The efficiency of treatment in patients with uterine-confined endometrial cancer

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Summary

Aim: To present our experience regarding the efficiency of treatment in patients with uterine-confined endometrial cancer.

Patients and methods: 775 patients with uterine-confined endometrial cancer (UCEC) were treated between July 1985 and June 2000 in the Krakow Branch of Sklodowska Memorial Institute.

Results: Among the 775 patients, 5-year disease-free survival was observed in 82.8% patients; 96% patients with low risk of disease recurrence, 93.6% patients with intermediate risk and 78.3% patients with high risk survived five years with no evidence of disease. In the group with a high-risk disease recurrence rate, 5-year disease-free survival was statistically higher among patients treated with adjuvant brachytherapy plus external beam radiotherapy (EBRT) in comparison to patients treated with adjuvant brachytherapy (BRT) alone (82.4% vs 72.1%).

Conclusions: The recommended treatment in patients with high and moderate differentiation of UCEC with FIGO Stage IA is surgery alone. Surgery with adjuvant EBRT in the group of patients with intermediate risk of cancer recurrence allows over 90% of patients to be cured. In the group of patients with a high risk of disease recurrence adjuvant BRT with EBRT is statistically more efficient in comparison to BRT alone.

Key words: Uterine-confined endometrial cancer; Treatment results.

Introduction

The recommended procedure in patients with non-advanced endometrial cancer (FIGO Stage I and II) is primary surgery – total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH and BSO) [4, 43]. Indications for adjuvant therapy of uterine-confined endometrial cancer (UCEC), especially radiotherapy, are based on dividing patients into three groups: high, intermediate and low risk of cancer recurrence [4, 28, 36, 43]. Qualifications of patients to one of the specified groups are different in respective centers and are generally based on prognostic factors as cancer grade by FIGO, histological type of cancer, histological differentiation, depth of myometrium invasion, age and hormonal status, etc. In the last few years, new immunohistochemical and molecular factors like DNA ploidy, proliferation index, S-phase size, MIB-1, p53, p21, HER-2/neu gene expression and angiogenesis are considered to be of prognostic value [3-6, 21, 22, 29, 33, 36, 43, 45, 49].

The value of adjuvant postoperative irradiation in UCEC patients is still unclear, with reference to both indications and treatment methods [2, 4, 8, 10, 13, 16, 22, 26, 28, 40, 42, 46-48]. It is generally thought that adjuvant irradiation reduces the number of local vaginal and pelvic recurrences compared to surgery alone, especially among patients with high risk of disease recurrence, but its influence on distant survivals remains controversial [8, 9, 13, 16, 18, 23, 30, 31, 34, 39, 46].

The aim of this publication is the presentation of 15 years of experience of the Krakow Branch of Sklodowska Memorial Institute in the treatment of UCEC patients with special consideration to postoperative adjuvant radiotherapy.

Material and Methods

Between July 1985 and June 2000, 922 patients with endometrial cancer were treated at the Krakow Branch of Sklodowska Memorial Institute (CB-SMI). Seven hundred and seventy-five (84.1%) patients were diagnosed with UCEC by FIGO [20]. The average age of the patients was 58 (range 30-80). One hundred and seventeen (15.1%) patients had the following concurrent diseases: 22 patients - arterial hypertension, two patients - diabetes mellitus, 69 - both arterial hypertension and diabetes mellitus, 17 patients - circulatory insufficiency, seven patients - all of the afore mentioned diseases.

In the study group there were 140 (18.1%) nulliparous, 131 (16.9%) uniparous, 230 (29.7%) biparous and 274 (35.3%) multiparous women.

Six hundred and one (77.5%) patients were diagnosed with Stage I endometrial cancer by FIGO; 72 (9.3%) with IA, 189 (24.4%) - IB and 340 (43.8%) - IC. In 174 (22.5%) patients the diagnosis was Stage II endometrial cancer (FIGO), in 85 (11%) patients - IIA and in 89 (11.5%) patients - IIB.

