Preoperative Transvaginal Ultrasound (TVS) in the Description of Pelvic Tumor Spread in Endometrial Cancer: Results of a Prospective Study

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Abstract. Background: Various diagnostic methods are applied preoperatively in patients with suspected and histologically proven endometrial cancer, but no standard diagnostic tool exists for the accurate preoperative evaluation of tumor spread and staging. The aim of this study was to evaluate the diagnostic value of transvaginal sonography (TVS) as a staging tool, by determining tumor size and infiltration of the adjacent organs and correlating sonographic results to the respective intraoperative findings. Patients and Methods: Overall, thirty patients with endometrial cancer were included in the study prospectively. Systematic staging regarding tumor size (T), infiltration of the cervix (Cx) and ovaries (OV), peritoneal carcinomatosis (PC), bladder invasion (BI), intestinal invasion (II) and ascites (A) was assessed using TVS. Findings of B-mode ultrasound imaging were compared to intraoperative findings and histopathological results. Results: Preoperative diagnosis was correctly made by TVS in 93.4% of the patients [95% confidence interval (CI): 84% - 100%]. Preoperative staging was correctly achieved by TVS for T in 73.3% [95% CI: 58% - 89%], for Cx in 16.7% [95% CI: 13% - 46%], for OV in 100%, for BI in 97% [95% CI: 90% - 100%], for II in 97% [95% CI: 90% - 100%], for PC in 90% [95% CI: 79% - 100%] and for A in 100%. Conclusion: TVS is a sensitive and non-invasive method for preoperative diagnosis of suspected endometrial cancer. Of the tumors, 73% were correctly classified regarding size, whereas the detection rate of tumor spread in the ovaries and of ascites were high. Accuracy and sensitivity for the description of the infiltration of other adjacent organs, such as the bladder, intestine and peritoneal layers, were low. Further studies on the value of the combination of TVS and magnetic resonance imaging in the preoperative setting of patients with endometrial cancer are warranted.

Uterine cancer is the fourth most common cancer among women in Western countries, with an incidence of approximately 11,400 new cases diagnosed yearly in Germany alone (1). There is a 2.6% lifetime risk of developing endometrial cancer and it accounts for 6% of all cancer in women. Fortunately, 75-90% of the cases are diagnosed at an early stage (I), as they present with abnormal uterine bleeding (2). Five-year survival rates for localized, regional and metastatic disease have been reported to be 96%, 66% and 25% respectively (1-3).

There are two main types of endometrial cancer: Type I, estrogen-related, which usually presents histologically as a low-grade endometrioid tumor and is associated with atypical endometrial hyperplasia. Risk factors for type I include obesity, nulliparity, endogenous or exogenous estrogen excess, diabetes mellitus and hypertension. Type II endometrial carcinoma appears to be unrelated to estrogen stimulation or endometrial hyperplasia, and tends to present as a higher grade tumor, or a poor prognostic cell type, such as papillary serous or clear cell tumors. These patients are often older, while obesity, diabetes, and hypertension do not predispose to this type of endometrial carcinoma.

Surgery is the cornerstone of staging and treatment of endometrial cancer (4-6). In the era of multimodality therapy, accurate clinical staging is relevant as it affects therapeutic options and may assist in planning of the appropriate surgical procedure (such as simple hysterectomy versus additional pelvic and para-aortic lymphadenectomy), especially in elderly women or these with multiple morbidities. Significant prognostic factors of overall survival in endometrial cancer are histological type (serous, clear cell,
or high-grade histology), myometrial invasion over 50% thickness, tumor size (>2 cm in diameter or filling the endometrial cavity), cervical or lower uterine segment involvement, adnexal or pelvic tumor extension, peritoneal carcinomatosis and lymph node metastasis (6-7).

