Prediction of cervical infiltration in Stage II endometrial cancer by different preoperative evaluation techniques (D&C, US, CT, MRI)

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Summary

Objective: Our clinical practice for FIGO Stage II endometrial cancer consists of Wertheim's radical hysterectomy as first choice of treatment. The evaluation of patients is based on D&C. The accuracy of this preoperative staging method is examined here.

Methods: Twenty-nine patients with endometrial cancer with suspected cervical involvement (FIGO Stage II) based on endocervical curettage underwent Wertheim's radical hysterectomy between January 1, 1989 and December 31, 2001 at the Gynaecological Department of the National Institute of Cancer, Budapest, Hungary. In all cases surgico-pathological staging was performed to examine the accuracy of preoperative D&C and to find out whether radical surgery was necessary in all patients and how the preoperative evaluation of patients should be improved.

Results: Out of 29 patients who underwent Wertheim's hysterectomy the pathological examination found primary cervical cancer in two patients. These two patients were eliminated from further evaluation. Out of the remaining 27 patients only eight (29.6%) had cervical involvement of endometrial cancer documented by a pathologic review on the hysterectomy specimen. Extrauterine disease was documented in one of the patients with cervical infiltration (1/8) and in one in the cervix-negative group (1/19). Ovarian spread was found in the first case and ovarian infiltration with penetration of the tumour into the parametric tissue in the second case. According to the FIGO classification 18 (66.6%) patients had less extensive disease and two (7.4%) had more extensive disease. Only 26% of the patients (7/27) had surgical findings consistent with the Stage II disease.

Conclusion: We can conclude that "overtreatment" seems to have occurred in 19 patients, whose cervical infiltration by endometrial cancer could not be proved by pathological staging. It can also be assessed that understaging took place in two cases, which can be explained by two reasons; we did not make use of preoperative imaging techniques since US was applied in six patients, CT in 16 and the most accurate, MRI, on three patients only.

The other possible reason, which can point out the bad efficacy of the imaging techniques as well, could be that a major part of the patients received preoperative AL treatment, which could also have influenced the cervical progression.

This is possible, but has not been proved. The difference in the number of cervical infiltrations in the group of patients who received preoperative radiotherapy and in the group where they did not, is not significant ($p = 0.9742$), and infiltration of the endometrium was present in all cases. In the future, proper selection of imaging modalities can improve the staging of gynaecological disorders and preclude unnecessary procedures. In endometrial cancer cases US, especially with the use of TVUS, is often considered to be the primary imaging approach. However, in patients where ultrasound is suboptimal, where there is a large tumour present or the result of imaging studies will directly influence the choice of therapy and guide therapy planning then the higher accuracy of MRI warrants its use. CT is of use in the later stages of disease; differentiation between Stage I and II is difficult and CT is limited in the assessment of myometrial invasion.

Key words: Stage II endometrial cancer; D&C; Patient evaluation; Wertheim's hysterectomy; US, TVUS, CT, MRI.

Introduction

The management of women suspected of having cervical involvement of endometrial cancer based on endocervical curettage remains controversial. These patients present as having Stage II disease under the previous FIGO staging criteria [22].

Preoperative irradiation consisting of whole pelvic therapy and/or brachytherapy followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH BSO) has been and it is at many institutions the most common form of treatment of this condition [2].

The staging system adopted in 1989 [7] incorporated certain prognostic elements (the depth of uterine invasion, the site of metastasis) which require operative assessment. Examining the spreading characteristics of endometrial cancer infiltratively involving the cervical stroma has made it clear that the seeding of tumour cells is equal to that of primary cervical cancer. This similarity in the metastatic pattern of the two conditions made it obvious that the Wertheim procedure (or Piver type III radical hysterectomy) should also be the "first surgical intervention" in the management of FIGO Stage II endometrial cancer [4, 20, 27]. Unfortunately this radical hysterectomy is followed by many side-effects, which are

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not present after a simple hysterectomy (TAH BSO) or irradiation. It is important to put the patients into a proper treatment group to be able to find out who should undergo Wertheim's procedure and who should not [1].

