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Evaluation of deep myometrial invasion in endometrial cancer patients: is dual-energy CT an option?

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Abstract
Objectives Assessment of deep (>50%) myometrial invasion by dual-energy CT (DECT) and Trans-Vaginal US (TVUS) in patients with endometrial cancer.
Methods We retrospectively enrolled patients with endometrial cancer who underwent DECT and TVUS for pre-surgical staging. Three sets of images were evaluated: 70 keV (routine CT images), 50 keV, and iodine-water reconstructions. The gold standard was pathology after surgery. The agreement between the different imaging modalities and the gold standard was estimated. Sensitivity, specificity and accuracy for each imaging modality were evaluated with 95% confidence intervals (CI).
Results Thirty-nine patients were included. Median time from CT and TVUS to surgery was 23 and 18 days, respectively. The best agreement between evaluation of myometrial infiltration and the gold standard was 0.88 (0.72, 1.00) for the 50 keV images; the worst agreement was 0.43 (0.00, 0.88) for the 70 keV images. CT iodine reconstructions and US agreement were comparable. Specificity, sensitivity and accuracy were 0.91, 1.00, 0.94; 0.57, 0.86, 0.71; 0.82, 1.00, 0.87; 0.91, 0.77, 0.86 for 50 keV, 70 keV, iodine reconstructions and ultrasound, respectively.
Conclusions DECT is a promising tool for assessment of myometrial invasion in endometrial cancer patients, with a special focus on 50 keV images.

Keywords Myometrial invasion · Endometrial cancer · Dual Energy CT · Ultrasound · Imaging

Introduction

Endometrial cancer is the second most prevalent cancer among women after breast cancer, with an estimated prevalence of almost 830,000 women living in the United States in 2016 [1]. The standard of care for endometrial cancer patients with a good performance status and resectable tumor is surgical removal that may include hysterectomy, bilateral oophorectomy, pelvic and lombo-aortic lymphadenectomy, omental and peritoneal biopsies.

Lymph node metastasis, related to deep invasion (>50%) of the myometrium, is the most common form of extrauterine disease spread and the strongest predictor for recurrence. For patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%), lymphadenectomy is not recommended, and only hysterectomy with bilateral oophorectomy is performed. For intermediate-risk patients (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%) and high-risk

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patients (grade 3 with deep myometrial invasion >50%), lymphadenectomy can be considered for staging purposes (intermediate-risk) or even recommended (high-risk), along with omental and peritoneal biopsies [2].

According to the European Society of Urogenital Imaging guidelines for staging endometrial cancer [2, 3], the indications for MR, as helpful imaging for local staging, include: high grade, serous or clear cell adenocarcinomas, suspicion of deep myometrial invasion, and screening for lymphadenopathy. A prospective collaborative trial comparing MRI and ultrasonography (US), reported that the accuracy of US is comparable to that of MRI for local staging [4]. CT is not considered accurate for local staging, while MR and CT are considered equivalent in evaluation of lymph nodal invasion .

Recently introduced dual-energy CT (DECT) scanners use more than one energy peak for fast image acquisition and depict the interaction of tissues and materials with X-ray beams at different energies [5, 6]. These scanners generate virtual monochromatic images from material-specific images using a complex algorithm, thus providing images similar to those obtained with single-energy CT. DECT also yields processed images that increase iodine conspicuity (enhancement) in parenchymal tissue or vascular structures, and help to differentiate materials according to the different energies of the X-ray beam (so-called material decomposition).

Since CT is frequently recommended for distant staging (not only for N staging, but also for M staging), CT assessment of deep myometrial invasion would allow patients to avoid an additional examination for local staging, and could represent a one-stop radiological examination for staging endometrial cancer.

To the best of our knowledge, no study has hitherto evaluated the performance of DECT in evaluating deep myometrial infiltration by endometrial cancer. The objective of this study was a retrospective assessment of deep (>50%) myometrial invasion in patients with a diagnosis of endometrial cancer who underwent DECT for staging.

Materials and methods

Patient selection

Patients with a diagnosis of endometrial cancer who underwent CT with spectral imaging before surgery between 28/10/2015 and 28/04/2017 (18 months) were retrospectively selected for inclusion in this study. Exclusion criteria were: acquisition of CT scan without the use of spectral imaging, extensive pelvic artifacts caused by metallic hip prostheses, and surgery performed at other institutions. Written informed consent to CT examination, and to the use of anonymized clinical and imaging data for scientific and/or educational purposes was obtained from all patients at first access in our institution.

