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Learning objectives

To describe the technical challenges and advantages of 3T-MR spectroscopy (MRS) in evaluating gynecologic tumors.

To demonstrate the usefulness of MRS in distinguishing benign and malignant gynecologic tumors.

To recognize the meaning of various metabolites observed in gynecologic tumors for the differential diagnosis.

Background

Proton MR spectroscopy (MRS) provides metabolic information, which is useful for the differentiation of benign and malignant tumors in the brain, prostate and other various organs. 3T-MRI can offer high-quality MRS because of superior spectral separation and increased signal-to-noise ratio. We present the diagnostic impact of 3T-MRS in distinguishing benign and malignant gynecologic tumors, and in differentiating various gynecologic pathologies.

-MR Spectroscopy in the Female Pelvis-

Because biopsy is not commonly performed for ovarian tumors or uterine myometrial tumors, preoperative diagnosis based on imaging is important. The diagnostic value of MRS is typically based on the detection of elevated level of choline, which is a biomarker of cancer tissue and is increased in actively proliferating tumors. Choline is used for a biomarker for treatment response, and is expected as an early predictor for treatment response in patients with uterine cervical cancer. In the female pelvis other metabolites such as creatine, lipid, lactate, N-acetyl compound are useful in making differential diagnosis, especially in the estimation of histological types of gynecologic tumors.

Imaging findings OR Procedure details

[Metabolites]

Choline (3.2 ppm) peak reflects metabolic activity of cell membrane in solid tumors. High grade malignant tumors tend to show higher choline peaks. (Fig. 1-10)
Lipid (1.3 ppm) peak indicates necrosis and is detected in various tumors. In functioning ovarian tumor such as thecoma with abundant intra-cellular lipid contents, and in fat-containing tumor such as teratomas, high lipid peaks are observed. (Fig. 11-14)

Creatine (3 ppm) peak is observed in uterine myometrium and myogenic tumors such as leiomyoma. (Fig. 15-18)

N-acetyl (mucous) compound (2-2.1 ppm) peak is suggestive for mucinous tumors such as primary mucinous tumors, and secondary tumors containing mucinous materials. (Fig. 19-24)

Lactate (1.33 ppm) is produced via anaerobic glycolysis and concentrated in the necrotic portion of malignant tumors. Because lactate peak is overlapped with lipid peak, fat-suppression technique is useful for the detection of lactate peak. (Fig. 25-26)

[Techniques]

Device: Signa Excite HDx 3T, General Electric, USA

8ch body-array torso coils

Sequence:

PRESS (Point REsolved SpectroScopy)

Automatic shimming

TR/TE=2000ms/144msec. (long TE)

Measuring time 4:56 min.

Water suppression pulse sequence

Voxel size: 8ml (2x2x2cm3)

VOI setting:

Voxel of interest (VOI) should be prescribed peripherally in huge cystic mass at 3T, because signal decrease due to RF penetration/RF field (B1) inhomogeneity may lead to poor study. Susceptibility artifact due to hemorrhage may also cause signal decrease, and VOI should be prescribed in the tumor so as not to contain hemorrhagic areas as
much as possible by referring T1-weighted images with fat suppression. (Fig. 27 on page 33)

**Quantitative evaluation:**

Software: LCModel (version 6.1, Stephen Provencher Inc.)

The quantification of the metabolite levels (mM) were based on the unsuppressed water signal obtained from the same voxel.

[Choline]

Choline (3.2 ppm): Total choline compounds such as choline, phosphocholine and glycerophosphocholine reflect metabolic activity of cell membrane in solid tumors.

Choline is a biomarker of cancer tissue, and is increased in actively proliferating tumors. Solid components of high grade malignant tumors tend to show higher choline peaks, whereas intermediate to low choline peaks are observed in solid components of benign tumors.

- Choline peaks in huge myometrial masses (Fig. 1 on page 8)
- Choline peaks in intra-myometrial masses (Fig. 2 on page 8)
- Choline peaks in endometrial masses (Fig. 3 on page 9)
- Choline peaks in endometrial thickening (Fig. 4 on page 10)
- Choline peaks in solid ovarian tumors (Fig. 5 on page 11)

Quantitative evaluation of the choline concentration is helpful to distinguish between benign and malignant tumors. We evaluated the diagnostic ability of MRS for distinguishing benign and malignant lesions in 32 patients with uterine corpus tumors. The choline concentration was present in all 32 lesions including 14 malignant lesions (9.21 ± 2.21 mM), and 18 benign lesions (4.59 ± 2.22 mM) (p < 0.0001). Using a cut-off value of 7.00 mM for malignant lesions had a sensitivity of 93%, specificity of 83%, PPV of 81% and NPV of 94%. (Takeuchi M et al. Eur Radiol. 2010)

- Differentiation of benign and malignant uterine corpus tumors: Quantitative evaluation of the choline concentration (Fig. 6 on page 12)
Choline is used as a biomarker for treatment response. Decreased choline peaks after radiotherapy suggesting response to the therapy. Choline may be useful as a biomarker for the early predictor for treatment response.