Our clinical practice for FIGO Stage II endometrial cancer consists of Wertheim's radical hysterectomy as the first choice of treatment, and the evaluation of patients is based on dilatation and curettage (D&C). The accuracy of this preoperative staging method is discussed.

Materials and Methods

Between January 1, 1989 and December 31, 2001, 29 patients with endometrial cancer with suspected cervical involvement (FIGO Stage II) based on endocervical curettage underwent Wertheim's radical hysterectomy at the Gynaecological Department of the National Institute of Cancer, Budapest, Hungary.

Surgico-pathological staging was performed in all patients; the surgical specimens were sectioned along the longitudinal plane of the uterus. The depth of myometrial invasion was estimated grossly and confirmed microscopically. It was classified as absent (tumour confined to the endometrium), superficial (tumour invading less than 50% of the myometrial thickness), deep (tumour invading 50% or more of the myometrial thickness). Special attention was paid to the identification of cervical involvement by cancer, which was classified as superficial (tumour involving the endocervical mucosa only, FIGO Stage IIA), infiltrating (tumour penetrating into the deep layer of the cervix, FIGO Stage IIB) or absent.

Pelvic lymph node sampling including removal of the fat pad above the aortic bifurcation was performed in all patients.

Cytology of pelvic washing was obtained in all patients and classified as positive or negative.

Grade (1-3) was established according to FIGO criteria [7] and the definitive histotypes were assessed on surgical specimens. The cell type of the tumour was classified as endometrioid, special variant carcinomas and undifferentiated carcinoma, as suggested by the International Society of Gynaecological Pathologists [25]. A pathologist at the above-mentioned institute based on this classification reviewed histopathological samples.

All patients underwent certain preoperative check-ups including total blood sampling, urine analysis, chest X-ray and pyelography. These results will not be discussed here. Attention will be paid only to the results of examinations with preoperative medical imaging techniques like transvaginal ultrasound (TVUS), computed tomography (CT) and magnetic resonance imaging (MRI) and to the comparison of these to the results of pathological staging to show how these imaging techniques are able to predict the presence of cervical involvement.

Results

Out of 29 patients who underwent Wertheim's hysterectomy the pathological examination found primary cervical cancer in two patients. These two patients were dropped out of the study. Of the remaining 27 patients only eight (29.6%) had cervical involvement of endometrial cancer documented by pathologic review of the hysterectomy specimens (infiltrative type: 6, superficial type: 2) (Figure 1). Extrauterine disease was documented in one of the patients with cervical infiltration (1/8) and in one in the cervix-negative group (1/19). Ovarian spread was found in the first case and ovarian infiltration with penetration of the tumour into the parametric tissue in the second case. According to the FIGO classification 18 (66.6%) patients had less extensive disease and two (7.4%) had more extensive disease. Only 26% of the patients (7/27) had surgical findings consistent with Stage II disease.

Figure 1. — Endometrioid adenocarcinoma superficially infiltrating the mucosa of the cervix. In the bottom (left) a normal cervical gland can be seen (HE x 100).

Surgical pathological staging showed tumour restricted to the endometrium in 14 cases, tumour invading less then 50% of myometrial thickness in seven cases and deep infiltration in six cases.

Pelvic lymph node sampling was performed in all patients with no harm or serious injury except in two cases. In one patient a hypogastric vein injury occurred and in the other a right-side iliac communis vein and bladder injury together occurred. The highest level of lymph node sampling for frozen section was above the aortic bifurcation. All of these samples were negative. Obesity or peritoneal metastasis of the patients did not influence the procedure. The average number of pathologically examined lymph nodes was 12 (range 31 to 4). Among those only two samples turned out to be infiltrated by the underlying cancer.

Cytology of pelvic washings proved to be positive only in two patients with extrauterine disease.

According to histological grading of the 27 patients, 14 had grade 1 and seven grade 2 endometrial cancer. In five cases grade 3 cancer was found, and one case was not classified.