Several diagnostic modalities have been applied in order to provide accurate diagnosis and staging. These include computed tomography (CT), magnetic resonance imaging (MRI), sonography, hysteroscopy and curettage. Tissue evaluation by means of curettage still provides the most accurate diagnostic modality. Transvaginal ultrasonography is a noninvasive means of distinguishing bleeding due to atrophy in postmenopausal women, the most common cause of bleeding in this age group, from bleeding due to malignancy that will subsequently require tissue biopsy for confirmation and treatment (8). Postmenopausal women with an endometrial thickness of less than 4 to 5 mm measured by transvaginal sonography (TVS) are considered to have a low risk of endometrial pathology (9). Endometrial cancer Type I becomes more likely as endometrial thickness approaches 20 mm (8).

Although many studies have focused in evaluating the diagnostic power of transvaginal ultrasound in the early detection of endometrial cancer (9-13), only few studies exist that focus on preoperative staging of the tumor. The aim of this prospective study was to evaluate the diagnostic value of TVS as a diagnostic tool in the spread pattern of endometrial cancer by determining, aside from the tumor size, the infiltration of the cervix and ovaries, bladder and intestine and the peritoneum, as well as the presence of ascites.

Patients and Methods

A total of 30 consecutive patients were referred and operated due to endometrial cancer in the Department of Gynecology and Obstetrics in the Charité Campus Virchow Clinic. The majority presented with abnormal uterine bleeding. Histological diagnosis of endometrial carcinoma was confirmed preoperatively using hysteroscopy and curettage in all patients.

Clinical variables, such as patient’s age, FIGO stage, grading and histological type were documented. Only patients with a preoperative TVS, histologically proven endometrioid adenocarcinoma of the corpus uteri and an exact description of the intraoperative findings were included in the study. Patients with serous papillary or clear cell carcinomas were excluded, since these distinct histological types are associated with different patterns of metastatic spread and a higher presence of extruterine disease (14).

All preoperative TVS examinations were performed by one experienced examiner (WH). The KRETZ-Technik-Combison 420 and Siemens Sonoline Elegra ultrasound systems with a 5.7 MHz vaginal probe were used. The following parameters were examined systematically:

- maximal tumor size (T) (graded as: T1: <1 cm; T2: 1 - <3 cm; T3: 3 - <5 cm; T4: 5 - <10 cm; T5: >10 cm);
- invasion of adjacent organs: bladder, cervix, ovaries, peritoneum and intestinal segments below the arcuate line;
- detection of ascites.

Intraoperatively, all sites of the primary tumor and metastases as well as all macroscopically affected solid organs and structures were documented in detail by an independent person who was neither involved in the preoperative ultrasound examination nor in the surgical management. Histopathological findings were reported by an experienced pathologist who had no information about preoperative ultrasound findings. Similarly, the surgeon's reports on macroscopic invasion were documented separately.

Statistical analysis. Results are presented in raw numbers, rates, or medians and ranges, according to the underlying distribution.

Sensitivity, specificity, negative (NPV) and positive (PPV) predictive values were obtained from the underlying distribution. Binomial-exact 95% confidence intervals (CI) are also reported. STATA 8.0 statistical software (STATA Corp., TX, USA) was used for all analyses.

Results

Patient characteristics. Thirty patients with primary endometrial carcinoma were enrolled in this study. Patient characteristics are listed in Table I. Their median age was 66 years (range: 41-88 years). Two thirds of the patients presented at initial tumor stage FIGO I, whereas only 6% of the examined patients had distant metastases (FIGO IV).

Total abdominal hysterectomy and bilateral salpingooophorectomy with peritoneal cytology alone was indicated only for well- or moderately differentiated tumors not extending beyond the uterine body, invading less than a 50% of the myometrium and without invasion of the vascular space, based on preoperative staging. In more advanced cases para-aortic and pelvic lymph node dissection was added to the above procedure.

Ultrasound examination correctly indicated endometrial cancer in 28 out of 30 patients, with a sensitivity of 93.4%
TVS staging showed a high PPV regarding tumor size (100%), ascites (100%) and infiltration of the ovaries (100%).

