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A Preliminary Report Requiring Continuation of Research to Confirm Fallopian Tube Adenocarcinoma: A Non-Experimental, Non-Randomized, Cross-Sectional Study

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Background: Transvaginal ultrasound has fair characteristics, and pathology is an invasive technique for fallopian tube tumor diagnosis. Magnetic resonance images have better intra- and inter-observer reliabilities for detection of primary fallopian tube malignant tumor(s) than the other diagnostic modalities. The purpose of this study was to investigate parameters of different types of magnetic resonance images for women with fallopian tube adenocarcinoma and to compare these parameters with the FIGO grading system to improve the accuracy of diagnosis and prognosis.

Material/Methods: A total of 121 women who had clinically-proven fallopian tube adenocarcinoma were included in this cross-sectional study. A 3.0 T magnetic resonance images system was used for spin-lattice relaxation-weighted (T1WI), spin-spin relaxation-weighted (T2WI), diffusion-weighted, (DWI), and apparent diffusion coefficient (ADC) images. ANOVA following Tukey *post hoc* tests and Spearman rank correlation were performed at 99% confidence level.

Results: Axial T1WI, axial T2WI, and axial DWI, were provided low, intermediate, and high fluid signal intensity, respectively, for a tumor. Sagittal T1WI showed contrast uptake by the mass with necrosis. Sagittal T2WI showed a solid mass with well-defined walls. Sagittal DWI showed restriction to diffusion. ADC values were significantly higher for FIGO grade 1 women than for FIGO grade 3 women ($p<0.0001$, $q=16.591$). The Spearman correlation coefficient was 0.1012 between mean ADC and FIGO grading.

Conclusions: We recommend that magnetic resonance images be included in the FIGO guideline for grading of malignancies in the female genital tract.

MeSH Keywords: Diffusion Magnetic Resonance Imaging • Fallopian Tube Neoplasms • Genital Neoplasms, Female • Magnetic Resonance Imaging

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Background

Primary fallopian tube malignant tumors commonly occur in postmenopausal females, with a wide age range and a mean age of 52 years [1], and rarely occur among malignancies in the female genital tract [2]. An adenocarcinoma is the common histologic type. However, fallopian tube adenocarcinomas account for only 0.3–1% of all gynecologic malignant tumors [2]. There is a high risk of preoperative misdiagnosis due to the complex anatomy of the tumor [3].

The clinical signs of primary fallopian tube malignant tumor are nonspecific and insidious [4]. Transvaginal pelvic sonography by ultrasound is the first choice of investigations in primary fallopian tube malignant tumor, but early diagnosis is difficult. Moreover, thorough knowledge of the normal sonographic appearance is also required for diagnosis and prognosis [5]. Magnetic resonance images (MRI) are used for diagnosis of a myometrial invasion, the local aggressiveness of adenocarcinoma, and distant metastasis and/or lymph node [6]. MRI has good intra- and inter-observer reliabilities for detection of primary fallopian tube malignant tumor(s) [7]. MRI has a high signal-to-noise ratio [8]. Moreover, MRI is considered to be the criterion standard for incidentally detected, ultrasound-guided, adnexal lesions in non-pregnant females [9]. Transvaginal ultrasound has fair characteristics for diagnosis [10]. FDG (^{18}Fludeoxyglucose) PET (positron emission tomography) is a suitable method for identifying primary fallopian tube malignant tumors but has availability, cost, and radiation dose problems [4]. Moreover, computed tomography (CT) and ultrasound have inferior soft-tissue contrast [11]. Therefore, an accurate imaging study is required in the diagnosis of primary fallopian tube malignant tumor.

DW (diffusion-weighted) and PW (perfusion-weighted) MR imaging methods are more developed than SE (Spin echo), axial, T1WI (Spin-lattice relaxation-weighted imaging), and T2WI (Spin-spin relaxation-weighted imaging) in assessing cellular and microvascular parameters in pelvic and abdominal organs [12]. The changes in values of ADC (apparent diffusion coefficient) are correlated with prognosis of the tumor [13].