The cell type of tumours was classified as endometrioid in 24 cases and special variant carcinomas in three cases, two of which were clear cell cancer and one adenosquamous endometrial cancer. Two high-grade papillary cancers were found, but no undifferentiated type of endometrial cancer was noted. The histological grade 3 group consisted of two cancers with papillary differentiation, one adenosquamous cancer, one cancer with ciliated differentiation and one endometrial cancer with squamous differentiation.

Using the risk criteria for patients with endometrial cancer [23], eight patients were classified as high-risk and 19 as low-risk patients after pathological staging. All endometrial cancers infiltrating the cervical tissue were found to be in the high-risk group retrospectively. There were none in the low-risk group. All extrauterine cancers were also found in the high-risk group, while one patient with lymph node metastasis was assigned to the low-risk group (Table 1).

However, the treatment decision of all patients in this study was primarily based on the results of D&C, whereas other methods like vaginal ultrasound examination, CT and MRI were sometimes applied preoperatively.

The preoperative use of vaginal ultrasound examination was documented in six of 27 patients only (22%) and in three out of the eight patients where cervical infiltration was documented by histopathological examination; in only one of these three patients was the cervical involvement detected by ultrasound (US).

CT scan prior to the operation was more frequently introduced as a preoperative examination (16 of 27 patients). In four patients out of eight where cervical infiltration was present, a CT scan was carried out, and the scan confirmed infiltration of the cervix uteri in three cases. In the fourth case, where the infiltration by histopathological examination was present superficially only, the scan remained negative. In five of the nine patients with no infiltration in the cervix the CT scan raised the suspicion of a present infiltration. In three of 16 patients the result of the scan was not present at the time of the operation, however the result was equal to the histopathological stage and was negative.

MRI was used as a pre-staging method for patients in three cases only. In one case cervical infiltration was detected, while in the two other cases infiltration was not found to correspond to histopathological stage.

In three patients none of the above-mentioned diagnostic imaging examinations were performed before the operation.

Preoperative irradiation was applied in ten out of 27 patients as an intracavital after-loading technique (AL) with a 7 GY dose at the surface of the uterus, and was repeated one to four times before the operation individually. Infiltration of the cervical tissue was observed in three cases in this group and in five cases in the other group (patients had not had preoperative irradiation). The difference regarding the number of cervical infiltrations between the two groups was not significant (p = 0.9742).

Table 1. — *Distribution of FIGO Stage II endometrial cancer patients by Kucera's risk criteria [23] and by infiltration of the cervix, extrauterine disease and lymph-node metastasis.*

Risk criteria	No. of patients	No. of cases of cervical infiltration	No. of cases of extrauterine disease	No. of cases of lymph-node metastasis
Low-risk patients: G1-G2, pure adenocarcinoma confined to the endometrium or involving as much as the inner portion of the myometrium (M0-M1).	19	0	0	1
High-risk patients: all G3 pure adenocarcinomas and/or deep myometrial infiltration (M2), and/or clear cell, serous papillary, adenosquamous carcinomas.	8	8	2	1

Discussion

Endometrial cancer is the most common gynaecologic malignancy and accounts for 13% of all cancers in women [23]. In approximately 75% of the cases it is clinically confined to the uterus at the time of diagnosis. As early symptoms (bleeding) are present in a large number of patients, direct sampling of the endometrium by D&C reveals early stages of the disease in a high percentage, and gives information about the involvement of the uterine cervix as well. The staging of endometrial cancer is a critical part of any oncological consultation. A cancer staging system may yield prognostic information and may also identify patients with a good prognosis who would derive no benefit from potentially toxic and costly adjuvant therapies, or allows patients to be grouped for research purposes or direct treatment planning. Clinical practice has shown that the spread of endometrial cancer involving cervical tissue is similar to that of primary cervical cancer, and a FIGO Stage II endometrial cancer patient should undergo Wertheim's hysterectomy. This decision however should be made before the operation, and when making a preoperative decision for a Wertheim hysterectomy the gynaecological oncologist cannot accept the results of only D&C because they are not always predictive of final pathology due to sampling errors observed in 20% [13]. In our study, according to the FIGO classification, 18 (66.6%) patients had less extensive disease and two (7.4%) had more extensive disease. Only 26% of the patients (7/27) had surgical findings consistent with Stage II disease. The inaccuracy of D&C alone calls for further assessment of the extent of disease preoperatively in order to determine the aggressiveness of initial surgery and to guarantee individualised treatment.

