Postoperative radiotherapy in Stage I endometrial adenocarcinoma

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Summary

Objective: To evaluate postoperative whole pelvic radiation for high-risk patients with Stage I endometrial adenocarcinoma.

Methods: One hunderd and twenty-two patients with irregular premenopausal or postmenopausal haemorrhage were included into the study. Fractional curettage was performed in all cases. When the pathohistological report confirmed endometrial adenocarcinoma, abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Low-risk patients include women with Stage IA tumours and Stage IB grade 1 or 2 histology. High-risk group include patients with Stage IB grade 3 tumours and Stage IC carcinomas. High-risk patients received whole pelvic radiotherapy between two and four weeks after surgery.

Results: Eighty-two patients (67.21%) were low-risk and forty patients (32.79%) were high-risk. In the low-risk group of patients, CA-125 was negative in ten cases and positive in 72 patients with a mean value of 30.12 ± 12.42 U/ml serum. In the high-risk group of the patients, CA-125 was negative in two cases and positive in 38 patients with a mean value of 60, 48 ± 20, 14 U/ml serum. Locoregional recurrences were diagnosed in four patients (4.87%) in the surgery group and in two patients (5.00%) assigned to radiotherapy. The incidence of distant metastases was 2.43% in the surgery group and 2.50% in the radiotherapy group. Overall survival at five years was 90.25% in the low-risk group and 87.50% in the high-risk group of patients.

Conclusion: Five-year overall survival, locoregional and distant metastasis were similar in the low-risk and high-risk groups of patients. That emphasizes the value of whole pelvic radiation in patients with unfavourable prognostic factors in Stage I endometrial cancer.

Key words: Stage I endometrial adenocarcinoma; High-risk patients; Postoperative pelvic radiotherapy.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract. Increased life expectancy in many countries today has led to an increased number of patients being diagnosed with endometrial carcinoma, which is predomintly a disease of postmenopausal women. Adenocarcinoma is the most common subtype and is often associated with unopposed estrogen exposure, obesity and a history of endometrial hyperplasia. The primary treatment for endometrial cancer consists of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Staging should be completed with peritoneal washing and lymph node dissection, including the pelvic and the para-aortic node groups. Most cases are discovered in Stage I when the disease is confined to the uterine corpus. Recommendations for adjuvant radiation in women with Stage I endometrial cancer vary considerably among gynecologic oncologists.

Pelvic radiation became popular after a randomized trial demonstrated that the incidence of vaginal recurrence could be decreased with the addition of whole pelvic radiation in patients who had previously been treated with surgery and vaginal cuff radiation [1]. Many of the oncologists who use whole pelvic radiation therapy do so only when there is an outer-third uterine invasion or lymph-vascular space involvement [2]. Some gynecologic oncologists never use radiation in Stage I endometrial cancer and they have demonstrated excellent survival in women after a complete surgical staging procedure alone, even high-risk subgroups [3].

The purpose of this study was to evaluate postoperative whole pelvic radiation for high-risk patients with Stage I endometrial adenocarcinoma.

Patients and Methods

One hundred and twenty-two patients, mean age 59.18 ± 8.32 years, were included in the study. Irregular premenopausal and postmenopausal haemorrhage was reported in 20 and 102 patients, respectively. Initial evaluation included pelvic examination, Pap smears, transvaginal ultrasound and endometrial curettage with separate endocervical and endometrial sampling. Preoperative evaluation included medical history and physical examination, chest radiography, complete blood count, blood-chemistry tests and serum concentration of CA-125 tumour marker. At the time of surgery, a vertical midline abdominal incision was performed with peritoneal washing of the pelvis and abdomen done immediately. Abdominal exploration with careful palpation for suspicious or enlarged nodes in the aortic and pelvic nodal areas was done. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The diagnoses of endometrial carcinoma, histological type, grade of differentiation and depth of myometrial invasion were made by a pathologist.

Postoperative FIGO Stage I was assigned on the basis of surgical and pathological findings. The low-risk group of patients comprised women with Stage IA tumours and Stage IB grade 1 or 2 endometrial adenocarcinoma. The high-risk group included

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patients with Stage IB grade 3 tumours and Stage IC endometrial adenocarcinoma. Women with adenosquamous carcinoma, papillary serous and clear-cell carcinoma were not included in this study. Patients were excluded if they had previously received radiotherapy or chemotherapy.

