Prognostic Value of Pelvic Lymphadenectomy in Surgical Treatment of Apparent Stage I Endometrial Cancer

MARCELLO CECCARONI1, LUCA SAVELLI1, ALESSANDRO BOVICELLI1-2, CARLO ALBONI1, MICHELA CECCARINI1, ANTONIO FARINA1,3 and LUCIANO BOVICELLI1

1Department of Obstetrics and Gynecology and
2Institute of Histology and Embryology University of Bologna, School of Medicine, Bologna, Italy;
3Shabro Institute for Cancer Research and Molecular Medicine, Temple University, Philadelphia, PA, U.S.A.

Abstract. Background: The role of pelvic lymphadenectomy in early endometrial carcinoma is still being debated. Materials and Methods: We retrospectively analyzed a total of 131 patients with FIGO stage I endometrial cancer undergoing surgery without (Group 1) or with (Group 2) pelvic lymphadenectomy. Kaplan-Meier and Cox analyses were used to calculate crude and adjusted survival rates. Moreover, the overlap of pre- and post-surgical staging was analyzed. Results: Overall survival rate at 5 years was 90.1%. The difference in crude survival rates of the two groups is not statistically significant (p-value= 0.3777, log rank test). Five patients of Group 2 presented positive pelvic nodes. Therefore our results showed a pre-surgical understaging, referring to nodal involvement, in 9.1% of cases (5/55). Conclusion: Pelvic lymphadenectomy is a useful procedure for prognostic and staging purposes, but does not improve survival in FIGO stage I endometrial carcinoma.

Endometrial carcinoma is currently the most common female pelvic malignancy. The incidence has increased in recent years and 150,000 endometrial carcinomas are diagnosed annually in the world. The American Cancer Society estimated that there were 37,400 new cases in the US in 1999 (1-3), while in Italy 5,000 new cases occur each year and this malignancy represents 5-6% of all female cancers (4). It is a typical peri- and post-menopausal tumor, the age of onset being approximately sixty years. Many assessments indicate that 1-3% of women approaching menopause will develop endometrial cancer before the age of 75 (5).

Correspondence to: Dr. Marcello Ceccaroni, c/o Sanna, Via delle Lame 61, 40122, Bologna, Italy. Tel: +39 347 2423475, Fax +39 051/304751, e-mail: mceccaroni@libero.it

Key Words: Endometrial cancer, pelvic lymphadenectomy, staging, prognostic value, surgery, hysterectomy.
oophorectomy (TAH-BSO) and lymphadenectomy alone, without radiotherapy (33). Since radiation therapy is inadequate to kill all cancer cells in positive nodes (34), the value of lymphadenectomy has been investigated.

The purpose of this study was to analyze, retrospectively, the efficacy of lymphadenectomy in improving lifetime expectancy. Moreover, we evaluated the reliability of pre-surgical staging (FIGO 1971) (35) and compared it with post-surgical staging (FIGO 1988) (22), calculating the pre-surgical understaged cases.

**Materials and Methods**

**Patients.** We reviewed the medical records of 179 patients affected by endometrial cancer who underwent surgery between January 1986 and December 1994 at the Department of Obstetrics and Gynecology of the University of Bologna, Italy, and identified 131 cases that satisfied the following inclusion criteria: a) pre-surgical FIGO stage I, b) surgical treatment at least consisting of total abdominal hysterectomy and removal of existing adnexal structures, c) no other malignancy within 5 years before or after the diagnosis of endometrial cancer.

**Pre- and post-surgical staging.** Pre-operative clinical and instrumental evaluation, according to FIGO 1971 criteria (35), included physical and gynecological bi-manual examination, hysteroscopy with endometrial biopsies, endocervical curettage, abdominal and transvaginal pelvic ultrasonography, chest X-ray, abdominal-pelvic MRI or CT, rectosigmoidoscopy and assessment of Ca 125 serum levels. Cystoscopy, intravenous urography or double contrast enema and lymphography were optional.

Post-surgical staging was retrospectively performed according to the FIGO surgical staging system from post-surgical pathologic assessments (22, 36). Histological classification was performed following the World Health Organization (WHO) criteria (37). Grading was defined according the FIGO guidelines (36).

**Surgery.** In all cases, surgical procedures were performed by the same gynecologic-oncologic surgical team. All patients were submitted to TAH-BSO, without (Group 1) or with (Group 2) pelvic lymphadenectomy. No specific risk factors influenced the choice of performing lymphadenectomy. Surgical staging consisted of an accurate inspection of omentum and abdominal viscera with pelvic exploration and biopsies of suspicious lesions. Peritoneal cytology (washing) was performed in all cases. Systematic pelvic lymphadenectomy was performed according to the common surgical techniques (38, 39).

**Follow-up.** Follow-up information was collected from patients’ clinical records, but information about survival or recurrence were obtained from death certificates, telephone calls and/or letters sent to patients and family physicians.