Various diagnostic investigations besides D&C are available today; these can be used to individualise the surgical treatment of endometrial cancer patients with suspected cervical involution.

Although in our study ultrasound examination was performed only in six out of 27 patients, with only one cervical infiltration out of three patients being detected, this method is the most frequently used preoperative staging system. It is well known that US is not a reliable staging modality for endometrial carcinoma [3, 10, 31]. On the other hand TVUS may reliably depict the depth of myometrial invasion in Stage I endometrial cancer but it is unsuitable for general tumour staging (e.g., extension of the tumour to the uterine cervix) [5, 34]. The limitations of US appear to be in suboptimal soft-tissue contrast-resolution (the tumour and the adjacent myometrium often have similar echogenicity) and a relatively small field of view precluding assessment of large tumours [12, 18].

By applying colour Doppler imaging, tumour vascularity and therefore the process of angiogenesis can be observed in vivo. The technique has the potential to differentiate between benign and malignant neoplasms [8], to predict the clinical behaviour of a malignant disease, to detect the infiltration of the tissue [19] and to monitor the efficacy of treatment [11]. Colour Doppler sonography adds useful information to the diagnosis and management of the disease. At the present time, however, the few reports on this topic in the literature are either contradictory or inconclusive [11]. The small number of US examinations carried out in our study is not enough to draw any conclusions about the contribution of this technique to patient selection, especially since it was not colour Doppler. In a Hungarian study an 88% accuracy rate of the transvaginal Colour Doppler procedure in predicting myometrial infiltration and tumour extension to the cervix was reported [29]. Looking at the potential benefit of TVUS and colour Doppler in early recognition of the cervical involvement of endometrial cancer suggests that this technique should be used where MRI is not routinely available.

Other diagnostic oncologic imaging of the female pelvis includes CT and MRI techniques with MRI playing a major role.

CT is most frequently used in the preoperative staging of gynaecological cancer. In our study a CT scan prior to surgery was applied as a preoperative examination in 16 of 27 patients. In four patients out of eight where cervical infiltration was present a CT scan was performed, and the scan confirmed infiltration of the cervix uteri in three cases. In the fourth case, where the infiltration according to the histopathological examination was present superficially only, the scan remained negative. In five of nine patients with no infiltration to the cervix the CT scan raised the suspicion of cervical infiltration, however this was not confirmed by histological staging. In three out of 16 patients the result of the scan was not present at the time of the operation, but it corresponded with the histopatological stage and was negative. Both conventional- and angio-computer tomography [14, 18] have been used for the evaluation of endometrial carcinoma with emphasis on the evaluation of the depth of myometrial invasion and assessment of lymph node status. The accuracy of CT staging of endometrial carcinoma is reported to be from 84% to 88% [14, 18]. Some studies demonstrate that conventional CT is limited in the assessment of myometrial invasion and that only the use of angio-CT will provide such information accurately [12, 14, 18]. Angio-CT, however, is an invasive procedure requiring intravascular injection in the iliac artery. CT is of use in the later stages of disease, but differentiation between Stage I and II is difficult, as is assessment of the depth of myometrial invasion (Figure 2).

Reports in the literature show the superiority of MRI when compared with ultrasound in both the evaluation of tumour extension into the cervix (ultrasound vs MRI, 50% vs 80%, respectively) and myometrial invasion (ultrasound vs MRI, 40% vs 60%, respectively) [18, 31].

Figure 2. — *Endometrial carcinoma, Stage 1C.* Contrast enhanced CT image: The endometrium is widened but the reliable assessment of myometrial invasion is not available on the CT scan.

