Analysis of vaginal recurrences in Stage I endometrial adenocarcinoma

Y. Salihoğlu[1], *Prof.*; N. Keskin[2], *M.D.*; S. Topuz[2], *M.D.*; S. Küçücük[2], *M.D.*; C. Iyibozkurt[2], *M.D.*

[1]Department of Obstetrics and Gynecology, [2]Department of Radiation Oncology
Istanbul University, School of Medicine, Istanbul (Turkey)

Summary

Objective: To determine the risk of vaginal recurrence in Stage 1 endometrial cancer and treatment morbidity associated with different therapeutic approaches

Material and Methods: Between 1995 and 2005, 341 patients with clinical Stage I endometrial cancer were treated at Istanbul Medical Faculty. One hundred and forty-four women were included in this study as the follow-ups and records were complete. The patients with no myometrial invasion received no further therapy following hysterectomy. When there was superficial myometrial invasion postoperative vaginal vault radiation was used, and if deep myometrial invasion was present, external pelvic radiation was given.

Results: Overall 5-year survival rate for all patients with Stage I disease was 80%. Nine patients (6.25%) developed recurrent disease, three of whom had vaginal recurrences. All three vaginal recurrences were small and diagnosed at routine follow-up exam within 51 months of primary therapy.

Conclusion: This selective treatment protocol for patients with Stage I endometrial cancer avoided radiation entirely in 38% of the patients while achieving a very low rate of vaginal recurrence and good overall survival.

Introduction

Adenocarcinoma of the endometrium generally has a good prognosis with 5-year survival rates for Stage I disease ranging from 70% to 96% [1]. Many different treatment schemes have been suggested for Stage I disease but total abdominal hysterectomy and bilateral salpingo-oophorectomy is the basis of therapy. However in those patients treated by surgery alone the incidence of local recurrence varies from 6% to 12% with half of these occurring at the vaginal vault [1]. The addition of vaginal radiation or the use of external pelvic irradiation can successfully reduce the incidence of vaginal and pelvic recurrences but adds cost, time and potential morbidity to the therapy [2, 3].

At Istanbul Medical Faculty, patients with Stage I endometrial cancer have been managed with a protocol involving primary hysterectomy with selective use of radiation depending on the depth of myometrial invasion and grade of the tumor. We have reviewed our patients with Stage I disease to determine the risk of vaginal recurrence and treatment morbidity associated with this therapeutic approach.

Material and Methods

Between 1995 and 2005, 341 patients were treated at Istanbul Medical Faculty, Department of Gynecological Oncology with a diagnosis of adenocarcinoma of the endometrium. Following clinical examination and fractional dilatation and curettage (D&C), staging was established according to the FIGO guidelines [5]. A total of 144 patients (follow-up and records were fully complete) with Stage I endometrial carcinoma were treated according to the protocol outlined in Figure 1.

Initially, all patients were treated with total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing and partial or total omentectomy. In 92 patients (63.8%) pelvic and paraaortic lymph node biopsies were also obtained. Enlarged or suspicious nodes were sampled, and when no suspicious notes were noted random nodes from the internal and external iliac chains were sampled. No further therapy was recommended for those patients with negative washings, negative nodes and no myometrial invasion. When nodes and washings were negative but superficial myometrial invasion was present and the grade of tumor was over one, brachytherapy was used. In case of greater than 50% myometrial invasion, whole pelvic external radiation therapy was used postoperatively. Those patients who were found to have lymph node metastases were treated with external radiation and when papillary serous or malignant peritoneal cytology was obtained chemotherapy was used following hysterectomy.

At the time of initial surgery peritoneal washings were obtained by irrigating the pelvis and para-colic gutters with a total of approximately 150 cc of normal saline. Standard extra facial total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The fallopian tubes were clamped at the uterus at the beginning of the procedure. Following hysterectomy, the vaginal cuff was closed in all cases. Low-dose subcutaneous heparin for prophylaxis against venous thrombosis was used in most of the patients especially in the obese ones.