CT imaging technique

All CT examinations were performed on a Discovery CT750 HD scanner (General Electric Healthcare, Milwaukee WI, USA). Patients were asked to fast for at least 6 h beforehand. Contrast medium was divided into two different intravenous (iv) pushes administered by an automated injector at 4.0 ml/s and 2.0 ml/s, respectively, followed by 40 ml of saline injected at 2.0 ml/s. During the selected period, the contrast agent used was Ultravist® 370 (Bayer, Leverkusen, Germany), and the amount of iodine administered was always proportional to the patient's weight (1.7 ml/kg). All scans extended in a cranio-caudal direction from the lung apices or from the liver dome to the pubis in the portal venous phase (90–120 s after iv administration of contrast medium). All images were archived in digital format.

Scans were acquired during a single breath-hold with the following parameters: tube rotation time: 0.5 s; spiral pitch factor: 0.984; standard algorithm reconstruction; total collimation width 40 mm (64 × 0.625 mm); slice thickness 2.5 mm; reconstruction interval 2.5 mm; display field of view 330–400 mm; tube voltage 80 and 140 kV; fixed tube current 630 mA.

Evaluation of CT images

Each examination was evaluated using the GSI viewer-GSI Liver and Kidney tool on the Aw Server (GE Medical Systems), where images were reconstructed at different keV levels and evaluated in the axial, sagittal and coronal planes by a radiologist with 12 years of experience in gynecological imaging (SR). Evaluation of CT images included: assessment of deep (>50%) myometrial invasion in the following three sets of images: 70 keV (corresponding to usual CT images), 50 keV, and iodine material decomposition images. At the time of CT scan assessment, the radiologist was aware of the diagnosis of endometrial cancer, but was blind to the results of surgery and the pathology report.

On the three sets of images the radiologist described endometrial cancer as: not assessable (na); stage Ia, if the tumor was confined to the endometrium or invaded the inner half (<50%) of the myometrium; stage Ib, if the tumor invaded the outer half (>50%) of the myometrium [7].

Ultrasound

All patients underwent gynecological transvaginal US as part of their standard presurgical local staging when evaluation of myometrial invasion was always performed and recorded.

The reference gold standard (GS) for comparison of the radiological assessment was the pathological examination after surgery.

Statistical analysis

The agreement between the three sets of CT images (50, 70 keV and iodine), the US and the GS for evaluation of deep myometrial invasion was estimated by the Cohen's Kappa statistic (k) and tabulated with 95% confidence intervals (CI). The power of the observed agreement for each set vs the null hypothesis of $k = 0.50$ using a two-sided significance test at the 5% level was also calculated. All significance tests were at the 5% level and two-sided. Summary statistics (counts, mean, median, min and max as well as percent) for patient's age, days from CT/US to surgery and grading were also produced.

Based on the comparison with the GS, sensitivity, specificity and accuracy of images at 50, 70 keV, iodine material decomposition and US were evaluated and tabulated with the proper 95% CI.

Results

The study included 39 patients with a median age of 61 years (47–89). All the histological examinations showed endometrioid adenocarcinomas; 11/39 (28%) with a differentiation grade 1; 15/39 (38%) with a differentiation grade 2; 13/39 (33%) with a differentiation grade 3 (Table 1). Median time between CT scan and surgery was 23 days; median time between US and surgery was 18 days (Table 1).

Among the three sets of CT images, myometrial invasion was not assessable in 24/39 (61%) patients at 70 keV, in 1/39 (2%) patients at 50 keV, and in 14/39 (35%) in the iodine material decomposition images.

The agreement between evaluation of myometrial infiltration and the GS at 50, 70 keV, iodine reconstructions and US is summarized in Table 2. The best agreement, equal to 0.88 (0.72, 1.00) was for the 50 keV images; the worst agreement, equal to 0.43 (0.00, 0.88) was for the 70 keV images. Agreement for CT iodine reconstructions and US was comparable: 0.71 (0.42, 1.00) and 0.69 (0.44, 0.94), respectively. However, the post hoc power calculation showed that among the three sets of CT images, only those at 50 keV had enough power (88%) to test the hypothesis of no difference with respect to the GS (power for 70 keV, iodine reconstruction and US agreement with the GS were 7, 16 and 21%, respectively). Sensitivity, specificity and accuracy with 95% CI are summarized in Table 3, demonstrating that 50 keV images showed the best accuracy (0.94).

Discussion

The standard of care for endometrial cancer patients is surgical removal that may include hysterectomy, bilateral oophorectomy, pelvic and lombo-aortic lymphadenectomy, omental and peritoneal biopsies.

