancement of the tumoral stalk on early acquisition (F). Delayed phase images (G) show persistent tumoral enhancement.

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Fig. 20

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**Fig. 22:** High signal intensity of the endometrial tumor on diffusion weighted-image (C) and restriction diffusion on ADC map (D). Myometrial invasion is inferior to 50% on surgical specimen analysis. FIGO stage IA

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**Fig. 23:** Sagittal dynamic acquisition after gadolinium chelates injection shows heterogeneous enhancement on early acquisition (E), with an enhancement homogenization on delayed phase images (F). 18 months after initial diagnosis, follow-up computed tomography disclose peritoneal carcinomatosis (not shown).

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**Fig. 19:** 63 year-old woman, who presents obesity, dyslipidemia and arterial hypertension. Carcinosarcoma composed of an endometrioid adenocarcinoma, associated with a leiomyosarcoma component. Sagittal and axial T2-weighted images (A, B) show a large endometrial mass distending the uterine cavity, stretching the hypointense junctional zone (white arrow).

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**Fig. 24:** Axial oblique T2 weighted image (A) shows a hyperintense carcinosarcoma that invades the full thickness of the myometrium, the parametria, and the cervical stroma (arrows). Bilateral external iliac lymph node metastases are seen on axial oblique T2 weighted images (B). Histological analysis showed a grade III carcinosarcoma with
a predominant epithelial component and a chondrosarcoma heterologous component.
FIGO stage IIIC1

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Fig. 25: 63 year-old woman with post-menopausal bleeding. Obesity, arterial hypertension and diabetes. Carcinosarcoma with a poorly differentiated endometrioid adenocarcinoma and an undifferentiated sarcomatous component invading the deep myometrium and the cervical stroma. Lymphovascular space invasion is seen at the periphery of uterine tumor. FIGO stage II

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Fig. 26: 16 months after initial diagnosis of endometrial carcinosarcoma, right common iliac lymph node metastasis is diagnosed on computed tomography (C, white arrow) and 18-FDG PET-CT (D)

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**Fig. 27:** Rapid tumoral progression of retroperitoneal lymphatic involvement with contiguity extension to vertebral body of L4, exhibiting low signal intensity on sagittal T1-weighted images (E) and heterogeneous enhancement on gadolinium-enhanced sagittal fat-suppressed T1-weighted images (F)

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**Fig. 28:** 76 year-old woman. Sagittal T2-weighted images (A) show a hyperintense large bulky mass distending the uterine cavity, with a heterogeneous enhancement on axial T1 weighted TSE images (B). Pathological examination of the resection specimen (C) shows a pedunculated mass corresponding to a carcinosarcoma composed of a homologous sarcomatous component containing a spindle cell tumoral proliferation (D) and a papillary serous epithelial component (E). Explorative laparotomy found numerous millimetric tumoral granulations on pelvis peritoneum, ovaries, small bowel loops and sigmoid, corresponding to a FIGO stage IVB.

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Conclusion

MR findings of high risk endometrial adenocarcinomas and carcinosarcomas, are not pathognomonic, although some features may be suggestive. However, when reporting an MRI for endometrial carcinoma of such histological subtypes at endometrial biopsy, radiologist should be alerted on the risk of a wider locoregional extension, even in the presence of a minimal uterine disease.
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