The objective of this study was to investigate parameters of different types of MR images for women with fallopian tube adenocarcinoma. The secondary endpoint of the study was correlating these parameters with pathological findings to improve the accuracy of diagnosis and prognosis.

Table 1. Clinical parameters of the enrolled women.

Characters		Women (percentage)	
Sample size		121	
Age (years)	35–45	6	(5)
	46–55	75	(62)
	56–65	25	(21)
	≥66	15	(12)
Abnormal vaginal bleeding		15	(12)
Vaginal watery discharge		18	(15)
Menstruation status	Postmenopausal	120	(99)
	Premenopausal	1	(1)
Abdominal swelling		27	(22)
Abdominal pain		53	(44)
Elevated serum CA-125*		28	(23)

* CA-125 assay. Data were represented as number (percentage).

Material and Methods

Ethics approval and consent to participate

The study had been registered in the research registry (*www.researchregistry.com*), UID No. researchregistry3745, dated 1 January 2014. The protocol (RD/HU/13/14, dated 15 December 2013), was approved by the Maternal and Child Health Care Hospital, Xiamen, China review board. The study adhered to STROSS guidelines, the law of China, and the 2013 Declarations of Helsinki. All enrolled women signed an informed consent form regarding radiology, pathology, and publication of the study (including a personal image of women, if any) in all formats (electronic and hard) irrespective of the time and language. All data and materials used in the study were available from DICOM files of women.

Inclusion criteria

All women admitted from 2 January 2014 to 1 February 2018 to the Department of Obstetrics and Gynecology of the Maternal and Child Health Care Hospital, Xiamen, China were included in the study. We included women age 35 years and above, with vaginal watery discharge, vaginal bleeding, abdominal swelling and pain, and the elevated serum CA-125 antigen level (based on CA-125 assay). Clinical parameters of the enrolled women are summarized in Table 1.

Exclusion criteria

Women who had the secondary fallopian tube malignant tumor, extensive ovarian cancer, and fallopian tube malignant

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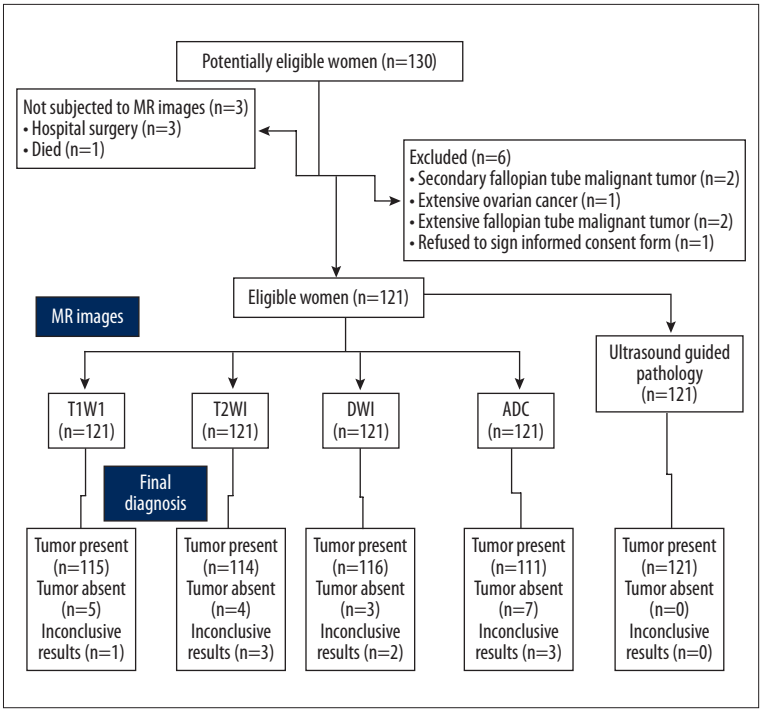

Figure 1. STARD flow diagram of the study. MR: Magnetic resonance.