Since systematic lymphadenectomy carries disadvantages such as a 7–10% risk of lymph cyst formation after surgery [8, 9], bilateral irreversible lymphedema, increased anesthesia and operating time, and the need for a specialized surgical oncologist, many attempts have been made to stratify patients according to risk of lymphadenopathies to select patients who can avoid para-aortic lymph nodal dissection. A combination of preoperative imaging and intraoperative evaluation is considered helpful to determine if this surgical procedure is necessary in each patient [10].

Specifically, for patients with low-risk endometrial cancer and for endometrial cancer patients in childbearing age, pre-operative assessment of myometrial invasion might be considered [2, 11, 12]. Yamashita et al. demonstrated that the greatest difference in MR contrast enhancement between invaded and non-invaded myometrium is visible 120 s after contrast medium injection, where the tumor invading the myometrium demonstrated decreased enhancement

Table 1 Patients' characteristics

	N	Mean (median)	Min, max
Age (years)	39	62.6 (61.0)	47, 89
Days			
From CT to surgery		23.7 (23.0)	1, 56
From ultrasound to surgery		23.6 (18.0)	1, 93
Grading	*N* (%)		
G1	11 (28.1)		
G2	15 (38.5)		
G3	13 (33.3)		

Table 2 Agreement between myometrial infiltration measures and the gold standard

	Infiltration	Infiltration at surgery (gold standard)		Kappa (95% CI)	*P* value[b]
		N (col %)[a]			
		<50%	≥50%		
50 keV	<50%	20 (90.9)	0	0.88 (0.72, 1.00)	
	≥50%	2 (9.1)	13 (100)		
	Total	22	13		0.16
70 keV	<50%	4	1	0.43 (0.00, 0.88)	
	≥50%	3	6		
	Total	7	7		0.32
Iodine reconstructions	<50%	14 (82.4)	0	0.71 (0.42, 1.00)	
	≥50%	3 (17.7)	6		
	Total	17	6		0.08
Ultrasound	<50%	20 (90.9)	3 (23.1)	0.69 (0.44, 0.94)	
	≥50%	2 (9.1)	10 (76.9)		
	Total	22	13		0.65

P value indicates significant difference between the imaging measures and the gold standard

[a] Column percent values not shown for column counts <10

[b] McNemar's test

Table 3 Sensitivity, specificity and accuracy with 95% CI in evaluation of myometrial infiltration

	Specificity	Sensitivity	Accuracy
50 keV	0.91 (0.71, 0.99)	1.00 (0.75, 1.00)	0.94 (0.81, 0.99)
70 keV	0.57 (0.18, 0.90)	0.86 (0.42, 1.00)	0.71 (0.42, 0.92)
Iodine reconstructions	0.82 (0.57, 0.96)	1.00 (0.54, 1.00)	0.87 (0.66, 0.97)
Ultrasound	0.91 (0.71, 0.99)	0.77 (0.46, 0.95)	0.86 (0.70, 0.95)

compared to the strong enhancement of the normal myometrium [13]. According to this time delay, CT scans were acquired in our cohort during the portal venous phase, between 90 and 120 s after contrast medium injection.

Many centers, including ours, stage endometrial cancer patients by second-level US (for local staging) and CT scan (for distant staging). If a CT scan could assess myometrial invasion, it might offer additional information for local staging, especially in case of doubtful results, and serve for distant staging.

CT scanning has never been considered reliable for local staging of endometrial cancer because it is not sensitive or specific enough to assess the depth of myometrial or cervical involvement, due to the poor contrast difference between tumor and myometrium [14], the tumor itself being barely visible on CT images. Indeed, conventional CT uses a single energy X-ray beam to acquire images, where the pixel values and HU are based on how many photons reach the detectors and how many are absorbed by the different tissues compared to those absorbed by water. Therefore, materials with a different elemental composition may have the same CT density, with a limited possibility of differentiating diverse materials within a single anatomical structure. This traditional limit of CT in evaluating the local extent of endometrial cancer was confirmed in our series, where the tumor itself was barely visible in the 70 keV images, corresponding to the routine images acquired at 100 kV. Accordingly, on virtual monochromatic images at 70 keV, myometrial invasion could only be assessed in 39% of patients, and the consequent agreement with surgery was as low as 0.43.

DECT may overcome this limitation because an additional attenuation measurement is obtained at a second energy, allowing the differentiation of two materials and quantification of their mass density. This approach is currently implemented with different methods: fast kVp switch between high and low energy (from 140 to 80 keV), dual X-ray sources and a multilayer detector, in which the innermost layer collects the low-energy data, while the high-energy data are collected by the outermost layer. The CT device used in this study adopted the fast kVp switch solution: a complete description of the advantages and disadvantages of each technique is provided by McCollough et al. [15].