Postoperative vaginal vault radiation in patients with superficial myometrial invasion was accomplished with after loading TORE applicators. An approximately 6000 cGy vaginal vault surface dose was given. When external radiation was used, 4500 to 5600 cGy was delivered through anterior and posterior pelvic fields using 180 to 200 cGy fractions. Radiation was begun after satisfactory postoperative healing, usually between three and six weeks after surgery.

Revised manuscript accepted for publication December 18, 2006

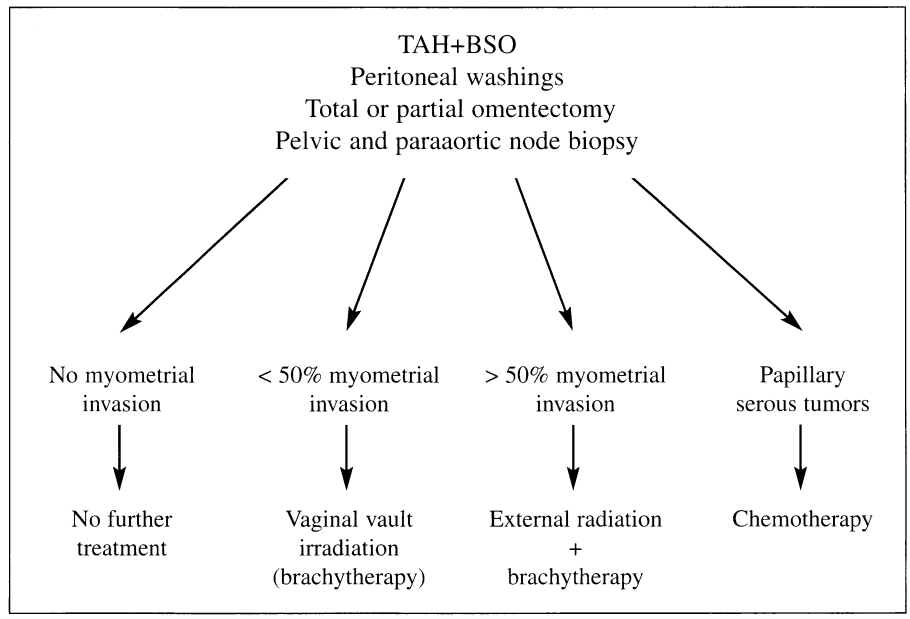
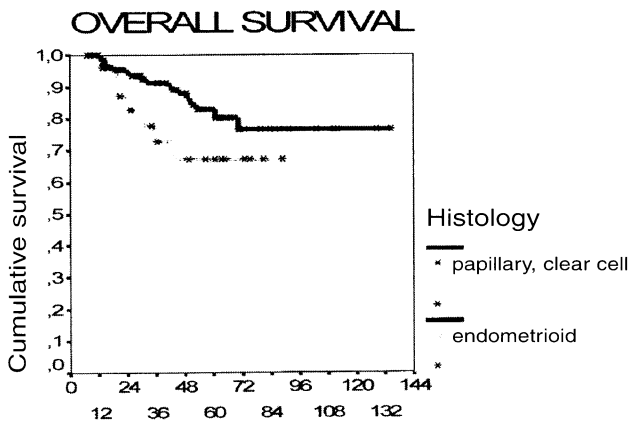
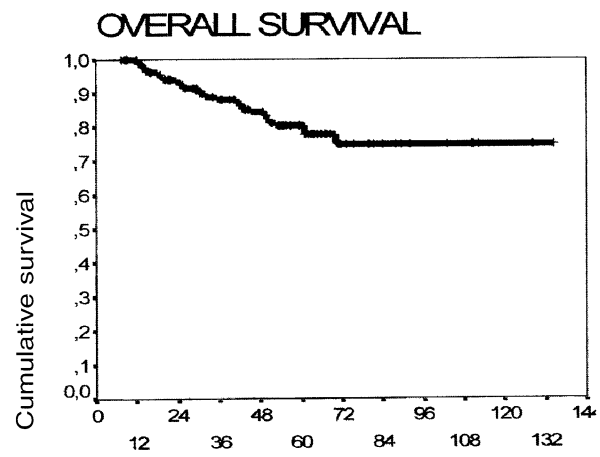


Figure 1. — Therapeutic algorithm of Stage 1 endometrial cancer (Grade 2 and 3 tumors receive radiotherapy without looking at the stage).