In 755 (97.4%) patients the histological type of cancer was endometrial adenocarcinoma, in 381 (49.2%) – G1, in 234 (30.2%) – G2 and in 160 (20.6%) – G3. In 72 (9.3%) patients only the mucous membrane was involved, in 305 (39.3%) the inner half of the myometrium and in 398 (51.4%) the outer half of the myometrium was involved.

Since 1985, the study group was arbitrarily divided into three groups: low, intermediate and high risk cancer recurrence (Table 1).

Fifty (6.5%) patients with well and moderately differentiated cancer in Stage IA were included into the group of low risk of cancer recurrence. One hundred and seventy-three (22.3%)

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Table 1. — *Group of recurrence risk among UCEC patients.*

Risk of cancer recurrence	FIGO stage and cancer differentiation	Number of patients	%
Low	IA - G1, G2	50	6.5
Intermediate	IA - G3, IB–G1, G2	173	22.3
High	IB - G3, IC, II	552	71.2
All	I, II - G1, G2, G3	775	100.0

patients with poorly differentiated cancer in Stage IA or well differentiated cancer in Stage IB were included in the group of intermediate risk of cancer recurrence. Five hundred and fifty-two (71.2%) patients with poorly differentiated cancer in Stage IB and all cancer patients in Stage IC and II were put in the high-risk cancer recurrence group.

In all the study patients the routine preoperative diagnostics of endometrial cancer were performed, i.e., physical examination, the per vaginam/rectum gynecological examination with speculum, fractionary scraping of the channel of the cervix and corpus cavum or guided biopsy during hysterectomy with microscopic examination of the obtained material. All patients had chest X-ray, routine blood and urine tests, biochemical tests of kidney and liver status as well as routine tests (coagulation tests, electrolytes, glycemia, etc.). In patients with suspicion of a more advanced process, additional cystoscopy, urography, rectoscopy, proctoclysis and other tests targeting exclusion of a possible metastatic process, i.e., skeletal scintigraphy, abdominal ultrasonography (US) or computed tomography (CT) were performed.

Advancement of a malignant process was evaluated based on preoperative clinical, biochemical and imaging examination results as well as intraoperative macroscopic assessment. Likewise, patient efficiency was assessed by the Karnofsky scale.

All 50 patients treated with surgery alone and the 720 patients adjuvantly irradiated were followed-up. For five (0.7%) patients the exact date of death was unavailable. Patients treated with surgery alone were followed-up every six months in the first two years and every 12 months in the following years. Patients treated with adjuvant irradiation were followed-up every three months during the first two years, and every six months during the following years. The follow-up included physical examination, gynecological examination, X-ray of the chest (once a year) and ultrasonography of the abdomen (once a year). When recurrence or dissemination were suspected, abdominal, chest or brain CT, scintiscanning of the skeleton and other investigations were performed.

In the group of 725 patients who received adjuvant irradiation, an evaluation of tolerance and complications of radiotherapy was conducted. For estimation of the intensification of radiotherapy-related effects, the SOMA-LENT scale and "Glossary for reporting complications of treatment in gynecological cancers" worked out by Chassagne *et al.* [12, 38] were applied (Table 2).

All 775 patients received primary surgery (TAH & BSO). If suspected or enlarged, lymphatic glands were submitted to microscopic examination. In 50 patients with low-risk cancer recurrence (Stage IA - G1, G2) no adjuvant treatment was performed.

In 173 patients with medium risk of recurrence (IA - G3, IB - G1, G2), external beam radiotherapy was applied. Among 552 patients with high risk of disease recurrence (IB - G3, IC, II), 222 (40%) patients were treated with vaginal brachytherapy (BRT) alone and 330 (59.8%) with both brachytherapy and external beam radiotherapy (BRT + EBRT). The decision about the choice of method of irradiating was made each time by the therapeutic team.