Table 2. The scanning parameters of different types of magnetic resonance images.

Parameters	Different types of magnetic resonance images			
	T1WI	T2WI	Diffusion-weighted imaging	ADCI
Technique	2D-GE	2D-TSE	2D single-shot EPI	2D
Repetition time (msec)	7344	7344	7344	7344
Echo time (msec)	2.299	89.9	63.9	20
Flip angle	1420	1420	1990	1420
Field of View (mm^2)	320×320	320×320	320×320	320×320
Metrix	320×224	288×224	288×224	96×128
Spatial resolution (mm^2)	1×1	0.5×0.6	3×4	1.5×2
Section thickness (mm)	5	5	5	5
Section gap (mm)	6.5	6.5	6.5	6.5
Numbers of sections	6	4	8	500
Numbers of signals acquired	1	1	2	1
Echo train length	20	20	30*	40
Sensitivity encoding	1	1	3	1
b value (sec/mm^2)	–	–	0, 500, 1000	0, 500, 1000
Respiration	Free breathing	Free breathing	Free breathing	Breath holding
Fat suppression	–	–	Spectral attenuation with inversion recovery	–
Imaging time (min: sec)	1: 0	3: 50	3: 20	0: 1

T1WI – spin-lattice relaxation-weighted imaging; T2WI – spin-spin relaxation-weighted imaging; FSE – fast spin echo; GE – gradient echo; D – dimensional; TSE – turbo spin echo; EPI – echo-planar imaging; ADCI – apparent diffusion coefficient imaging.

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Table 3. International Federation of Gynecology and Obstetrics grading system.

Grade	Differentiation	% non-squamous solid component
1	Well-differentiated	<5
2	Moderate	6–50
3	Poor	>50

tumor, or who refused to sign informed consent form were excluded from the study.

A total of 121 enrolled women were subjected to non-experimental, non-randomized, cross-sectional study. The STARD flow diagram of the study is shown in Figure 1.

Different types of MR images and imaging analysis

The 3.0 T MR imaging system (Siemens Healthcare, Germany) was used for image scans. The scanning parameters of different types of MR images are as reported in Table 2. The scanning range was to the renal hilum from the inferior pubic symphysis and extended beyond the dome of the tumor if a huge mass was present. MRI was reviewed by the authors and characterized for size, laterality, and shape of the tumor, physical structures of the tumor (solid or cystic), the intensity of the signal (fat and myometrium), and value of ADC. ADC was measured on ADC maps with a region of interest (ROI), placed at solid targeted areas of the homogeneous signal on conventional MRI (30-pixel). The extra-fallopian tube characters like the intrauterine fluid collection, peritoneal implant, hydrosalpinx, lymphadenopathy, and ascites were also evaluated.

Histopathologic analysis

Specimens were collected by ultrasound (Koninklijke Philips N.V.)-guided automatic gun biopsies (Millennium Surgical Corp, USA) by a pathologist who was blinded to radiology results. The development of primary fallopian tube malignant tumor was characterized using hematoxylin-eosin staining as per the FIGO (International Federation of Gynecology and Obstetrics) grading system (Table 3) [6].

Reagents

Hematoxylin, eosin, and glycerin were purchased from Mark Specialties (Germany).