5-year survival
endometrioid + adenosquamous cancer 83%
papillary serous and clear cell cancer 67%
} p value: 0.05

Figure 2. — Survival according to histologic types.



Five-year survival rate was 80%.

Figure 3. — Overall survival of the whole series.

Patients were followed at 3-month intervals during the first year, 4-month intervals during the second year and 6-month intervals until five years. After five years they were followed at yearly intervals. History, pelvic examination and vaginal cytology were routinely done. At yearly intervals magnetic resonance (MRI) imaging or computed tomography (CT) was obtained. No other studies such as chest X-rays, intravenous pyelogram, etc. were done routinely but only as indicated by history or clinical findings.

Results

Among 144 patients with Stage I endometrial carcinoma, histology showed 106 patients with endometrioid adenocarcinoma. There were 13 patients with papillary serous adenocarcinoma, ten with clear cell carcinoma and 15 with adenosquamous carcinoma. The overall survival rate in endometrioid and adenosquamous cancer was 83% and in papillary serous and clear cell cancer 67%, respectively (Figure 2). Fifty-five patients had well differentiated tumors. There were 63 patients with grade 2 lesions and 17 were poorly differentiated. Nine patients were not graded. The median age was 59.2 years with a range from 32 to 88 years.

No myometrial invasion was demonstrated in 29 patients (20.1%). At the time of hysterectomy 67 patients (46.5%) were found to have superficial myometrial invasion and 38 patients (26.3%) had tumor with invasion

greater than 50% of the myometrial thickness. Ten patients (6.9%) were not Staged. Overall, a total of 32 women had positive nodes (22.2%), 14 of whom also had malignant cells in their peritoneal cytology.

Complications of the surgical therapy were minimal with a total of four wound infections, one case of postoperative thromboembolism, three cases of prolonged postoperative ileus, and five cases of diarrhea during external radiation but this was managed with medication. There were no fistulas or serious bowel or urinary tract complications related to the surgery or radiation.

One hundred forty-four patients with Stage I endometrial carcinoma were followed for a median of 54.5 months. The probability of survival using the life table analysis is shown in Figure 3. The estimated 5-year survival for all Stage I patients was 80%.

A total of nine recurrences were diagnosed in this group. Three of the 144 patients (2.08%) developed an isolated vaginal recurrence. Two were Stage IC and one was Stage IB. All three patients with vaginal recurrences died from disease (median survival was 27 months, 13, 19 and 51 months, respectively). Two of the patients died although they received chemotherapy for the recurrences but one died before taking any further therapy for recurrence. All three patients had endometrioid-type tumors.

Discussion

The vagina is one of the most common sites of recurrence in patients with Stage I endometrial adenocarcinoma. In patients who were treated with hysterectomy alone vaginal vault recurrences have been reported in about 10.3% [2]. Both external and internal radiation therapy have been shown to decrease the incidence of vaginal vault recurrence but routine use of radiation therapy in patients with Stage I endometrial cancer increases cost and morbidity without necessarily increasing survival [3, 4]. Using the protocol outlined above we have been able to obtain excellent 5-year survival results while minimizing the risk of vaginal recurrence through the selective use of postoperative radiation. Overall 38% of the patients in this study received no further radiation therapy following hysterectomy. Sixty-two percent of the patients received radiotherapy by brachytherapy or pelvic radiation or both. In this group of 89 patients, there were three patients with vaginal recurrences.

