Complete Pelvic Lymphadenectomy in Patients with Clinical Early, Grade I and II Endometrioid Corpus Cancer

STELIOS FOTIOU1, EDWARD L. TRIMBLE3, KATERINA PAPAKONSTANTINOU1, AGATHA KONDI-PAFITI2, THEO PANOSKALTSIS1, GEORGE DELICONSTANTINOS1 and GEORGE CREATSAS1

1Second Department of Obstetrics and Gynecology and 2Department of Pathology, University of Athens, School of Medicine, Aretaieion Hospital, Athens, Greece; 3Gynecologic Cancer Therapeutics, National Cancer Institute, Bethesda, MD, U.S.A.

Abstract. Aim: To investigate the risk of pelvic lymph node metastasis in patients with a preoperative diagnosis of early endometrial cancer with favorable histological characteristics, assessed by complete pelvic lymphadenectomy. Patients and Methods: A total of 108 patients with clinical early endometrioid grade I or II endometrial carcinoma underwent complete pelvic lymphadenectomy between 2001-2007. Only cases with at least 15 nodes histologically examined were included. All operations were performed by the same team. The preoperative tumor histology was compared with the final pathological findings. The incidence of pelvic nodal involvement was estimated in relation to the final grade and depth of myometrial invasion in halves. Results: The median age of patients was 63 years. In the final histology, 10 tumors (9.3%) of non-endometrioid histology were found. The discordance between pre- and postoperative tumor grade was 32.4%, with 24.1% being upgraded. Nine patients (8.3%) had poorly differentiated tumors and 23 (21.3%) deep (>50%) myometrial invasion in the final pathology. A total of 11 patients (10.2%) had pelvic nodal metastasis. The rate of lymph node metastasis in relation to final grade I and II and myometrial invasion was as follows: grade I, 1.8% (inner half 0%, outer half 14.3%); grade II, 15.9% (inner half 12.1% outer half 27.3%). Overall 19.4% of patients were upstaged at surgery. Conclusion: A significant proportion of patients presenting with early endometrial cancer of optimal characteristics will have a more advanced disease at surgical staging. Complete pelvic lymphadenectomy may increase the possibility of detecting metastatic disease in the lymph nodes.

Endometrial cancer is the most common gynecological malignancy in the Western world. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the baseline surgical treatment with high cure rates in early disease (1). However, recurrence takes place in about 20% of patients with this malignancy and they eventually die of this disease (1). Several prognostic factors such as age, tumor histology, grade, myometrial invasion, cervical involvement and extrauterine spread are related to survival and risk of recurrence. Lymph nodes represent the most common site of extrauterine metastatic disease (2, 3).

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) established the current surgical staging system, in which lymphadenectomy is also included. However, the requirements for surgical staging are not clearly defined and the role and extent of lymphadenectomy remain controversial. In most centers, patients with grade III tumors, unfavorable histological type, deep myometrial invasion, cervical involvement and signs of extrauterine spread are considered for full staging (4). Patients presenting with clinical early disease and endometrioid grade I or II tumors are often considered at low risk and do not undergo comprehensive staging. However, it has been shown that in these patients, surgical staging will disclose a more advanced disease in about 15-25% (5-7). Yet it has been reported that in only 24.4% of the centers in Western Europe is lymphadenectomy practiced routinely (8), while in some countries lymph node dissections are not carried out in any patient (9, 10). On the other hand, the risk of pelvic lymph node metastasis in clinical early disease has not been clearly determined. This is partly due to the variety in the extent of lymphadenectomies and the number of lymph nodes recovered in the reported studies (11, 12).
In this study, a prospective cohort of women presenting with early endometrioid grade I or II endometrial carcinoma underwent complete lymphadenectomy by the same surgical team. The preoperative histological findings were compared with the final pathological results and the risk of nodal involvement as related to tumor grade and depth of myometrial invasion was determined.

Patients and Methods

The study group consisted of 108 patients undergoing surgery for endometrial cancer in our institution between 2001-2007. The diagnosis was made by curettage. The preoperative work-up included computed tomography (CT) or magnetic resonance imaging (MRI). All patients had apparent early disease, without signs of extrauterine spread, and a preoperative histological diagnosis of endometrioid grade I or II disease. Patients with other histological cell types, grade III tumors, or those considered at poor risk for extensive surgery were excluded from this study. All operations were performed by the same team.

Complete pelvic lymphadenectomy was considered as a systematic lymph node dissection from the common iliac vessels (included) superiorly to the obturator fossa (above the homonymous nerve) inferiorly and the histological demonstration of at least 15 lymph nodes recovered. For the purpose of the study, para-aortic lymph node dissection was not taken into account.

The records of the patients were retrieved and the data concerning disease characteristics, surgical findings and final histopathological results were reviewed and evaluated.