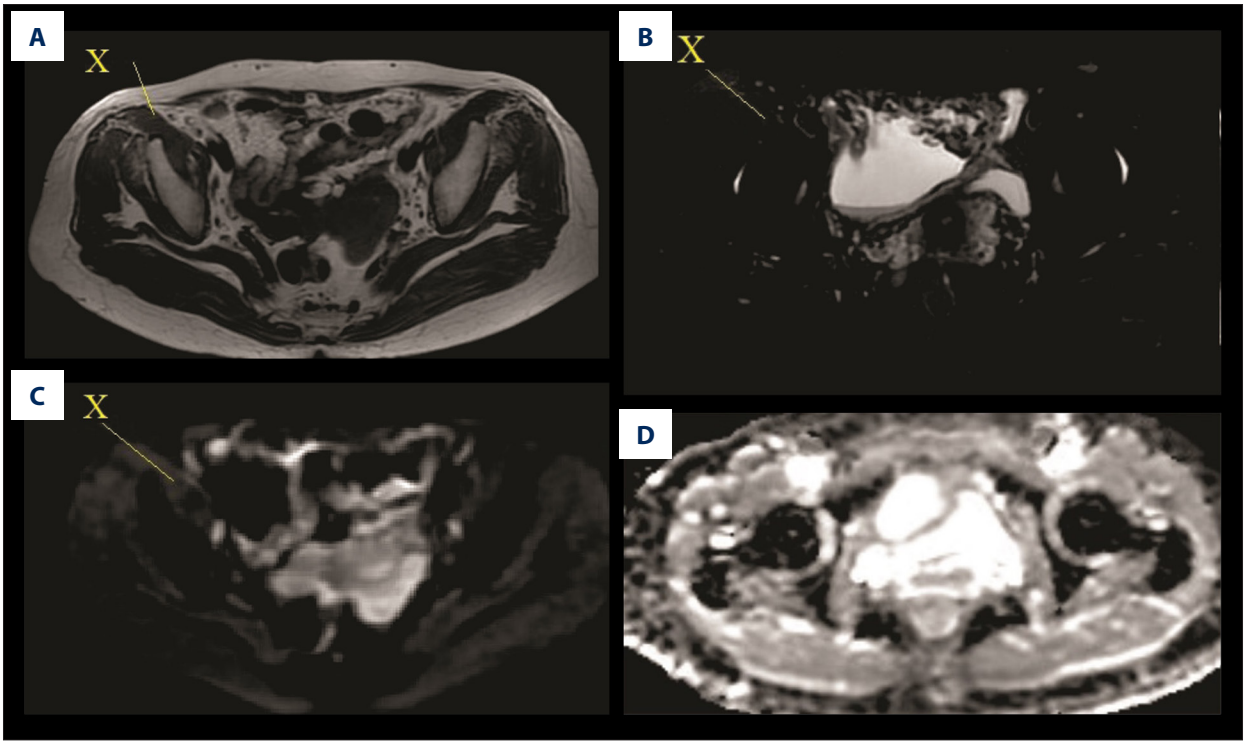

Figure 2. Axial MR images of the primary fallopian tube with a malignant tumor of a 67-year-old woman who had CA-125 level: 157 U/mL. (**A**) T1WI, (**B**) T2WI, (**C**) DWI, (**D**) ADC image. X – a small amount of cancerous tissue with degeneration in the right fallopian tube; MR – magnetic resonance.

