Preoperative selection of patients with low-stage endometrial cancer at high risk of pelvic lymph node metastases

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The goal of this study was to determine diagnostic accuracy of preoperative transvaginal sonography (TVS) to assess myometrial infiltration in patients with endometrial cancer and to determine the possibility of preoperatively selecting low-stage endometrial cancer patients at high risk of lymph node metastases. The depth of myometrial infiltration of endometrial cancer was assessed using TVS before or after curettage. Infiltration was classified as superficial if less than half of the myometrium was involved, otherwise it was classified as deep infiltration. Results were compared with the histology results of the definitive specimens. Patients were classified as high risk when they satisfied two of the following three criteria: 60 years of age or older; deep myometrial infiltration; and poorly differentiated or undifferentiated tumor. A total of 93 patients from 11 clinics were analyzed. The mean age was 66.1 years (SD ± 11.4). The sonography and histology findings were in agreement in 69 of 93 patients. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), of "deep infiltration" by preoperative TVS were 79% (95% CI 0.65–0.93), 72% (95% CI 0.61–0.83), 61% (95% CI 0.46–0.75), and 86% (95% CI 0.76–0.96), respectively. Combining tumor grade and myometrial infiltration in the hysterectomy specimen and age, 30 of 81 patients were classified as high-risk patients. Sensitivity and PPV, specificity, and NPV for preoperative diagnosis of high risk were 80% (95% CI 0.65–0.94) and 88% (95% CI 0.79–0.97), respectively. Preoperative assessment of myometrial tumor infiltration using just TVS is only moderately reliable in endometrial cancer patients. If the results of TVS, however, are combined with the patient's age and the degree of tumor differentiation in curettings, it is possible to preoperatively select endometrial cancer patients with a high risk of pelvic lymph node metastases with sufficient reliability.

KEYWORDS: endometrial cancer, risk analyses, transvaginal ultrasonography.

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Endometrial cancer is diagnosed in 1400 women each year in The Netherlands[1]. The majority of these women have early stage endometrial cancer without pelvic lymph node metastases. However, since 20–30% are at high risk of such metastases, the policy in most Anglo-Saxon countries is to conduct elective pelvic lymphadenectomy in this latter group[2,3]. By pelvic lymphadenectomy it is determined which patients are eligible for adjuvant radiotherapy. Also, lymphadenectomy might be therapeutic. It is important to select a high-risk group preoperatively and to identify patients with early stage endometrial cancer with a low risk for metastases that do not need pelvic lymphadenectomy or radiotherapy. Patients with low-stage endometrial cancer who might benefit most from radiotherapy are characterized by the presence of two of the following three criteria: age $\geq$ 60 years, poorly or undifferentiated (grade III) tumor, and deep myometrial infiltration. These criteria are based on the recently published randomized Dutch study of the value of adjuvant pelvic radiotherapy for low-stage endometrial cancer, the so-called PORTEC study[4].

Transvaginal sonography (TVS) has been used during the past few years to preoperatively determine the myometrial infiltration of endometrial cancer[5–15]. The present study was undertaken to evaluate preoperative TVS for myometrial invasion assessment in daily practice in various university and nonuniversity hospitals. In addition, we investigated whether it was possible to preoperatively select patients at high risk of pelvic lymph node metastases using the three above-mentioned risk factors.

Patients and methods

Between January 1998 and December 1998 gynecologists from 11 hospitals were asked to judge the myometrial infiltration depth of endometrial cancers using TVS, before total extirpation of the uterus. It was up to the gynecologist to decide the moment when the assessment would take place (before or after dilatation and curettage) and what equipment should be used. Conforming to the FIGO staging of endometrial cancers, a distinction was made between superficial (or none) (<50%) and deep ($\geq$50%) infiltration of the myometrium. After surgical removal of the uterus, the pathologist also classified the myometrial involvement. Data regarding the degree of tumor differentiation in the curettings and definitive pathology specimens (uterus) and tumor staging were collected from the original histologic reports. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals (95% CI) were calculated and compared.