Table 2. — *Treatment methods used in the study group.*

Treatment methods	Group of patients - risk of cancer recurrence							
	Low (IA - G1, G2)		Moderate (IA - G3, IB - G1, G2)		High (IB - G3, IC, II)		Total	
	No.	%	No.	%	No.	%	No.	%
Surgery alone	50	100.0	–	–	–	–	50	6.5
Surgery + External beam radiotherapy (EBRT)	–	–	173	100.0	–	–	173	22.3
Surgery + Vaginal brachytherapy (BRT)	–	–	–	–	222	40.4	222	28.6
Surgery + EBRT + BRT	–	–	–	–	330	59.8	330	42.6
Total	50	100.0	173	100.0	552	100.0	775	100.0

Adjuvant irradiating started four weeks after the surgical intervention. Therapy of patients treated with BRT + EBRT usually started with vaginal BRT, and then after three to four weeks EBRT was applied.

The active source used in vaginal BRT was radium-226. The target volume was the upper half of the vagina. Depending on anatomical conditions, primary focus of disease and uterine wall involvement, two types of radium applicators were used: cylindrical (dose rate ~ 67.6 r/h, average treatment time ~ 76 hrs, used in most patients with Stage I disease) and asymmetrical (dose rate ~ 78 r/h and average treatment time ~ 65 hrs, used in most patients with Stage II disease). In both cases the dose of radiation on the applicator surface was ~ 5000 cGy.

Postsurgical (adjuvant) external beam radiotherapy was administered as telegammatherapy (cobalt 60) in 50 patients or 10 MeV energy X-ray therapy (linear accelerator) in 675 patients. The "box technique" (4 opposite beams: front, rear, left and right) was applied. The size of entry fields oscillated from 14 x 14 cm to 16 x 16 cm at the front and rear fields and from 15 x 8 cm to 16 x 10 cm at the side fields. The lower limit of the irradiated volume was the line running along the lower rim of the obturator foramen, the side border lines were running 1 cm laterally on both sides of the *linea terminalis* and the upper limit reached the upper rim of the L5 vertebra. The front border was a plane surface running contiguously to the frontrim of the symphysis pubis and the rear was the surface running vertically through the middle of the sacral bone. The so-defined area was treated with a dose of 50.4 Gy in 24 fractions over five weeks. The reference point of dose calculation was the intersection of all four beam axes. Dose contribution of all four fields was equal and measured 12.6 Gy.

In 50 patients treated with surgery alone, no serious postoperative complications followed. In three patients, the surgical wound closed up by granulation. Distant radiotherapy-related complications including intervention demanding colorectal stenosis (4 patients), fistula rectovaginal fistula (2 patients), protracted hematuria and urinal incontinency (2 patients) were found in eight (1.1%) of the irradiated patients. Patients with colorectal stenosis were successfully operated on and the fistulas closed up after two to three years of conservative treatment. Dysuric manifestations ceased in one patient after two years of treatment, while in one patient they still remain. Seven patients with serious radiotherapy-related complications survived five

years with no evidence of disease. One patient, operated on because of colorectal stenosis, died from a pulmonary embolism five days after surgery.

As an efficacy criterion, 5-year disease-free survival (DFS) beginning from surgery date was assumed. All patients were observed for five years, unless they died earlier. The medium time of observation was eight years. For assessment of differences found in our material, the log-rank test by Peto *et al.* was used [41]. For estimation of the influence of chosen factors on the patient survival model, the Cox proportional hazard model was used [14]. The assumed level of statistical significance was $p < 0.05$.

Results

Of the 775 study patients, 5-year disease-free survival was found in 642 (82.8%) patients. Age, fecundity, concurrent diseases, the microscopic form of the cancer and depth of uterine wall invasion had no statistically significant influence on the results of the treatment. These results were affected however by advancement of the malignant process and histological differentiation of the cancer (Table 3).