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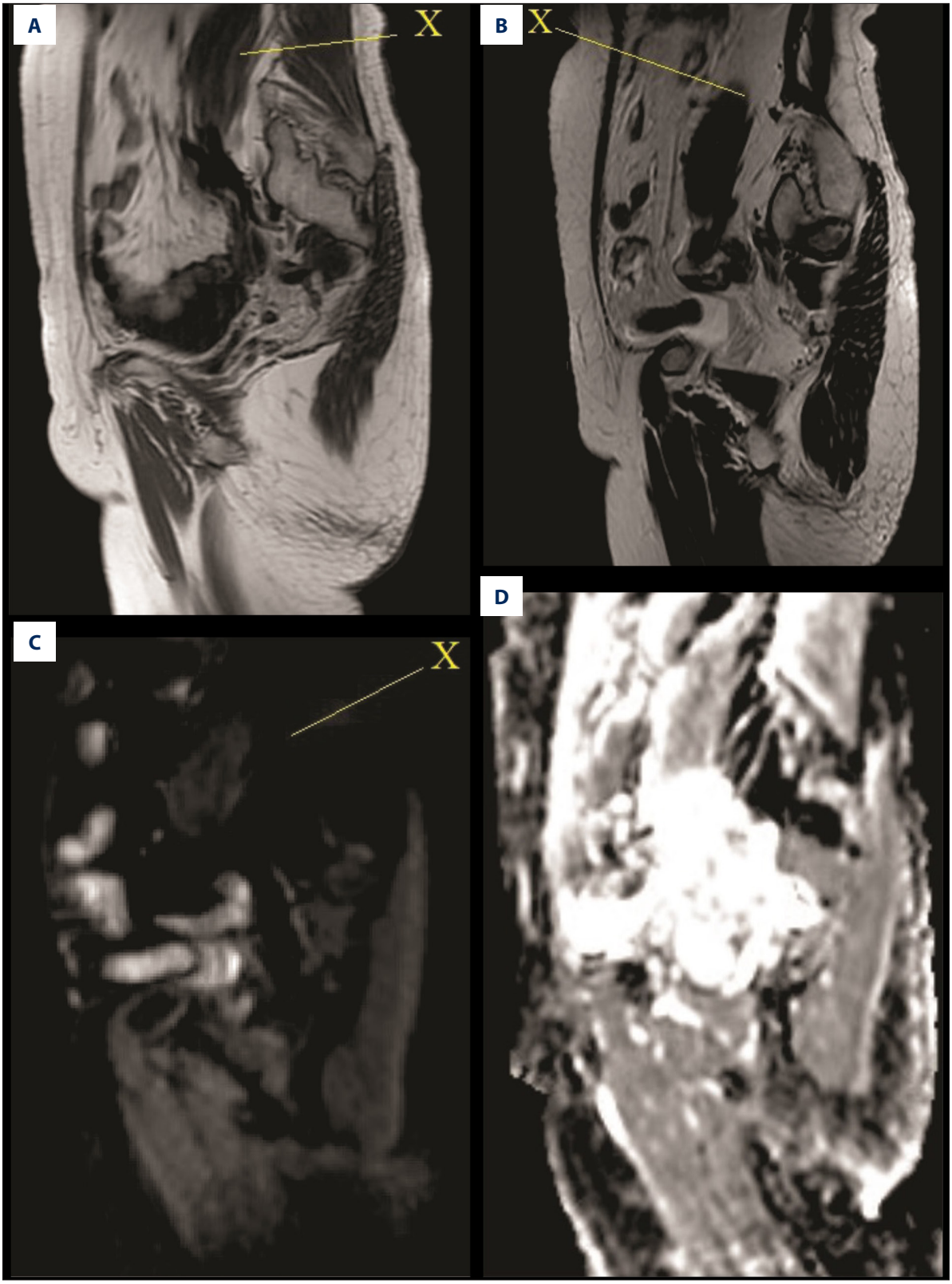

Figure 3. Sagittal MR images of the primary fallopian tube with a malignant tumor of a 67-year-old woman who had CA-125 level: 157 U/mL. (**A**) T1WI, (**B**) T2WI, (**C**) DWI, (**D**) ADC image. X – a small amount of cancerous tissue with degeneration; MR – magnetic resonance.

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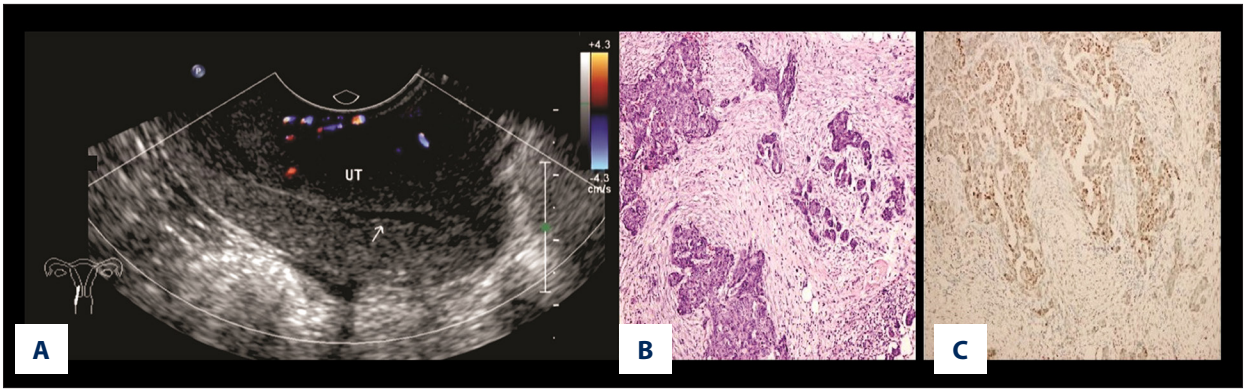