- MRS of Uterine cervical cancer (Fig. 7 on page 13)
- Biomarker for Treatment response (Fig. 8 on page 14)
- Early predictor for treatment response: Complete Response (Fig. 9 on page 15)
- Early predictor for treatment response Partial Remission (Fig. 10 on page 16)

[Lipid]

Lipid (1.3 ppm): Lipid peak indicates necrosis, or the presence of lipid/fat.

Surrounding fat tissue may introduce contamination into spectra in relative small lesions. Even small amounts of extraneous fat can cause intense lipid signals and may mask other metabolites peaks.

Lipid peak from necrosis may be detected in various tumors. Malignant tumors with necrosis show bimodal high peaks of choline and lipid. However, high grade malignant tumors with massive necrosis may occasionally show high lipid peak with low or no choline peak because of the decrease of viable tumor cells, and may mimic benign lesion.

- Lipid peaks in ovarian tumors with necrosis (Fig. 11 on page 17)
- Lipid peak in ovarian tumor with massive necrosis (Fig. 12 on page 18)

In functioning ovarian tumor such as thecoma with abundant intra-cellular lipid contents, bimodal high lipid peak and intermediate peak of choline are observed.

- Lipid peaks in functioning ovarian tumors (Fig. 13 on page 19)

In fat-containing tumor such as mature cystic teratoma, very high lipid peak is observed. Even rather fat-scanty teratoma shows high lipid peak.

- Lipid peak in fat-containing tumor (Fig. 14 on page 20)

[Creatine]
Creatine (3 ppm): Creatine peak is observed in uterine myometrium and myogenic tumors such as leiomyoma. Creatine peak suggests its myometrial origin, or the presence of residual muscle fibers within infiltrative tumors.

- Creatine: Myomas vs Ovarian tumors (Fig. 15 on page 21)

In uterine leiomyomas, bimodal creatine and choline peaks are observed. The presence of creatine peak is useful in differentiating subserosal leiomyoma from ovarian fibroma/thecoma. Low intense pelvic mass on T2-weighted images exhibiting bimodal choline and creatine peaks is suggestive for uterine subserosal leiomyoma, whereas ovarian fibroma shows single choline peak. Low intense pelvic mass on T2-weighted images exhibiting bimodal choline and lipid peaks is suggestive for thecoma/fibrothecoma.

- Leiomyomas of the Uterus (Fig. 16 on page 22)

- Differentiation of low intense mass on T2WI (Fig. 17 on page 23)

Residual myometrium within the mass with infiltrative myometrial invasion may cause creatine peak. Typically, bimodal creatine and choline peaks are observed in low grade endometrial stromal sarcoma with characteristic "worm-like" infiltrative myometrial invasion. Malignant tumor cells and residual muscle fibers within infiltrative tumors may cause choline peak and creatine peak, respectively.

- Tumors with infiltrative myometrial invasion (Fig. 18 on page 24)

[N-acetyl (mucous) compounds]

N-acetyl (mucous) compounds (2-2.1 ppm): N-acetyl compounds peak mimicking N-acetyl-aspartate (NAA) is observed in mucinous tumors. This peak is from N-acetyl compounds in mucus glycoproteins.

Intermediate to high N-acetyl compounds peaks suggest the presence of mucinous material, and may contribute to the diagnosis of mucinous tumors. Especially, bimodal high peaks of choline and N-acetyl compounds in solid mass may be characteristic for malignant mucinous tumors (i.e. Krukenberg's tumor, mucinous adenocarcinoma).

- N-acetyl (mucous) compounds: Mucinous vs Non-mucinous ovarian tumors (Fig. 19 on page 25)

- N-acetyl compound peaks in Mucinous vs Serous loculi of mucinous cystadenoma (Fig. 20 on page 26)

- N-acetyl compound peaks in ovarian Mucinous tumors (Fig. 21 on page 27)
- Krukenberg's tumor (Fig. 22 on page 28)

- N-acetyl compound peaks in ovarian Mucinous tumors: Solid mass-like lesions (Fig. 23 on page 29)

- N-acetyl compound peaks in Mucinous tumors of cervix (Fig. 24 on page 30)

[Lactate]

Lactate (1.33 ppm) is produced via anaerobic glycolysis and concentrated in the necrotic portion of malignant tumors. Abscess caused by aerobic bacteria may present lactate peaks.

Because lactate peak is overlapped with lipid peak, fat-suppression technique is useful for the detection of lactate peak.