**Statistical analysis.** Survival curves were calculated according to the product-limit method (Kaplan-Meier algorithm) (40). Time zero was defined as the date of the patient’s initial diagnosis. The log rank test was used to explore the differences among survival curves stratified for the variable of interest. Cox regression analysis was then applied to determine the single contribution of covariates on survival rate.

<table>
<thead>
<tr>
<th>Table I. Pathologic characteristics of the surgical specimens.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
</tr>
<tr>
<td>Ia</td>
</tr>
<tr>
<td>Ib</td>
</tr>
<tr>
<td>Ic</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Endometrioid</td>
</tr>
<tr>
<td>Papillary Serous</td>
</tr>
<tr>
<td>Clear Cell</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>Well (G1)</td>
</tr>
<tr>
<td>Moderate (G2)</td>
</tr>
<tr>
<td>Poor (G3)</td>
</tr>
<tr>
<td><strong>Nodal Status</strong></td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
</tbody>
</table>

If the associated probability was less than 5% (p-value <0.05) the difference was considered statistically significant. All patients have been followed for 5 years after the surgical treatment or until death.

**Results**

Of the 131 patients included in the study, the median age was 60 years (range 35-85). All patients were Caucasians. No statistical differences were found in the risk factors and prognostic feature distributions in the two groups (data not shown). The two groups of patients were homogeneous simultaneously considering the main prognostic factors, such as tumor grade, depth of myometrial invasion and histological subtype. No patient had preoperative irradiation or presented suspected lymph node metastases at preoperative imaging.

The mean age at menarche was 13 years (10-21 years). Early menarche (<11 years) occurred in 4% of the cases and delayed menopause (>56 years) in 7% of the cases. The
The mean age of menopause was 48.5 years (35-59 years). Seventy-four percent of women were post-menopausal and 26% pre-menopausal. Nineteen percent of the patients were nulliparous. Thirty-five percent were obese. Diabetes and metabolic disorders were found in 16% of the cases. Suspicious genital bleeding was present in 74 cases during the preoperative time.

Seventy-five patients (58%) underwent TAH-BSO (Group 1), while 55 (42%) underwent TAH-BSO combined with pelvic lymphadenectomy (Group 2). The median number of lymph nodes sampled was 29 (range 21-33). Median hysterectomy time was 47 minutes (25-90 min). Bilateral pelvic lymphadenectomy took 45 minutes (35-75 min). Median blood loss was 280 ml (150-475 ml). The median hospital stay was 6 days (4-9 days). There was no difference in the two groups concerning anesthetic risks, transfusion need, wound infections, hospital stay and other major complications.

From histological analysis performed on surgical specimens to evaluate the depth of myometrial invasion, 9 of the 131 cases (6.9%) were found at FIGO stage Ia, 62 (47.3%) at Ib and 60 (45.8%) at Ic (Table I). One hundred and twelve patients (85.5%) had the common variety endometrioid adenocarcinoma while 15 (11.4%) had the papillary serous variety and 4 (3.0%) had clear cell tumor. There was concordance in histological type between curettage and surgical specimens in 86% of the cases. Grade 1 tumor accounted for 44.3% (58 cases), grade 2 for 47.3% (62 cases) and grade 3 for 8.4% (11/131) of the cases. No patients had positive washings.

The 9.1% (5/55) of patients submitted to lymphadenectomy, were found to have positive nodes (Table I). Of these 5 cases (9.1%), found with pelvic nodal metastases, 3 were presurgically staged as IcG2 and 2 as IbG2 and IbG3, respectively. All of these 5 cases had the endometrioid histotype. Only one patient with positive nodes died during the five-year follow-up.

Patients at high risk of recurrence, considering the main prognostic factors, received post-operatively external pelvic
irradiation and/or vaginal brachytherapy. Adjuvant radiotherapy was therefore performed for stages higher than IbG1. A total of 94 patients (71.8%) underwent complementary radiotherapy: 30 (22.9%) at IbG2 were submitted to brachytherapy (BRT) (Cs 137, 6000 cGy), 28 (21.4%) at IbG3-IcG1 to external radiotherapy (ERT) (4600-5000 cGy) and 36 (27.5%) at IcG2-G3 to ERT+BRT (4600-6000 cGy + 1500-2000 cGy). In 37 women (28.2%) at Ia(G1-G3)-IbG1, no post-surgical treatments were used (Table II).

Univariate survival analysis. The overall survival rate at 5 years reported in Figure 1 was 90.1% (118/131). Mean survival time was 58.2 months (95% C.I.=56.97-59.37). Two cases were lost for pulmonary embolism which occurred within one month of the surgical procedure. Two cases were lost at 22 and 23 months, respectively, for cardiovascular diseases.