Figure 4. Pathological images of the primary fallopian tube with a malignant tumor of a 67-year-old woman who had CA-125 level: 157 U/mL and FIGO grade 3. (**A**) Ultrasonography, (**B**) pathology by hematoxylin-eosin staining dye and (**C**) pathology by silver stain. Differentiation of serous adenocarcinoma in the peritoneum and omentum (metastasis due to the pathology-possible source of the Mullerian duct) went to a hospital surgery. FIGO – International Federation of Gynecology and Obstetrics.

Table 4. Comparison of the mean value of apparent diffusion coefficient among FIGO grading by statistical analysis.

Value		FIGO grading			Statistical analysis			
Sample size		1	2	3	p	*q*		
		32	40	49		1 *vs.* 2	1 *vs.* 3	2 *vs.* 3
Value of apparent diffusion coefficient ($\times 10^{-3}$ mm^2/sec)	Minimum	1.3	0.95	0.69	<0.0001	24.08	40.618	16.591
	Maximum	1.8	1.3	0.91				
	Standard deviation	0.16	0.12	0.07				

One-way ANOVA following Tukey *post hoc* tests were used for statistical analysis. A $p<0.01$ and $q>26.636$ were considered significant. FIGO – International Federation of Gynecology and Obstetrics.

Statistical analysis

Spearman rank correlation (considering coefficient (r) value 0.045 to 0.099 as the limit for significance) was performed between results of FIGO grading system and ADC values. One-way analysis of variance (ANOVA) following Tukey *post hoc* tests (considering critical value [*q*] >26.636 as significant) were performed to compare results of the FIGO grading system and mean ADC values. InStat (GraphPad, USA) was used for statistical analysis. The results were considered significant at 99% confidence level [6]. Intention-to-treat analysis method was used.

Results

Axial T1WI (Figure 2A), axial T2WI (Figure 2B), and axial DWI (Figure 2C) were provided low, intermediate, and high fluid signal intensity, respectively, for a tumor of the fallopian tube. Axial ADC images showed adenocarcinoma with restricted diffusion (Figure 2D). Sagittal T1WI showed contrast uptake by the mass, with necrosis (Figure 3A), sagittal T2WI showed a solid mass with well-defined walls (Figure 3B), and sagittal DWI showed restriction to diffusion (Figure 3C). Sagittal ADC images showed lower ADC values (Figure 3D).

The parameters of MRI were correlated with ultrasound-guided pathological findings before the decision of surgeries (Figure 4). Higher-grade tumors showed lower ADC values. ADC values were significantly higher for FIGO grade 1 women than for FIGO grade 3 women (Table 4). The Spearman r was 0.1012 between mean ADC and FIGO grading (Figure 5). In 4 women, differentiation of serous adenocarcinoma was shown in the peritoneum and omentum (metastasis due to the pathology-possible source of the Mullerian duct) and they underwent hospital surgery.