The superiority of MRI over CT has also been documented [6, 21, 30]. It is generally agreed that at present MRI provides the most accurate and consistent evaluation of patients with endometrial cancer. MRI is accurate in the staging of endometrial carcinoma, with a reported overall accuracy rate of between 83% and 92% [12, 15, 17, 18]. Tumours are considered to be confined to the endometrium (Stage IA) when the junctional zone is preserved or there is sharp tumour-myometrium interface. In Stage IB the junctional zone is disrupted and tumour signal intensity can be detected in the inner half of the myometrium. Stage IC (deep myometrial invasion) is indicated when high signal intensity tumour is seen in the outer half of the myometrium (Figure 3). Contrast-enhanced imaging significantly improves detection of endometrial abnormalities and the assessment of the depth of myometrial invasion [16, 17, 28].

Invasion of the cervix (Stage II disease) is easily assessed on multiplanar MR images. Tumour invasion may be confined to the glandular elements of the cervix (Stage IIA disease) in which case the cervical stroma remains of normal low signal intensity on the T2-weighted image (Figure 4). When the stroma is involved (Stage IIB disease) it demonstrates high signal intensity on the T2-weighted image. The unenhanced T2-weighted image is superior to contrast enhanced imaging in the evaluation of cervical stromal invasion. In our study MRI was used as a prestaging method in three patients only, but only one case of cervical infiltration was detected successfully, and in the other two cases infiltration was not confirmed in the histopathological stage of these cases.

A method that can also help individualise the treatment is intraoperative frozen section. However frozen section is not a preoperative technique; if used this to evaluate patients for the proper operative technique, all cases in this study with histologically verified cervical infiltration

by endometrial cancer would have fallen into the high-risk group retrospectively. This means that eight out of 27 patients would have undergone Wertheim's hysterectomy with pelvic lymph node dissection only, in good accordance with our histopathological findings (Table 1).

Summarising the above data, we can draw the conclusion, that "overtreatment" seems to have occurred in 19 patients whose cervical infiltration by endometrial cancer could not be proven by pathological staging. It should also be noted that understaging occurred in two cases, which can be explained by two reasons. Preoperative imaging techniques were not used since US was applied to six patients, CT to 16 and the most accurate MRI to three patients only. The other possible reason, which can point out the bad efficacy of the imaging techniques as well, could be that the major part of the patients received preoperative AL treatment, which could have also influenced the cervical progression. This is possible, but has not been proven, since the difference in the number of cervical infiltrations in the group of patients who received preoperative radiotherapy and in the group that did not was not significant (p = 0.9742). However cancerous invasion of the endometrium was present in all group. The influence of preoperative irradiation on prognostic factors is known and considering this, preoperative irradiation is not recommended anymore as the primary treatment for patients who would otherwise be fit for surgery [9, 26, 32, 33]. Nonetheless in our cases, to prove