Results

The characteristics of patients studied are presented in Table I. The median age was 63 years (range 34-82). In the final histology, 10 tumors of non-endometrioid histology were found (2 clear cell, 7 adenosquamous and 1 undifferentiated). Deep (>50%) myometrial invasion was present in 23 (21.3%), infiltration of the cervix in 9 (8.3%), adnexal involvement in 2 (1.9%) and positive cytology in 6 (5.6%) of the patients. A total of 11 patients (10.2%) had nodal metastases and in 5 of them only one positive node was diagnosed. Surgical stage was higher than I in 21 (19.4%) of the cases.

A comparison between the initial and final tumor grade is made in Table II. Discordance was found in 35 of the cases (32.4%), with upgrading in 26 (24.1%) cases and downgrading in 9 (8.3%). A total of 9 patients (8.3%) had poorly differentiated tumors in the final histology.

In Table III, the depth of myometrial invasion in relation to the preoperative tumor grade is shown. In 21.3% of patients presenting with grade I or II lesions, the tumor invaded the outer half of the myometrium.

The occurrence of nodal involvement as assessed by complete lymphadenectomy in relation to final grade I and II and depth of myometrial invasion is given in Table IV. Of a total of 11 patients (10.2%) found to have positive pelvic nodes, 4 were assessed in the preoperative histology as having grade I and 7 with grade II tumors. None of 48 patients with final grade I tumor and invasion of the inner half of the myometrium had positive nodes. In the group of patients with final grade II lesions, 4 out of 33 (12.1%) with inner half myometrial invasion and 3 out of 11 (27.3%) with deep infiltration had nodal involvement. Of 9 patients with grade III tumors in the final histology, 3 were positive for lymph node metastasis.

Discussion

The controversy regarding lymphadenectomy in endometrial cancer has been mainly focused on the management of patients with clinical early disease and favorable histological characteristics. At present, routine lymphadenectomy is not generally considered justifiable for all these patients (4). It has been shown that increasing tumor grade, depth of myometrial invasion and tumor size greater than 2 cm are strong predictors of nodal involvement (3, 13, 14). Therefore, many surgeons use intraoperative pathological assessment to identify patients at risk of nodal metastasis and avoid unnecessary lymphadenectomies. However, the ability of these methods to accurately detect high-risk patients remains limited. Case et al. reported diagnoses of myometrial invasion and tumor grade based on intraoperative
frozen section were upstaged in 28% and upgraded in 38% of the cases, respectively, in the final histology (15). Other clinicians have attempted to discriminate high-risk patients using information taken from the preoperative histology and imaging techniques. However, neither have these strategies proved accurate in selecting patients with adequate safety (16, 17). Consequently, surgical staging remains the only precise method for determining lymph node metastasis and several authors suggest that comprehensive staging should be considered for all patients with endometrial cancer (18). Yet, even in centers advocating lymph node assessment, recommendations for lymphadenectomy are inconsistent and clinical practices vary from sampling alone to complete lymphadenectomy (19).

In this study, we explored the risk of pelvic nodal involvement in a prospective cohort of patients with a preoperative diagnosis of clinical early grade I and II endometrioid cancer. All patients underwent complete pelvic lymphadenectomy and the occurrence of nodal metastasis was analyzed in relation to tumor grade and depth of myometrial invasion. The preoperative grade did not correlate with final grade in 32.4% of the cases and was upgraded in 24.1% (26/108), downgrade 8.3% (9/108).

Table II. Preoperative vs. final tumor grade.

<table>
<thead>
<tr>
<th>Preoperative grade</th>
<th>Final grade</th>
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<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>I (n=66)</td>
<td>46</td>
</tr>
<tr>
<td>II (n=42)</td>
<td>9</td>
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<tr>
<td>Total=108</td>
<td>55</td>
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</tbody>
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Discordance 32.4% (35/108), upgrade 24.1% (26/108), downgrade 8.3% (9/108).

Table III. Depth of myometrial invasion in relation to preoperative diagnosis of tumor grade.

<table>
<thead>
<tr>
<th>Myometrial invasion</th>
<th>Preoperative grade</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>≤50%</td>
<td>53</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>66 (61%)</td>
</tr>
</tbody>
</table>

Table IV. Incidence of pelvic nodal metastasis in relation to final tumor grade (I and II) and myometrial invasion*.

<table>
<thead>
<tr>
<th>Myometrial invasion</th>
<th>Final grade</th>
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<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>≤50%</td>
<td>0</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>1/7</td>
</tr>
<tr>
<td>Total</td>
<td>1/55 (1.8%)</td>
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*Another 3 node-positive cases were found in 9 patients with grade III tumors in the final histology (they were excluded from the analysis due to their small number).

including 1 undifferentiated and 2 clear cell carcinomas. These findings are in accordance with the data reported in previous studies. Frumovitz et al. found that 23% of endometrioid grade I and II tumors combined were upgraded in the final histology, with 5.9% grade III carcinomas (20). Similarly, in the study by Sanjuan et al., 7.9% of patients presenting with grade I or II disease had grade III tumors in the post-operative histology (21). These data show that about 10% of patients presenting with early disease of favorable histological characteristics harbor aggressive tumors.