It is of interest that all three patients with vaginal recurrence were asymptomatic and were diagnosed at the time of routine follow-up examination. In our study, deep myometrial invasion (two patients were Stage IC and one patient was Stage IB) was a stronger prognostic factor than non-endometrioid histological subtype. This finding may be explained by the relatively limited number of patients with non-endometrioid histology.

Classically, isolated vaginal recurrence in women with endometrial carcinoma is an indicator of poor prognosis. In a series of 18 patients, Greven and Olds reported only 33% surviving with no evidence of disease [5]. The majority of these patients had lesions larger than 2 cm and 12 patients died of recurrent disease.

There is expanding evidence in the literature that surgically staged patients with tumor confined to the uterine corpus (negative lymph nodes) do not benefit from external adjuvant radiotherapy in terms of survival [6-8]. Also some authors are still debating the cost-effectiveness of vaginal brachytherapy for the prevention of vaginal failure [9, 10]. In our series, although all three patients received radiotherapy postoperatively, they all recurred and died. However as the rate of vaginal recurrence is too small among Stage I endometrial cancer patients, we have shown that the selective use of vaginal vault or external pelvic radiation in patients with Stage I disease can minimize the risk of vaginal recurrence and yield excellent survival rates with minimal morbidity.

References

[1] Mariani A., Webb M.J., Kenney G.L., Lesnick T.G., Podratz K.C.: "Surgical Stage I endometrial cancer: predictors of distant failure and death". *Gynecol Oncol.*, 2002, *87,* 274.

[2] Roberts J.A., Brunetto V.L., Keys H.M., Zaino R., Spirtos N.M., Bloss J.D., Pearlman A., Maiman M.A., Bell J.G.: "A Phase III randomized study of surgery versus surgery plus adjunctive radiation therapy in intermediate risk endometrial carcinoma (GOG 99) (abstract). Proceedings of the Society of Gynecologic Oncologists 1998, 70.

[3] Ng T.Y., Perrin L.C., Nicklin J.L., Cheuk R., Crandon A.J.: "Local recurrence in high risk node negative Stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy". *Gynecol. Oncol.,* 2000, *79,* 490.

[4] Eltabbakh G.H., Piver M.S., Hempling R.H., Shin K.H.: "Excellent long term survival and absence of vaginal recurrences in 332 patients with low risk Stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: a report of a prospective trial". *Int. J. Radiat. Oncol. Biol. Phys.,* 1997, *38,* 373.

[5] Greven K., Olds W.: "Isolated vaginal recurrences of endometrial adenocarcinoma and their management". *Cancer,* 1987, *60,* 419.

[6] Larson D.M., Broste S.K., Krawisz B.R.: "Surgery without radiotherapy for primary treatment of endometrial cancer". *Obstet. Gynecol.*, 1998, *91,* 335.

[7] Orr J.W. Jr., Holiman H.L., Orr P.F.: "Stage I corpus cancer: Is teletherapy necessary?". *Am. J. Obstet. Gynecol.,* 1997, *176,* 777.

[8] Fanning J., Nanavati P.J., Hilgers R.D.: "Surgical staging and high dose rate brachytherapy for endometrial cancer. Limiting external radiotherapy to node positive tumors". *Obstet. Gynecol.*, 1996, *87,* 1041.

[9] Mariani A., Sebo TJ., Katzman J.A., Keeney G.L., Roche P.C., Lesnick T.G., Podratz K.C.: "Pretreatment assessment of prognostic indicators in endometrial cancer". *Am. J. Obstet. Gynecol.*, 2000, *182,* 1535.

[10] Chadha M., Nanavati P.J., Liu P., Fanning J., Jacops A.: "Patterns of failure in endometrial carcinoma Stage IB grade III and Stage IC patients treated with operative vaginal vault brachytherapy". *Gynecol. Oncol.,* 1999, *75,* 103.

Address reprint requests to:
Y. SALIHOGLU, M.D.
Istanbul Ünivetsitesi
Istanbul Tıp Fakültesi
Kadın Hastalıkları ve Doğum
Anabilim Dalı Çapa
(Fatish-Istanbul) Turkey