**Tumor size.** TVS estimation of tumor size (T 1-5) was congruent with the macroscopic findings in 73.3% [22 out of 30 cases; sensitivity: 73% (95% CI: 58-89%); NPV: 0% ; PPV: 100%]. In 3 cases (10%), tumor size findings were discordant by stage, whereas in 1 patient (3.3%) tumor size was discordant in more than one stage. In 4 patients (13%), no exact tumor size could be defined by ultrasound examination.

**Involvement of adjacent organs.** In 6 patients (20%), there was a histologically proven infiltration of the cervix. In only one patient (16.7%) was this correctly identified by ultrasound, providing a sensitivity of 17% (95% CI: 13-46%) and specificity of 96% (95% CI: 88-100%); (PPV: 50%, 95% CI: 19-100% and NPV: 83%; 95% CI: 69-97%).

Two patients had a unilateral and one patient a bilateral infiltration of the ovaries. These findings were correctly diagnosed preoperatively by TVS. Twenty-seven patients had no preoperative sonographic finding of involvement and indeed were found to have no invasion of the ovaries. Sensitivity and specificity for invasion of the ovaries were 100% (NPV: 100%; PPV: 100%).

One patient was intraoperatively found to have bladder infiltration. This was preoperatively missed by ultrasound examination. Twenty-nine patients had no sonographic findings of involvement of the bladder and this indeed confirmed by the intraoperative results; sensitivity: was 0% , specificity: 100% , NPV: 97% (95% CI: 90-100%) and PPV 0% .

Two women had invasion of adjacent intestinal segments (small and large bowel). This was diagnosed by TVS in only one case (50%). The remaining 28 presented with no
intestinal involvement; sensitivity was 50% (95% CI: 19-100%) and specificity 100%. PPV was 100% and NPV was 97% (95% CI: 90-100%).

Peritoneal carcinomatosis was not able to be correctly identified preoperatively by TVS in 3 patients. In the remaining 27 patients, TVS correctly excluded the presence of peritoneal carcinomatosis [specificity: 100% and sensitivity: 0%; NPV: 90% (95% CI: 90-100%); PPV: 0%].

Intraoperatively, only one patient was found to have ascites. Preoperative TVS correctly described ascites in the pouch of Douglas in this patient (100%). In the remaining 29 patients, TVS correctly predicted the absence of ascites (specificity and sensitivity: 100%).

Discussion

Our study indicates that TVS is a method with high sensitivity regarding the actual detection of cancer within the uterine cavity (sensitivity of 93%: 28 out of 30 patients); it shows a high predictive value regarding tumor size (sensitivity: 73%, 95% CI: 58-89%; PPV: 100%), presence of ascites (specificity: 100% and sensitivity: 100%) and infiltration of the ovaries (specificity: 100% and sensitivity: 100%). Regarding the infiltration of adjacent organs such as cervix, small and large bowel and bladder, as well as the detection of peritoneal carcinomatosis, in terms of an overall preoperative staging, additional invasive and noninvasive diagnostic tools will be required to optimally evaluate tumor extent.

Many studies have aimed to outline the role of sonography in endometrial cancer and have emphasized the high NPV (10). A large number of these have focused on the accuracy of TVS in diagnosing endometrial pathology per se, the grade of myometrial invasion and to whether evaluation of the endometrial thickness may potentially predict the presence of endometrial cancer (1-3, 15-20). An endometrial thickness of 4-5 mm is in general defined as an optimal cutoff value for the suspicion of endometrial cancer (10). Furthermore, the application of color Doppler studies has been established as a valuable tool in the evaluation of abnormal uterine bleeding (18) (see Figures 1 and 2).