High-risk patients received radiotherapy between two and four weeks after surgery.

Postoperative radiotherapy was administered to the pelvic region according to a standardised protocol. The total dose was 40-46 Gy in 20-23 fractions using 2 Gy daily fractions, five days a week. The radiation was delivered by anteroposterior and posteroanterior parallel ports.

Patients were followed-up every three months for the first two years, every six months during the next three years and then annually.

Results

From January 1993 to September 1998, 122 patients with FIGO Stage I endometrial adenocarcinoma were treated by abdominal hysteroctomy and bilateral salpingo-oophorectomy. Eighty-two patients (67.21%) were low-risk patients with Stage IA tumours and IB tumours histologically grade 1 or 2. Forty patients (32.79%) were high-risk patients and included women with Stage IB grade 3 histology and Stage IC tumours (Table 1).

Table 1. — *Distribution of patients with good and poor prognostic factors in Stage I endometrial adenocarcinoma.*

Prognostic factors	Number of cases	%
Low-risk (IA, IB grade 1, 2)	82	67.21
High-risk (IB grade 3, IC)	40	32.79

In the low-risk group of patients, out of 82 patients CA-125 was negative in ten cases and positive in 72 patients with a mean value of 30.12 ± 12.42 U/ml serum. In the high-risk group of 40 patients, CA-125 was negative in two cases and positive in 38 patients with a mean value of 60.48 ± 20.14 U/ml serum (Table 2). The difference was statistically significant ($p < 0.001$).

Table 2. — *The relationship between prognostic factors of Stage I endometrial adenocarcinoma and serum CA-125 (U/ml).*

Prognostic factors	Number of cases	CA-125 (X ± SD)
Low-risk (IA, IB grade 1, 2)	72	30.12 ± 12.42
High-risk (IB grade 3, IC)	38	60.48 ± 20.14

$t = 8.12$; $p < 0.001$.

For the low-risk group of patients no further therapy was applied, while high-risk patients received postoperative whole pelvic radiation. The median interval between the operation and the first radiotherapy session was 22 days. During radiotherapy, 68% of the patients were treated with medication or dietary measures, or both, for treatment-related symptoms.

Late complications of the primary treatment were reported in 15 patients: six (7.31%) in the surgery group and nine (22.50%) in the combined surgery and radiotherapy group. Most of the complications in the radiotherapy group were related to the gastrointestinal tract and 80% of them were grade 1.

Locoregional recurrences were diagnosed in four patients (4.87%) in the surgery and in two patients (5.00%) in the surgery and radiotherapy group. The difference was not statistically significiant. Distant metastases involving the abdomen or lung, or both, and the overall incidence was similar in both treatment groups: 2.43% in the surgery group and 2.50% in the surgery and radiotherapy group. Local relapses were treated by surgery and patients with distant metastases received adjuvant chemotherapy with doxorubicin, cyclophosphamide and cisplatin.

Overall survival at five years was 90.25% in the low-risk group and 87.50% in the high-risk group of patients (Table 3). The difference was not statistically significant.

Table 3. — *Five-year survival of our patients according to the treatment methods in relation to good or poor prognostic factors.*

Prognostic factors	Number of cases	Pelvic radiation	5-year survival (%)
Low-risk (IA, IB grade 1, 2)	82	No	90.25
High-risk (IB grade 3, IC)	40	Yes	87.50

Discussion

There is no satisfactory screening test for endometrial carcinoma. Cervical cytology is abnormal in less than half of the corpus carcinoma patients. Transvaginal ultrasound is often used to determine endometrial thickness with a value of 5 mm as a "cut-off", the level of normal thickness in postmenopausal women. Women with abnormal uterine bleeding over the age of 40, and patients with postmenopausal bleeding had fractional curettage and histological verification of endometrial tissue performed.

Once a diagnosis of endometrial carcinoma had been made, the next step was to determine the extent of the disease as expressed by its stage. In 1998 FIGO (International Federation of Gynecology and Obstetrics) changed the staging for endometerial cancer from a clinical to a surgical staging system. Clinical staging, however, still remains important in terms of preoperative assessment and planning for subsequent surgery, and correlates well with prognosis [4]. The serum CA-125 marker may also be of value in advanced disease. In the high-risk group of patients CA-125 was significantly higher than in the low-risk group.