Table 3. — *Results of treatment versus cancer stage and differentiation.*

	No. of patients	Five-year disease-free survival	
		No.	%
Cancer stage (by FIGO 1988):			
IA	72	64	88.9
IB	189	178	94.2
IC	340	287	84.4
IIA	85	63	74.1
IIB	89	50	56.2
Cancer differentiation (G):			
G1	381	350	91.4
G2	234	190	81.2
G3	160	102	63.8
Total	775	642	82.8

Of 601 patients with Stage I UCEC, 5-year disease-free survival was observed in 529 (88.8%) patients, and of 174 patients with Stage II UCEC – 113 (64.9%) patients, respectively. Five-year disease-free survival was observed in 91.4% patients with well differentiated cancer, 81.2% with moderately differentiated and 63.8% with poorly differentiated cancer, respectively. The differences are extremely statistically significant (log rank test, $p < 0.01$).

In the Cox multivariate analysis, the only independent prognostic factor for 5-year disease-free survival was cancer differentiation.

Table 4 shows the results of treatment in relation to risk factors of recurrence.

In the group of 50 UCEC patients with low risk of recurrence (Stage IA - G1, G2) treated with surgery alone, 5-year disease-free survival was observed in 48 (96%) patients. Two patients died of circulatory incidents (heart attack or stroke) with no evidence of cancer recurrence or dissemination. Of 173 patients with intermediate risk of recurrence, 162 (93.6%) patients survived five years with no evidence of disease, and of 552 patients with high risk of relapse - 432 (78.2%) patients, respectively. Both groups of patients were postoperatively irradiated.

Table 4. — *Treatment results versus risk of cancer recurrence.*

Patients risk of cancer recurrence	No. of patients	Five-year disease-free survival	
		No. of patients	%
Low risk (IA - G1, G2)	50	48	96.0
Intermediate risk (IA - G3, IB - G1, G2)	173	162	93.6
High risk (IB - G3, IC, II)	552	432	78.3
Total	775	642	82.8

Table 5 presents the results of treatment according to radiotherapy method in patients with high-risk of UCEC recurrence.

Table 5. — *Treatment results versus radiotherapy methods in UCEC patients with high-risk of cancer recurrence.*

Adjuvant radiotherapy methods	No. of patients	Five-year disease-free survival	
		No. of patients	%
Vaginal brachytherapy alone	222	160	72.1
External beam radiotherapy + vaginal brachytherapy	330	272	82.4
Total	552	432	78.3

Of 330 patients treated with postoperative EBRT + BRT, 5-year disease-free survival was observed in 272 (82.4%) patients, whereas only 160 (72.1%) patients survived five years with no evidence of disease in the group of 222 patients treated with postoperative vaginal BRT alone. Thus, patients with a high risk of disease relapse who received EBRT + BRT had a significantly higher chance of recovery (log rank test, $p < 0.02$).

Of the 775 study patients, 133 (17.2%) patients died within the 5-year follow-up period; no patient with unresolved disease survived five years. Table 6 shows causes of patient death and treatment failure.

Twenty-six (3.4%) patients died within the 5-year follow-up from concurrent disease (myocardial infarction – 11 patients, encephalorrhagia – 10 patients, brain embolism – 3 patients, viral pneumonia – 2 patients). One patient died from radiotherapy-related complications, six (0.8%) patients died from other malignancies (breast cancer – 3 patients, lung cancer – 1, stomach cancer – 1 and malignant brain glioma – 1 patient).

A basic cause of treatment failure in the study group was distant metastases in 71 (9.2%) patients; the metastatic sites were the lungs, liver, brain and bones. Pelvic recurrence was found in 33 (4.3%) patients.

No case of treatment failure was found in the group of 50 patients with low-risk of cancer relapse (Stage IA - G1, G2). Two patients in this group died from concurrent diseases.