Discussion

Identification of tumor stage in the diagnosis of fallopian tube adenocarcinoma is challenging before surgery because current guidelines for FIGO grade discrimination do not consider image analysis [6], and only consider pathology [14]. However, clinical

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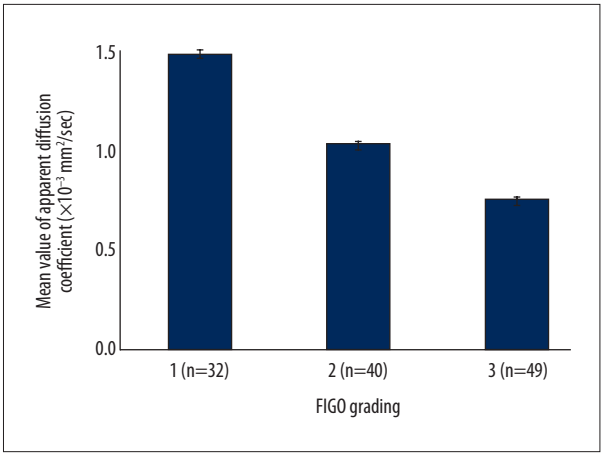

Figure 5. Comparisons of mean ADC value among FIGO grading by Spearman rank correlation coefficient (r). Data are represented as mean ±SE of them. Spearman r=0.1012. Considering 0.045 to 0.099 limit for the significance of Spearman r. ADC – apparent diffusion coefficient. FIGO – International Federation of Gynecology and Obstetrics.

symptoms are seen in less than 15% of these women [15]. Ultrasound-guided hysteroscopy is often used for diagnosis of fallopian tube adenocarcinoma, but hysteroscopy curettage and pathology can lead to metastasis by various sources such as Mullerian duct. Moreover, hysteroscopy-guided curettage has not improved carcinoma-specific survival [16]. However, MRI is a noninvasive technique for diagnosis of tumor and survival before surgeries [17]. In consideration of methods available for diagnosis of gynecological cancer, there is a need to update FIGO guidelines of diagnosis and prognosis of cancer.

The present study found no correlation between ADC values and pathological findings. ADC values are a measure of diffusion of water molecules in tissues [18]. Higher-grade tumors have lower ADC values because of high cellular density [19]. These results are not in line with other studies [6,20,21] but do agree with the other available reports on evaluations of the efficacy of chemotherapies by MRI [18, 22]. Moreover, The b-value also affects values of ADC [21]. The values of ADC are useful for assessing the effectiveness of chemotherapy [23], but not useful prior to chemotherapy for prognosis of disease [18]. It is difficult to identify threshold values of ADC for differentiation of tumors [24]. We found that ADC values were not useful in the diagnosis of fallopian tube adenocarcinoma. Advanced techniques with ADC values and voxel-by-voxel histogram analysis are required.

The present study was a qualitative and quantitative MRI assessment of fallopian tube adenocarcinoma. T2WI had intermediate fluid signal intensity, T1WI has low fluid signal intensity core, and DWI has high fluid signal intensity [25]. With respect to the design of the study, there were few intra-observer errors.

DWI succeeded in providing crucial diagnostic information regarding the architecture of fallopian tube adenocarcinoma. DWI depends on a complex interaction between the Brownian motion of water molecules and biological membranes. Brownian motion occurs less freely in a compartmentalized arrangement than in a highly cellular arrangement [26]. Fallopian tube adenocarcinoma consists of tightly packed cells and therefore has restricted diffusion. We found that DWI is a good state-of-the-art method for grading of fallopian tube adenocarcinoma.

There are certain limitations of this study: interpretations of imaging analysis were not confirmed by another experienced radiologist; intra- and between-observer variabilities between different types of MRI were not evaluated; and contrast-enhanced MRI and PWMRI affect the microcirculation of the body [27], so methods using gadopentetate dime glutamine or other dyes were not used for women.

Conclusions

This non-experimental, non-randomized, cross-sectional study recommends different MRI images in FIGO guidelines for grading of malignancies in the female genital tract since histopathology is the only criterion standard for diagnosis of fallopian tube adenocarcinoma. Further studies with large sample sizes are warranted.

Acknowledgments

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Conflict of interest

None.

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