Recent studies have suggested that a CA-125 "cut-off" level of 20 U/ml may be more appropriate in endometrial carcinoma then the traditional level of 35 U/ml used in ovarian cancer. This level could detect myometrial invasion to more than one-half of the myometrium with a sensitivity of 69.9%, specificity of 74.1%, positive predictive

value of 58,8%, and negative predicitive value of 81.6% [5]. To conclude, the CA-125 level of 20 U/ml or grade 3 tumours or both of these, could correctly predicte 87% of patients requiring surgical staging [6]. The combination of serum CA-125 with a "cut-off" of 15 U/ml and histological grade after curettage could identify 65% of patients who required a lymphadenectomy or sampling [7]. The concentration of the CA-125 marker, with a "cut-off" value of 5 U/ml was significantly higher when the tumour penetration exceeded one-third of the uterine wall [8]. When the tumour metastasised out of the uterus, concentrations of the marker were considerably higher [9]. Other noninvasive methods have also been employed in diagnosis, most commonly transvaginal sonography (TVS), computed tomography (CT) and magnetic resonance imaging (MRI). The sensitivity of TVS was significantly higher than CA-125 in predicting myometrial invasion of endometrial cancer. No difference was found in terms of specificity [10]. All these methods can be used in planning an adequate surgical procedure and postoperative radiotherapy.

The standard surgical procedure in Stage I endometrial carcinoma is a total abdominal hysterectomy with bilateral salpingo-oophorectomy. Due to the staging system, lymphadenectomy of the para-aortic and pelvic areas remains controversial. Lymphadenectomy lengthens the operation time and causes operative complications [11, 12]. From our experience indications for node sampling are suspicious in enlarged para-aortic and pelvic lymph nodes.

Low-risk patients include women with Stage IA tumours and Stage IB grade 1 or 2. The recurrence risk is very small in this group, and no further therapy is generally recommended. The majority of gynecologic oncologists advocate adjuvant radiation when the tumour exhibits deep myometrial invasion or grade 3 histology with any myometrial invasion, often with whole pelvic radiation [13]. Pelvic radiotherapy is indicated to reduce the risk of locoregional recurrences in high-risk patients. Some studies of Stage I endometrial carcinoma treated surgically followed by whole pelvic radiation in cases of poor prognostic factors report 4-7% locoregional recurrences and 7-17% distant metastases [14-16]. In our radiotherapy group locoregional recurrences were seen in two patients (5.00%) and were located in the vaginal vault. Distant metastases in our group of patients were observed in only one case (2.50%). A high rate of distant metastases suggests that the cancer has spread to distant sites before the initiation of radiotherapy. Our patients received radiotherapy between two and four weeks after surgery but in some other studies radiotherapy was started six to eight weeks after surgery [17].

In our study in the surgery group of patients locoregional recurrences were diagnosed in four cases (4.87%) with Stage IB grade 2 disease. Distant metastases in two cases (2.43%) occurred in one patient with Stage IA grade 3, and another in a patient with Stage IB grade 2 disease. A few gynecologic oncologists include Stage IA grade 3 and Stage IB grade 2 tumours in the intermediate-risk group and advocate radiotherapy in the form of vaginal radiation. In reports on patients treated with postoperative vaginal radiotherapy, vaginal recurrence rates vary from 3-5% [18-20]. Patients with high-risk surgical Stage I endometrial cancer treated with surgery and postoperative whole pelvic radiotherapy have a 5-year overall survival of 80-94% [17, 21]. In our study the 5-year overall survival rate in the low-risk, only surgery group, and the high-risk, surgery and radiotherapy group, was similar, 90.25% and 87.50%, respectively. That emphasizes the value of whole pelvic radiation in patients with unfavourable prognostic factors in Stage I endometrial adenocarcinoma. For patients in the intermediate-risk group it seems that postoperative vaginal radiotherapy is preferable.

References

[1] Aalders J., Abeler V., Kolstad P., Onsrud M.: "Postoperative external irradiation and prognostic parameters in stage I endometrial clinical and histopathologic study of 540 patients". *Obstet. Gynecol.,* 1980, *56,* 419.

[2] Naumann R.W.: "The role of radiation therapy in early endometrial cancer". *Curr. Opin. Obstet. Gynecol.,* 2002, *14,* 75.

[3] Larson D.M., Broste S.K., Krawisz B.R.: "Surgery without radiotherapy for primary treatment of endometrial cancer". *Obstet. Gynecol.,* 1998, *91,* 355.