- MRS with Fat suppression (Fig. 25 on page 31)

- Lactate peak in the necrotic portion of Malignant tumor (Fig. 26 on page 32)

**Take home points:**

High choline (Cho) --> suggestive Malignancy

N-acetyl mucous compounds (NAMC) --> Mucinous tumor

Lipid (Lip) in solid mass --> Functioning tumor (Thecoma/Fibrothecoma)

Very high Lip in cystic mass --> Mature cystic teratoma

Creatine (Cr) --> Myogenic tumor (Leiomyoma) or residual muscle fibers within infiltrative tumors (Low grade endometrial stromal sarcoma)

Tumor with necrosis --> high Lip/high Lactate (with Fat Suppression)

Malignant tumor with necrosis --> High Cho + Lip

High grade malignant tumor with massive necrosis --> High Lip + Low-no Cho (pitfall)

T2-low mass:

Cho --> Fibroma
Cho + Lip --> Thecoma/Fibrothecoma

Cho + Cr --> Leiomyoma (subserosal)

Solid ovarian mass

High Cho --> suggestive Malignancy

High Lip + Cho --> Functioning tumor (Thecoma)

NAMC + Cho --> Krukenberg’s tumor/Colon cancer metastasis/Mucinous adenocarcinoma

Images for this section:

Fig. 1: Choline peaks in huge myometrial masses
**Fig. 2:** Choline peaks in intra-myometrial masses

Well-demarcated myometrial masses exhibiting high signal intensity on T2WI.

It is difficult to distinguish benign and malignant tumors on T2WI.

Benign myoma with edema shows high intensity on T2WI, and their hypocellularity causes low to intermediate Cho peak.

Choline peak reflects metabolic activity of cell membrane in solid tumors.

Malignant myometrial mass shows high Cho peak.

Malignant lymphoma

Edematous leiomyoma
Both benign and malignant endometrial masses show high signal intensity on T2WI.

Malignant endometrial mass shows high Cho peak, whereas benign endometrial polyp or hyperplasia show low to intermediate Cho peaks reflecting edematous, hypocellular histological feature.

Fig. 3: Choline peaks in endometrial masses
Fig. 4: Choline peaks in endometrial thickening

Both benign and malignant endometrial thickening show high signal intensity on T2WI. Malignant endometrial mass show high Cho peak, whereas benign endometrial hyperplasia show low to intermediate Cho peaks reflecting edematous, hypocellular histological feature.
Fig. 5: Choline peaks in solid ovarian tumors

Choline peak reflects metabolic activity of cell membrane in solid tumors

Solid portions of malignant ovarian tumor show high Cho peaks, whereas benign solid tumors show low to intermediate Cho peaks.
Differentiation of benign and malignant uterine corpus tumors

Quantitative evaluation of the choline concentration

Hyperintense uterine corpus tumors on T2WI have a diagnostic dilemma in the differentiation from malignancies.

Both benign endometrial polyps/hyperplasia and endometrial cancer, and both malignant myometrial tumors (sarcomas) and some benign myometrial lesions (leiomyomas and adenomyotic lesions with edema or myxoid degeneration) showed high signal intensity on T2WI, and quantitative evaluation of the Choline concentration is helpful to distinguish between benign and malignant tumours.

Takeuchi M, Eur Radiol 2010

Fig. 6: Differentiation of benign and malignant uterine corpus tumors: Quantitative evaluation of the choline concentration
Fig. 7: MRS of Uterine cervical cancer
Fig. 8: Biomarker for Treatment response

**Choline peak** reflecting cellular proliferating activity may be **decreased with increased lipid peak** suggesting the presence of radiation-associated necrosis of the tumor cells.
Fig. 9: Early predictor for treatment response: Complete Response
Fig. 10: Early predictor for treatment response Partial Remission
Fig. 11: Lipid peaks in ovarian tumors with necrosis
Fig. 12: Lipid peak in ovarian tumor with massive necrosis
**Fig. 13:** Lipid peaks in functioning ovarian tumors
Fig. 14: Lipid peak in fat-containing tumor
**Creatine:**
*Myomas vs Ovarian tumors*

Creatine peak is observed in uterine myometrium and myogenic tumors (leiomyoma)

<table>
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<th>Ovarian tumors</th>
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Creatine is observed in Myoma 100% (17/17)
in Ovarian tumors 26% (16/61)

Fig. 15: Creatine: Myomas vs Ovarian tumors
Fig. 16: Leiomyomas of the Uterus
**Fig. 17:** Differentiation of low intense mass on T2WI
**Fig. 18:** Tumors with infiltrative myometrial invasion
Fig. 19: N-acetyl (mucous) compounds: Mucinous vs Non-mucinous ovarian tumors
Fig. 20: N-acetyl compound peaks in Mucinous vs Serous loculi of mucinous cystadenoma
**Fig. 21:** N-acetyl compound peaks in ovarian Mucinous tumors
Careful examination of primary gastric cancer should be made, when the ovarian tumor is the first manifestation of the disease.

Mucin-containing signet ring cancer cells

Bimodal high peaks of choline and N-acetyl compound in solid mass may be characteristic for malignant mucinous tumor such as Krukenberg’s tumor.
**Fig. 23:** N-acetyl compound peaks in ovarian Mucinous tumors: Solid mass-like lesions
Fig. 24: N-acetyl compound peaks in Mucinous tumors of cervix
Because lactate peak is overlapped with lipid peak, fat-suppression technique is useful for the detection of lactate peak.

Fig. 25: MRS with Fat suppression
Fig. 26: Lactate peak in the necrotic portion of Malignant tumor
Fig. 27: VOI setting
Conclusion

3T-MRS can provide useful information for the differential diagnosis of gynecologic tumors.

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References