Studies have shown that virtual monochromatic images depict more subtle contrast enhancement and improved attenuation than the default polychromatic images of single-energy CT [16]. Specifically, low-energy virtual monochromatic images provide higher contrast between adjacent structures because of higher beam attenuation by iodine; the drawback is that these images show more noise, particularly in heavier patients. On the other hand, high-energy images have less noise but provide less contrast between adjacent structures. Virtual monochromatic images generated at 60–77 keV are reported to have optimal peak contrast-to-noise ratio for soft tissue evaluation, while those generated at 50–55 keV are optimal for evaluating blood vessels and depicting slow flow [6].

Accordingly, in addition to the 70 keV images, we evaluated virtual monochromatic images at 50 keV, as well as images reconstructed according to the material decomposition amplifying the presence of iodine (iodine reconstructions). Virtual monochromatic images at 50 keV displayed a subtle line of hyperdensity delineating the outer margin of the tumor, and this allowed us to delimit the tumor and its relative invasion of the myometrium (Fig. 1). Consequently, myometrial invasion was discernible in this set of images in 35/39 patients and the agreement with the GS was as high as 0.88, with a narrow range of CI (0.72, 1.00).

Evaluation of iodine material decomposition images was more effective than that at 70 keV, with 14/39 not assessable tumors, and a percentage of agreement with surgery of 0.71, comparable to that of US (0.69).

Our results show that for the evaluation of deep myometrial invasion, images reconstructed at 50 keV performed better than iodine reconstructed images and monochromatic 70 keV images (Fig. 2), with sensitivity, specificity and accuracy of 0.91, 1.00 and 0.94, respectively. Iodine reconstructions and US showed comparable results, while images reconstructed at 70 keV were not reliable.

There are some limitations in this study. First, the CT images were evaluated by a single experienced radiologist in a single center (monocentric study), and this may have affected the results. However, since this is the first study to evaluate deep myometrial invasion in endometrial cancer by DECT, we decided not to add an additional assessment bias. Future larger validation studies may consider an evaluation of inter-observer agreement. Second, we did not compare the results of CT scan with MR as our Institution prefers the approach of second-level US combined with a CT scan for distant staging. Since we had no previous evidence of DECT performance in the evaluation of myometrial invasion, we decided not to alter the usual local management of endometrial cancer patients by adding an MR examination. This comparison will be reserved for future evaluations. Third, the number of cases evaluated in this study is relatively small ($n = 39$) to determine the accuracy of DECT as a pre-operative imaging modality for local staging of endometrial cancer patients. However, the power analysis performed showed that this number would have been enough to reach an agreement equal to the maximum of the observed agreement ($k = 0.88$). These encouraging results suggest that DECT may be considered for assessment of deep myometrial invasion at first as an adjunct to other assessments and, after further validation, as an alternative to other pre-operative imaging examinations.