Table 6. — *Cause of death and treatment failure.*

Cause of death and treatment	Group of patients vs risk of cancer recurrence								Total	
	Low risk		Intermediate risk		High risk: EBRT+ vaginal BRT		High risk: vaginal BRT alone			
	No	%	No	%	No	%	No	%	No	%
Distant metastases	–	_	3	27.3	41	70.7	23	37.1	67	50.4
Pelvic recurrence	–	–	–	–	2	3.4	27	43.6	29	21.8
Distant metastases + pelvic recurrence	–	–	1	9.1	1	1.7	2	3.2	4	3.0
Another malignancy	–	–	2	18.2	3	5.2	1	1.6	6	4.5
Concurrent diseases	2	100.0	4	36.3	11	19.0	9	14.5	26	19.5
Radiotherapy-related complications	–	–	1	9.1	–	–	–	–	1	0.8
Total	2	100.0	11	100.0	58	100.0	62	100.0	133	100.0

In the group of 173 patients with intermediate risk of cancer relapse (Stage IA - G3, Stage IAB - G1, G2), only one (0.6%) patient had pelvic recurrence. Similarly, only three (0.9%) patients in the group with a high risk of cancer relapse, treated with postoperative EBRT + BRT, had pelvic recurrence. However, among 222 patients with a high risk of cancer relapse, treated with postoperative vaginal BRT alone, 29 (13.1%) patients developed pelvic relapse of disease. The difference is statistically significant (log rank test, $p < 0.05$). It is worth emphasizing that almost a half of the patients from this group who died within the 5-year follow-up had local recurrence, similar to 29 (55.8%) patients from the group of 52 patients with disease relapse.

Discussion

Of the 775 patients, the 5-year disease-free survival (DFS) rate was 82.8% (642 patients).

The obtained results are in agreement with the literature data, where the 5-year DFS rate oscillates from 65% to 86% [9, 11, 22, 23, 26, 27, 31, 48]. According to Cox's multivariate analysis the grade of cancer differentiation was the only independent prognostic factor for 5-year DFS. Among patients with well-differentiated cancer (G1), the 5-year DFS rate was 91.3%, with moderately differentiated cancer (G2) - 80%, and with poorly differentiated cancer (G3) - 63.8%. Our results are comparable with the literature data and show that grade of cancer differentiation is one of basic prognostic factors in patients with endometrial cancer [7, 15, 17, 21, 22, 25, 35, 39, 43, 45, 46, 49] . The recovery percentage in patients with grade 1 UCEC ranges from 91% to 98% for well-differentiated cancer, from 82% to 90% for moderately differentiated cancer and from 64% to 80% for poorly differentiated cancer [25, 49]. Many authors indicate that the poorer the grade of differentiation the higher the risk of myometrium invasion and cancer dissemination beyond the uterus, particularly to the regional lymph nodes [7, 15]. Moderately and poorly differentiated cancer is considered to be the basic indication for adjuvant postoperative radiotherapy in patients with UCEC [17, 28, 49].

The study patients were allocated into three subgroups: high, intermediate and low risk of cancer relapse. Such division is supported by the data obtained from the literature that show a significantly higher rate of 5-year DFS in patients with low and intermediate risk of recurrence compared to the high-risk group (94.2% vs 78.3% of 5-year DFS). Definitions of high, intermediate and low risk of cancer relapse available in the literature are comparable to ours (13, 36, 39, 46).

UCEC patients with low risk of recurrence

Of 50 patients with a low risk of cancer relapse (Stage IA - G1, G2) treated with surgery alone, the rate of 5-year DFS was 96% (48 patients). Two patients died of concurrent diseases with no evidence of cancer. Our results are comparable with the literature data, according to which surgery alone is the treatment of choice in patients with well and moderately differentiated UCEC in Stage IA [4, 9, 15, 24, 28, 34, 35, 36].