Results

A total of 93 patients, 25 in an academic center, were included in 11 clinics. The mean age was 66.1 years (SD ± 11.4); 64 patients were 60 years of age or older. The postoperatively diagnosed stage of the endometrial cancers was retrospectively retrieved for 81 of 93 patients: 60 had FIGO stage I tumors, 13 stage II, and 8 stage III. In 60 of the 93 patients, either no residual tumor was found in the definitive (uterine) specimen ($n = 2$) or the infiltration was superficial. Deep myometrial infiltration was found in the remaining 33 patients.

Assessment by sonography and histology of the depth of myometrial infiltration produced comparable results in 69 of 93 patients. TVS overestimated the depth of infiltration in 17 patients and underestimated it in 7 (Table 1). Sensitivity, specificity, PPV, and NPV of the sonographic "deep infiltration" result were 79% (95% CI 0.65–0.93), 72% (95% CI 0.61–0.83), 61% (95% CI 0.46–0.75), and 86% (95% CI 0.76–0.96), respectively. TVS was conducted in 44 patients before the curettage. The sensitivity, specificity, PPV, and NPV in this group were 77% (95% CI 0.54–1.00), 74% (95% CI 0.59–0.76), 56% (95% CI 0.33–0.79), and 88% (95% CI 0.76–1.00), respectively. These values were 81% (95% CI 0.64–0.98), 68% (95% CI 0.50–1.01), 65% (95% CI 0.47–0.84), and 83% (95% CI 0.67–1.14), respectively, in the 49 patients who underwent TVS after curettage. There is no difference in the accuracy of ultrasound before or after curettage.

Table 1. Determination of the myometrial infiltration: transvaginal sonography (TVS) versus histology

	Histology		
	Deep myometrial infiltration	None or superficial myometrial infiltration	Total
TVS: deep myometrial infiltration	26	17	43
TVS: no or superficial myometrial infiltration	7	43	50
Total	33	60	93

Table 2. Degree of differentiation of the endometrial cancer: histology of curettage specimen versus histology of definitive specimen

Curettage specimen	Well differentiated (grade I)	Moderately differentiated (grade II)	Poorly or undifferentiated (grade III)	Total
	Definitive specimen			
No classification	2	5	1	8
Grade I	17[a]	6		23
Grade II	2	30	5	37
Grade III		1	12	13
Total	21	42	18	81

[a]With regard to two of the grade I tumors in the curettage specimen, a tumor was no longer found in the definitive specimen.

Information with regard to the degree of tumor differentiation both in the curettings and definitive specimens was collected for 81 patients. No degree of differentiation could be established in the curettings of eight patients (Table 2). The degree of differentiation in the two types of specimens was comparable in 61 patients. The definitive specimens of older patients (≥60 years old, *n* = 54) contained grade III tumors more often than those of younger patients (<60 years) (24% versus 18%). Deep myometrial infiltration was also seen more often in the older age group (44% versus 17%).

If the factors age, preoperative TVS-estimated depth of myometrial infiltration, and degree of tumor differentiation in the curettings are combined, 30 of 81 patients were preoperatively classified as high-risk patients (Table 3). This preoperative classification was correct for 24 of the 30 patients. TVS overestimated the depth of infiltration in six patients (all ≥60 years old); that is, they were incorrectly classified as high-risk patients. Six of the 51 women classified preoperatively as "low-risk" cases turned out to be high-risk patients after surgery. The differentiation of the tumor in the definitive specimen of two of these six patients (55 and 73 years old) was considered grade III, while one of them was diagnosed as a "possible" cancer and the other as a moderately differentiated (or grade II) tumor in the curettage specimens. TVS did not recognize deep infiltration as such in the other four patients with false "low-risk" status Based on the three factors, sen-

sitivity and PPV are 80% (95% CI 0.65–0.94) and specificity and NPV are 88% (95% CI 0.79–0.97) for the preoperative selection of high-risk patients.