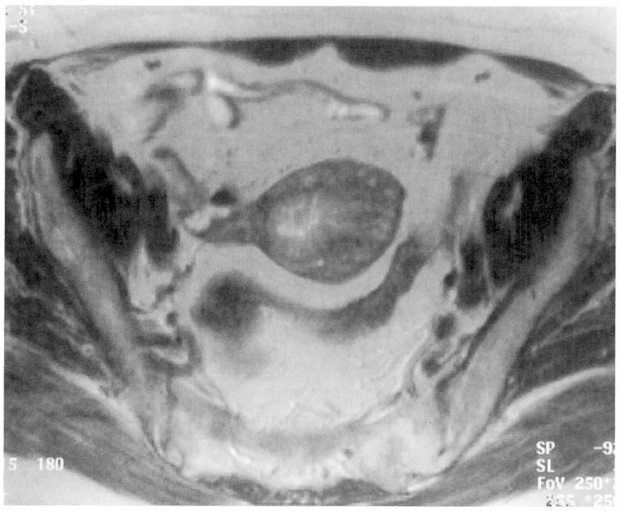

Fig. 3A

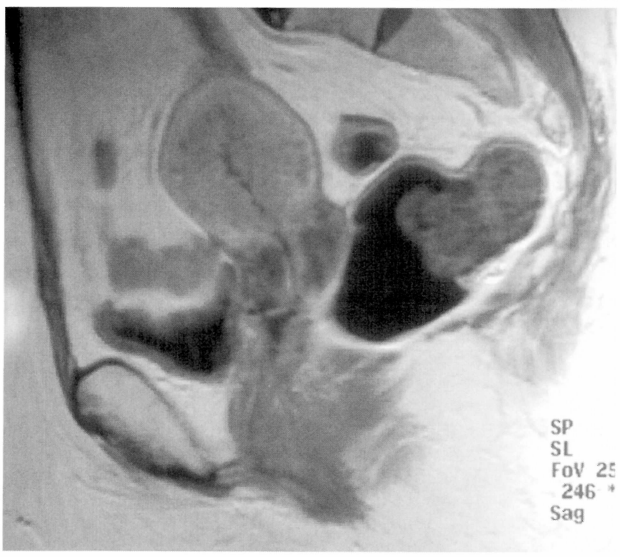

Fig. 3B

Figure 3. — *Endometrial carcinoma, Stage 1C.* **A.** Axial T2-weighted FSE image. The hyperintense disruption of the junctional zone is indicative of myometrial infiltration. Disease is characterised by deep myometrial involvement extending to the outer half of the myometrium. **B.** Sagittal contrast-enhanced T1-weighted image. Assessment of myometrial tumour infiltration is facilitated by contrast enhanced T1-weighted imaging.

Fig. 4A

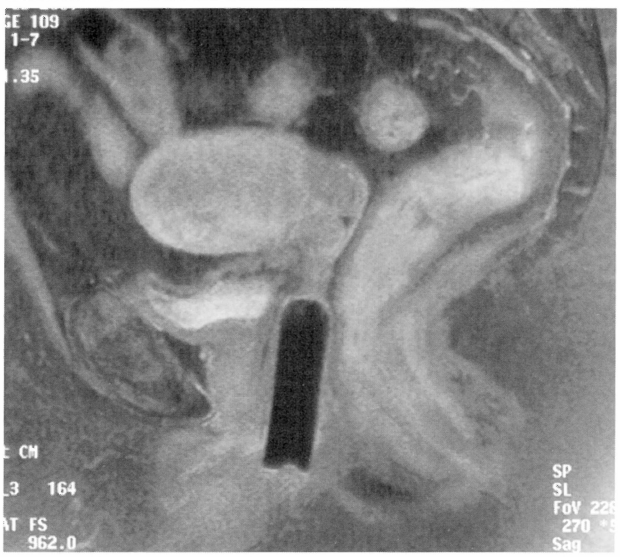

Fig. 4B

Figure 4. — *Endometrial carcinoma, Stage II A.* **A.** Sagittal T2-weighted FSE image. T2-weighted image depicts endometrial carcinoma as a medium signal intensity mass with pathological infiltrative thickening of the endometrium, containing heterogeneous areas: high signal intensity nabothian cyst in the cervix. **B.** Sagittal contrast-enhanced T1-weighted image with fat suppression. On the contrast enhanced image myometrial invasion is better visualised. The large tumour in the endometrial cavity demonstrates direct extension into the endocervical canal.

the altering effect of preoperative AL on histological prognostic factors, more prospective studies are needed.

Putting all of this into consideration the following conclusions can be drawn:

1. There is no doubt that Wertheim's operation is the treatment of choice in FIGO Stage II endometrial cancer. However the diagnosis can not be based on D&C only; it should be supported by imaging techniques, primarily by MR and secondly by TVUS examination to avoid overtreatment.

2. These imaging examinations should be carried out prior to preoperative AL treatment, thus preventing the influence of irradiation on the histopathological findings. We also find the elimination of preoperative AL treatment to be acceptable.

3. In the case of endometrial cancer without cervical infiltration the necessity of staging laparotomy should be decided intraoperatively with the help of frozen section. Patients can be classified into low or high-risk groups based on the histological type, grade and myometrial infiltration. TAH BSO should be performed in cases of low risk or TAH BSO with pelvic lymphadenectomy to be carried out in case of high risk. This should be completed with paraaortic lymphadenectomy if the tumour is poorly differentiated (G3), even if myometrial invasion is not present, and also in all cases where three-thirds of the myometrium is infiltrated.

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