[4] Benedet J.L., Pecorelli S.: "Staging classifications and clinical practice guidelines of gynecologic cancers". *J. Gynecol. Obstet.,* 2000, *70,* 207.

[5] Kurihara T., Mizunuma H., Obara M., Andoh Kazneno., Ibuki Y., Nishimura T.: "Determination of a normal level of serum CA125 in postmenopausal women as a tool for preoperative evaluation and postoperative survellance of endometrioal carcinoma". *Gynecol. Oncol.,* 1998, *69,* 192.

[6] Dotters D.J.: "Preoperative CA125 in endometrial cancer: is it useful?". *Am. J. Obstet. Gynecol.,* 2000, *182,* 1328.

[7] Koper N.P., Massuger L.F., Thomas C.M., Kiemeney L.A., Verbeek A.L.: "Serum CA125 measurements to identify patients with endometrial cancer who require lymphadenectomy". *Anticancer Res.,* 1998, *18,* 1897.

[8] Kukura V., Zaninović I., Hrdina B.: "Concentrations of CA-125 tumor marker in endometrial carcinoma". *Gynecol. Oncol.,* 1990, *37,* 388.

[9] Kukura V., Zovko G., Ciglar S., Markulin-Grgić L., Šantek F., Podgajski M., Duić Ž.: "Serum CA-125 tumor marker in endometrial adenocarcinoma". *Eur. J. Gynaecol. Oncol.,* 2003, *24* (2), 151.

[10] Alcazar J.L., Jurado M., Lopez-Garcia G.: "Comparative study of transvaginal ultrasonography and CA 125 in the preoperative evaluation of myometrial invasion in endometrial carcinoma". *Ultrasound Obstet. Gynecol.,* 1999, *14,* 210.

[11] Trimble E.L., Kosary C., Park R.C.: "Lymph node sampling and survival in endometrial cancer". *Gynecol. Oncol.,* 1998, *71,* 340.

[12] Mohan D.S., Samuels M.A., Selim M.A.: "Long-term outcomes of therapeutic pelvic lymphadenectomy for Stage I endometrial adenocarcinoma". *Gynecol. Oncol.,* 1998, *70,* 165.

[13] Grigsby P.W.: "The role of irradiation in endometrial cancer". *Oncol. Spectr.,* 2001, *2,* 343.

[14] Poulsen H.K., Jacobsen M., Bertelsen K.: "Adjuvant radiation therapy is not necessary in the management of endometrial carcinoma Stage I, low-risk cases". *Int. J. Gynecol. Cancer,* 1996, *6,* 38.

[15] Podczaski E., Kaminski P., Gurski K.: "Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery". *Gynecol. Oncol.,* 1992, *47,* 323.

[16] Irwin C., Levin W., Fyles A., Pintili M., Manchul L., Kirkbride P.: "The role of adjuvant radiotherapy in carcinoma of the endometrium - results in 550 patients with pathological stage I disease". *Gynecol. Oncol.,* 1998, *70,* 247.

[17] Creutzberg C.L., van Puten W.L., Koper P.C., Lybeert M.L., Jobsen J.J., Warlam-Rodenhuis C.C. *et al.*: "Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomised trial". *Lancet,* 2000, *355,* 1404.
[18] Anderson J.M., Stea B., Hallum A.V., Rogoff E., Childers J.: "High-dose-rate postoperative alone for stage IB and IC endometrial cancer". *J. Radiat. Oncol. Biol. Phys.,* 2000, *46,* 417.
[19] Alektiar K.M., McKee A., Venkatraman E., McKee B., Zelefsky M.J., Mychalczak B.R. *et al.*: "Intravaginal high-dose-rate brachytherapy for Stage IB (FIGO Grade 1, 2) endometrial cancer". *J. Radiat. Oncol. Biol. Phys.*, 2002, *53,* 707.
[20] Yalman D., Ozsaran Z., Anacak Y., Celik O.K., Ozkok S., Ozsaran A. *et al.*: "Postoperative radiotherapy in endometrial carcinoma:analysis of prognostic factors in 440 cases". *Eur. J. Gynaecol. Oncol.*, 2000, *21,* 311.
[21] Ayhan A., Taskiran C., Celik C., Guney I., Yuce K., Ozyar E. *et al.*: "Is there a survival benefit to adjuvant radiotherapy in high-risk surgical stage I endometrial cancer?". *Gynecol. Oncol.,* 2002, *86,* 259.

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