Discussion

This study investigated whether preoperative TVS, conducted in a multicenter setting, could sufficiently differentiate between superficial and deep myometrial infiltration of an endometrial cancer. Our results were similar to those of earlier studies: sensitivity was 79% and NPV 86% with a lower specificity (72%)[5–15]. In contrast with the other studies, ours was performed in several clinics as part of the routine workup by sonographers or gynecologists. The numbers in our study were too small to estimate age-specific rates, so we cannot state whether TVS is equally trustworthy for different age groups. Theoretically there is a greater risk of judgment errors for women younger than 60 years of age because myomas and adenomyosis occur more often at a younger age and may incorrectly influence depth involvement. Overestimation of the infiltration can also be caused by a pyometrium, a small uterus volume, an atrophic myometrium, or exophytic tumor growth. Furthermore, when a tumor grows halfway into the myometrium, both the sonographer and the pathologist experience difficulty determining the depth of infiltration[15–17]. Two sonography techniques were described in the literature recently that may support the diagnosis of the depth of infiltration,

Table 3. Preoperative versus postoperative classification of high-[a] and low-risk endometrial cancer

	Postoperative high-risk patient	Postoperative low-risk patient	Total
Preoperative high-risk patient	24	6	30
Preoperative low-risk patient	6	45	51
Total	30	51	81

[a]High-risk patient: less than 60 years of age, grade III tumor, and deep infiltration, or more than 60 years of age, grade III tumor, and/or deep infiltration.

namely Doppler and hydrosonography[18–21]. However, since the predictive values of these techniques are not yet known with regard to measuring the depth of myometrial infiltration, it does not seem probable that they will play an important role in the near future. Earlier studies compared the magnetic resonance imaging (MRI) and computed tomography (CT) with TVS. Some of the authors reported that MRI predicted the depth of infiltration better than TVS[8,15], while others found the two methods to be similar[17]. Also, MRI appears to be more reliable than a CT scan because of its greater soft-tissue contrast[8]. Nevertheless, because of the costs, logistics problems, and time investment necessary to conduct an MRI, we find TVS to be a much more attractive choice for the preoperative selection of high-risk patients.

It is also possible to determine the depth of myometrial infiltration during surgery by means of either macroscopic investigation of the uterus or intraoperative frozen section diagnosis[22–25]. The most important drawback of these two techniques, however, is that preoperative selection of high-risk patients is not possible, so qualified surgery for pelvic lymphadenectomy as well as surgery time is difficult to plan.

Our research was aimed at the sonographic assessment of the myometrial infiltration of an endometrial cancer. The inclusion of patients was independent of the (clinical) stage of the tumor. The relative overrepresentation of patients treated in academic centers (26%) explains the relatively large number of patients with tumor stage II or higher (26%).

We had data for 81 of 93 patients at our disposal for the retrospective part of the study, that is, the preoperative selection of high-risk patients. The histology results of the curettage and definitive specimens were comparable in 74% of the patients. The tumor was poorly differentiated in the definitive specimen more often than in the curettings, a fact already known from the literature[12,23,25]. When the factors age, preoperative TVS results, and histology results (curettings) were combined, we correctly identified 24 of the 30 high-risk patients; 6 were incorrectly classified as high-risk patients (specificity 88%, PPV 80%).

These results are better when compared to those of just using the TVS. The most important explanation for this is that the three factors—age, depth of myometrial infiltration, and degree of tumor differentiation—are not independent: women older than 60 years of age already have, by definition, one of the risk factors (age). Moreover, older women have poorly differentiated tumors (24% versus 18%) and/or tumors that grow deeply into the myometrium (44% versus 17%) more often than younger women. Both of these histo-

logic risk factors were present in 19% of the older women, but only in 11% of the younger women.

We conclude therefore that it is possible to preoperatively select patients at high risk of pelvic lymph node metastasis using the factors age, transvaginal sonographic determination of myometrial infiltration, and degree of tumor differentiation in the curettings. Pelvic lymphadenectomy is considered to be a worthwhile addition to the surgical treatment of these women.

Acknowledgments

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