In Groups 1 and 2 the crude survival rate was 88.2% and 92.7%, respectively (p-value=0.3777, log rank test), as shown in Figure 2. The mean survival time was 57.80 (95% C.I.=56.02-59.59) and 58.7 (95% C.I.=57.26-60.11) months, respectively. There was no statistical evidence when Group 2 was stratified according to the presence of positive nodes (p-value=0.2919, log rank test) as shown in Figure 3.

Multivariate survival analysis. Stepwise Cox regression did not show any significant value in predicting survival of the covariates (stage, grade, histotype, age at diagnosis, presence of positive lymph nodes) used to adjust survival (Cox regression output is not reported).

Discussion

The removal of regional lymph nodes is still a cardinal principle in the surgical management of many cancers today. As regards the importance of lymphadenectomy in apparent stage I endometrial carcinoma, many controlled clinical studies have been performed with the purpose of evaluating if such a technique is effective in improving survival and relapse-free survival (41-48). Pelvic lymph node metastases in endometrial cancer at pre-surgical stage I are expected in 4-10% of cases; grade and myometrial invasion seem to be correlated with the detection of lymph node metastases (8, 16-18, 42). Patients with more than 50% gross myometrial invasion have a 6.4-fold higher prevalence of pelvic lymph node metastases and a 6.9-fold higher prevalence of paraaortic lymph node metastases than patients with less than 50% myometrial invasion (14). In cases at stage I with G1 tumor grade, 3% of lymph node metastases are expected, 9% at IG2 and 18% at IG3 (8). The same author reported variable rates (5-25%) of nodal involvement, related to the depth of myometrial invasion. In our study the rate of lymph nodes metastases was 9.1% (5/55). Forty percent (2/5) of these patients presented a tumor invasion limited to the inner half of myometrium, while 60% (3/5) had a deeper invasion. The degree of differentiation was moderate (G2) in 80% (4/5) of the cases and poor in 20% (1/5).

Nodal spread in endometrial carcinoma generally involves the external iliac, the internal iliac and obturator chains. Our technique of performing pelvic lymphadenectomy consisted of "en bloc" removal of all lymph node tissue surrounding the external and internal iliac vessels and above the obturator nerve. In many series, suggesting a successful surgical treatment, the mean numbers of nodes sampled are from 11 to 20 (13, 16), while in our study the median number of nodes sampled was 29 (range 21-33). Thus, the extent of lymph node dissection was adequate and the incidence of nodal metastases was not underdiagnosed.

The role of adjuvant radiotherapy in patients with apparent stage I disease is still controversial. Several authors reported excellent or comparable survival rates in subsets of patients treated with lymphadenectomy alone (26, 30, 43). Fanning suggested, as cost-effective post-operative treatment for early endometrial cancer, to reserve radiotherapy for high-risk tumors and teletherapy only in the case of nodal metastases (44). Other studies failed to prove the value of adjuvant radiotherapy on survival and to demonstrate this procedure as effective in protecting from recurrences in high risk patients (13, 19, 45-47). In our series the use of radiotherapy yielded similar survival rates in patients with known and unknown lymph node status. Our results raise the question of the value of adjuvant radiotherapy. The low incidence of nodal metastases in our series questions the need for this procedure. As Orr stated, in the absence of a clear proven survival benefit, the potential physical and economic costs of adjuvant radiotherapy must be weighed (13).

Our results showed a pre-surgical understaging, referred to nodal involvement, in 9.1% of cases (5/55). The 5 patients with positive nodes who had stage I disease, according to the FIGO 1971 clinical classification (35), were upstaged to stage IIIc according to the FIGO 1988 surgical staging system (22). The five-year survival rate of this group of patients was 80%. This stresses the need for pelvic lymphadenectomy in order to achieve correct staging and to estimate an accurate prognosis.

The therapeutic role of lymphadenectomy is still unclear. Two important studies found a survival advantage associated with this practice (16, 48), as unrecognized microscopic metastases could be present in many nodal samples (13). Other series showed no significant differences between the patients who underwent lymph node sampling and those who did not (49-51). In our experience, the overall survival of patients who underwent pelvic lymphadenectomy (92.7%) was not statistically different from that of those who did not undergo this treatment.
(88.2%). We may conclude that pelvic lymphadenectomy for endometrial carcinoma at apparent FIGO stage I is a useful procedure for prognostic and staging purposes, but does not improve survival. Its therapeutic effect reported by some authors (16, 47) could be in large part due to the importance of an accurate surgical staging (51). This permits definition of the need for adjuvant radiotherapy and to correct estimation of prognosis.

Therefore, even if in our series the incidence of histological nodal involvement is slightly lower than the rate reported by other authors (8), we consider lymphadenectomy a worthwhile diagnostic procedure, providing a definitive surgical staging, since the prediction of nodal disease based only on pre-operative and intra-operative investigations is inaccurate and insufficient (52). In the future, major prospective randomized multicentric studies should yield conclusive data regarding its therapeutic value.

References


Received January 13, 2004
Revised March 4, 2004
Accepted April 2, 2004