Our goal was to determine the role of TVS as a staging tool for tumor expansion within the small pelvis by describing tumor infiltration to the adjacent organs. Furthermore, we aimed to verify the sensitivity of sonographic measurements regarding tumor size, as evidence suggests that tumor size correlates with presence of extrauterine disease (21) and a higher probability of positive lymph node status (22). Shah and associates demonstrated in their results of 345 patients that tumor size did not constitute an independent prognostic variable, but it correlated with presence of extrauterine disease (21). Podratz and co-workers demonstrated in a study of 328 patients that patients with following characteristeric had no risk for lymph node involvement and presented an excellent overall prognosis: grade 1 or 2, myometrial invasion of equal or less than 50% thickness, no intraoperative evidence of macroscopic extrauterine spread and tumor diameter equal or less than 2 cm (22). Meeting all the requirements for an adequate surgical staging, preoperative sonographical determination of the tumor size can provide additional information for the indication of systematic lymph node dissection. This is of special relevance in patients of higher age and severe comorbidities (23).

In this study, we were able to show that 22 out of 30 patients were correctly preoperatively diagnosed regarding the size of the endometrial tumor, achieving a sensitivity of 73% (95% CI: 58-89%) and demonstrating TVS as a reliable method for preoperative tumor size evaluation.

Regarding the infiltration of the cervix, we calculated a sensitivity of only 17% (1/6 patients) with a relatively high specificity of 96% (23/24). Our results are lower than previously reported values of other groups, which range between 80% – 100% (24-27) and of 25% by Thoringer et al. (28). In a relatively recent study of Sawicki et al., tumor extension to the cervix was correctly assessed in 19 out of 22 women in which it was present (sensitivity: 86.4%, specificity: 85.3%, PPV: 85.5%, NPV: 95.1%) (29). A possible explanation could be the fact that all four of the six patients with cervical infiltration presented with a stage FIGO IIa, i.e. tumor which had spread to the glandular cells in the endocervical canal but not into the connective tissue (stroma) of the cervix. Nevertheless, we believe that TVS is not an appropriate tool for the description of an infiltration of the cervix. Hysteroscopy and endocervical curettage seem to be superior diagnostic methods (30). Due to the small number of patients with an infiltration of the bladder (n=1; none detected) or intestine (n=2; 1 detected) in our study cohort, we can only make limited statements about the accuracy of TVS in this regard. Georgiev et al. were also not able to identify 4 patients with bladder invasion by using TVS in a cohort of 64 patients (31).

Two studies of Houvenaeghel et al. (32, 33) on advanced or recurrent gynecological cancer of the endometrium, ovary, cervix and vagina showed, however, that the combination of transvaginal, transrectal and transvesical sonography could achieve significantly higher sensitivity and specificity values of 95-100% and 85-98%, respectively.

Since none of our peritoneal carcinomatosis cases were able to be correctly identified preoperatively by TVS, the accuracy of TVS was very low. Here it has to be noted though, that only one patient with peritoneal carcinosis presented with ascites; the detection of peritoneal carcinosis is significantly impaired in the absence of ascites; there are indirect parameters such as the presence of hypoechoic nodules in the pouch of Douglas or of the intestinal wall which can be described by TVS but are restricted to the
pelvic region. Therefore, other methods such as MRI may perhaps yield better information; a recent study of Fuji et al. showed a high sensitivity and specificity of 90% and 95.5%, respectively, when diffusion-weighted MRI was applied in detecting peritoneal dissemination in cases of gynecological malignancy (34).

Despite the small number of patients with ovarian invasion (n=3), our study showed a sensitivity and specificity of TVS as high as 100%. Our results are in accordance with those of applied in detecting peritoneal dissemination in cases of 95.5 %, respectively, when diffusion-weighted MRI was

ultrasoundrevealedthecorrectdiagnoses(sensitivity:72.7 %,

specificity: 97.5 %, PPV: 80 %, NPV: 96.3 %) (29).

In conclusion, TVS may reliably be utilized for the detection of endometrial carcinoma as well as for the preoperative assessment of tumor size, presence of ascites and adnexal metastases. It is less reliable for the assessment of cervical invasion or involvement of other organs such as the bladder, intestines or peritoneum. Therefore, further studies on the value of a combination of TVS and MRI in the preoperative setting of patients with endometrial cancer are warranted.

References