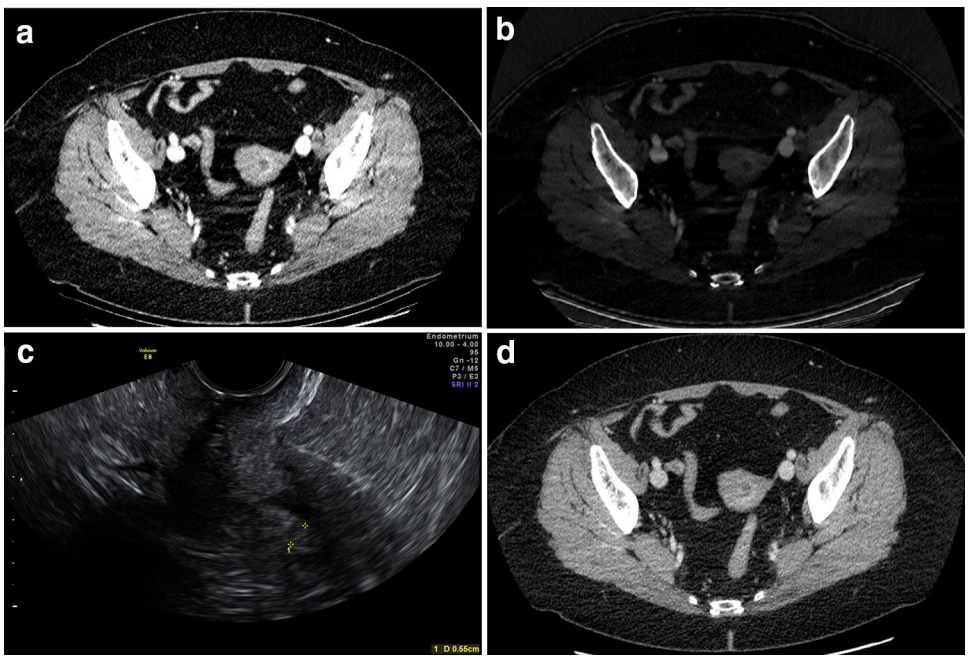

Fig. 1 A 54-year-old patient with endometrial cancer stage Ia. The small lesion was well depicted on the axial CT images at 50 keV (**a**) and iodine reconstructions (**b**), where it was delineated by a subtle rim of contrast enhancement, showing that the myometrium was infiltrated <50%; the lesion was also clearly visible in ultrasound (**c**), whereas its outer margins were difficult to see on the 70 keV images (**d**)

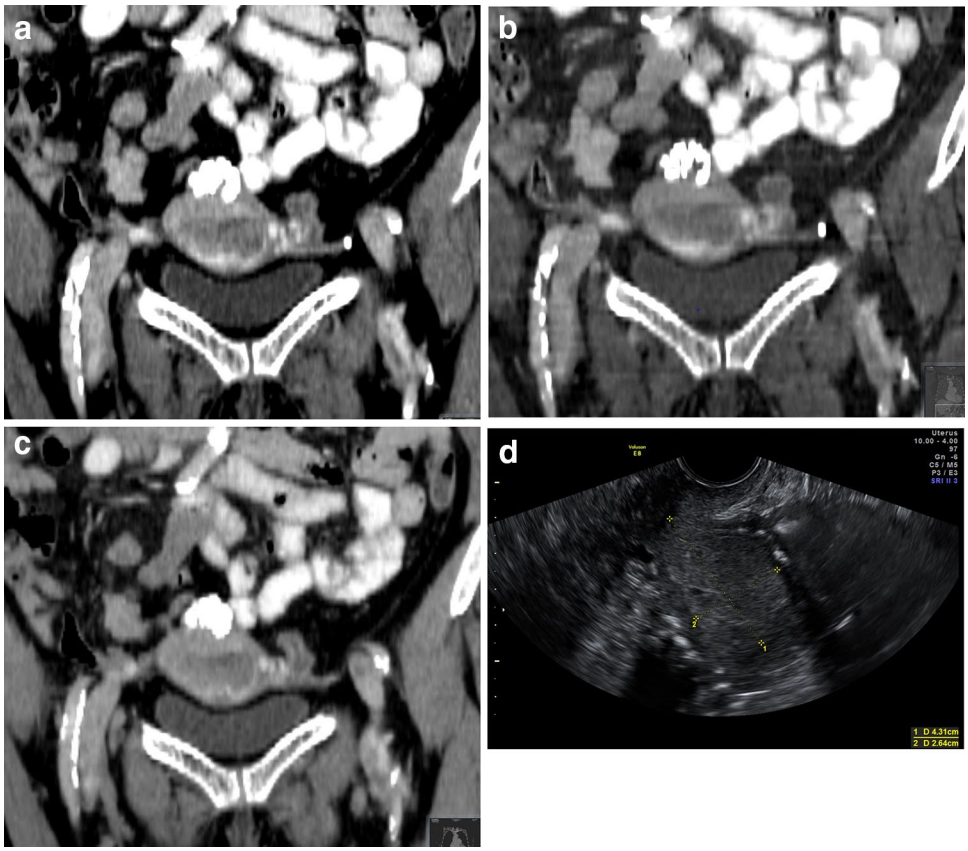

Fig. 2 A 70-year-old patient with endometrial cancer stage Ib. The lesion's margins, which infiltrated the myometrium >50%, especially on the right side, are better visible in the CT coronal reconstruction at 50 keV (**a**), although these images show more artifacts, and iodine reconstructions (**b**), whereas it is less delineated on the 70 keV images (**c**). The same lesion was also seen and measured in US (**d**)

Lastly, the selection of patients was retrospective, depending on the performance of DECT and TVUS at our Institution. However, in evaluation of CT images, the radiologist was blind to the results of pathological evaluation and the interpretation was consequently unbiased by the retrospective design.

In conclusion, our results show that DECT is a promising tool for assessment of myometrial invasion in endometrial cancer patients, with a special focus on images reconstructed at 50 keV.

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Compliance with ethical standards

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Conflict of interest The other authors declare that they have no conflict of interest. Alberto Mauro, an employee of GE Healthcare, helped the authors in setting up the CT protocol and had no influence on the data collected for this study.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in this study involving human participants, were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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