In the GOG report, in a group of 72 patients with well and moderately differentiated UCEC in Stage IA treated with surgery alone, no case of local recurrence was found [35]. According to Creasman *et al.* the rate of distant DFS in these patients is 90-96% and the risk of locoregional lymph nodes recurrence does not exceed 5% [15]. Today, no significant center recommends adjuvant pelvic irradiation for this group of patients [9, 35] and just a few propose vaginal brachytherapy, particularly in Stage IA, for patients with moderately differentiated UCEC [34].

UCEC patients with intermediate risk of cancer recurrence

Patients with intermediate risk of cancer relapse (Stage IA - G3, Stage IB - G1, G2) were treated with postoperative external beam radiotherapy of the pelvis. The rate of 5-year DFS was 93.6%. Only 2.3% (4 of 174) patients died from endometrial cancer dissemination, including one local recurrence. Thus, the combination of surgery with postoperative EBRT proves to be effective in this group of patients. The results of treatment are similar to those in the group with low risk of cancer relapse.

The current opinions among authors regarding postoperative procedures in patients with intermediate risk of cancer relapse differ considerably. Some consider that no adjuvant treatment should be recommended if full cancer staging (including lymphadenectomy or microscopic assessment of regional lymph nodes) was performed during surgery [1, 9, 18, 28]. The GOG-99 and PORTEC controlled studies showed no survival improvement after postoperative irradiation [16, 42]. Carey *et al.* noted only 4% of local relapses in 227 patients with G1 or G2 UCEC in Stage IB treated with surgery alone, and Larson *et al.*

only 3% of local relapses in a comparable group of patients [9, 32]. Nevertheless, some authors claim that patients with intermediate risk of cancer should be adjuvantly irradiated, using BRT or EBRT alone [9, 19, 23, 29, 31, 47]. Most authors recommend EBRT alone [23, 27, 44, 46], however vaginal BRT is considered to be cheaper and brings about fewer complications [2, 23, 31, 36, 39, 47].

Both, the analysis of our material and the literature data is not enough to determine definitely if patients with intermediate risk of cancer relapse should be postoperatively irradiated and if so, which method to choose.

UCEC patients with high risk of cancer recurrence

In the group of 552 patients with a high risk of cancer relapse (Stage IB - G3, Stage IC, II), group A (222 patients) were treated postoperatively with vaginal brachytherapy alone and group B (330 patients) with both brachytherapy and external beam radiotherapy. The rate of 5-year DFS was significantly higher in group B (82.4% vs 72.1%). The reason for the poorer results of treatment in group A was the higher rate of pelvic recurrence (13.1% vs 0.9%). These findings imply that postoperative EBRT, with a dose of 50 Gy in 24 fractions for four to five weeks over the whole pelvis, significantly reduces the risk of local recurrence in UCEC patients with a high-risk of cancer relapse.

The available literature data do not answer the question as to whether the group of UCEC patients requires both methods (vaginal BRT + EBRT) of adjuvant radiotherapy [23, 28, 39, 46]. Some investigators propose limiting the adjuvant treatment to vaginal brachytherapy only [2, 24, 37, 39] or more often to EBRT only [9, 19, 28, 29, 31, 44] if surgical staging has been performed correctly, however, most authors consider postoperative EBRT followed by BRT to be necessary, especially for patients with Stage IC and II by FIGO [9, 18, 19, 22, 23, 28, 29, 36]. According to Eltabbakh and Moore, the rate of 5-year DFS in patients with Stage II disease, treated with EBRT followed by BRT, was 90% [19]. The combination of both methods of irradiation significantly improved the results of treatment in our material.

Conclusion

The treatment of choice in patients with Stage IA UCEC is surgery alone. No adjuvant treatment is necessary. Surgery followed by pelvic EBRT allows cure of over 90% of UCEC patients with intermediate risk of cancer recurrence (Stage IA - G3, Stage IB - G1, G2). UCEC patients with high risk of cancer recurrence (Stage IB - G3, I, II) treated with EBRT and vaginal BRT, have a significantly higher chance of recovery compared to patients treated with BRT alone. External beam radiotherapy reduces the risk of pelvic recurrence in this group of patients.

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