In 23 of our patients (21.3%), deep (>50%) myometrial invasion was demonstrated in the final pathological evaluation. Thirteen of these patients had presented with grade I and 10 with grade II tumors. Ben-Shachar et al. also reported that 25% of patients presenting with endometrioid grade I tumors had deep myometrial invasion with or without extruterine disease (6).

A total of 11 patients (10.2%) had pelvic nodal involvement as documented in the final pathology. Four of them had presented with grade I and 10 with grade II tumors. According to these findings, the probability of pelvic lymph node metastasis in patients presenting with clinical early endometrioid grade I or II disease is 6% and 16.7% respectively. Another 10 node-negative patients were finally upstaged due to metastases found in other sites. The overall 19.4% stage migration at surgery in this series is similar to the 21-23% reported in previous studies, in which more cases of non-endometrioid histology and grade III tumors were included (5, 7, 13).

In our modest series, increasing tumor grade and myometrial invasion was associated with higher risk of pelvic nodal involvement. This finding has been well demonstrated in the seminal Gynecologic Oncology Group (GOG) studies (3, 13) and in the recent large study by Chi and co-workers on the incidence of pelvic lymph-node metastasis based on tumor grade and depth of myometrial invasion (7). None of our patients with final grade I tumors invading only the inner...
half of the myometrium had nodal metastasis, while one out of seven with deeper invasion (14.3\%) was node positive. In the GOG study, a lower but comparable incidence of pelvic lymph node metastasis was found (2/18=11\%) in patients with grade I tumors invading the outer third of the myometrium (3). However, in the series of Chi et al., no patient with these characteristics had nodal involvement (7). A probable explanation for this difference lies in the small number of patients included in this category (5 in the study of Chi et al. and 7 in ours). Similarly, our data on the risk of nodal metastasis in patients with grade III tumors are based on a very small sample size and should be disregarded.

The occurrence of pelvic nodal involvement in patients with final grade II lesions (overall=15.9\%, invasion of inner half=12.1\%, invasion of outer half=27.3\%) was higher than that reported for this group in previous studies (3, 7, 14). This difference is considerable given the comparable percentage of patients with deep myometrial invasion in this category, included in the present as well as in the previously published series: For tumors invading the outer half, 25% in the present study and 22.5\% in the Chi et al. series (7) and for tumors invading the middle and outer third, 24% and 10\% respectively in the GOG study (3). Furthermore, Mariani et al. reported no incidence of pelvic nodal involvement in 59 patients with grade I and grade II tumors smaller than 2 cm invading the inner half of the myometrium and suggested simple hysterectomy for these patients in the absence of extrauterine macroscopic disease (14).

The small sample size of this study might be a sufficient explanation for the above differences. However, the extent of lymphadenectomy may also have an impact regarding the increased incidence of nodal involvement. In a recent study of 11,443 patients, Chan et al. examined the probability of detecting at least one positive lymph node in relation to the number of nodes removed. They found that sampling of up to 5 nodes diagnosed only 27.6\% of patients with nodal metastasis and the chance of detecting at least one positive node increased with the number of lymph nodes recovered, needing more than 20 nodes to ensure adequate assessment of the nodal status (12). In the GOG series, various types of lymphadenectomy were performed and no minimal number of nodes removed was defined for including patients in the study (3). In the study of Chi et al., patients with at least 8 nodes examined were included and the mean number of lymph nodes recovered was 15 (7). Finally, in the Mariani et al. series, lymphadenectomy was considered as the removal of at least one lymph node (14). In our study, the cut-off limit for patient inclusion was 15 nodes and the mean number of nodes examined was 23, which may have attributed to finding a higher incidence of pelvic nodal involvement. Notably, in 5 out of 11 patients having nodal metastasis in this study, a single positive node was found in the final pathology.

While adequate lymph node dissection is important to ensure the absence of nodal metastasis, the number of lymph nodes that need to be removed in order to define a complete lymphadenectomy has not been established. However, several authors have argued that pelvic lymphadenectomy performed routinely may properly guide adjuvant treatment decisions, reducing the costs and potential complications of pelvic radiotherapy, based on the presence of uterine risk factors (22-24).

It has to be acknowledged that our data suffer the limitations of small sample size and a high rate of discordance between pre- and postoperative tumor grading. Despite these limitations, these findings show that among patients presenting with clinical early endometrial cancer with favorable histological characteristics, about 1 in every 10 harbor tumor of aggressive histology and 1 in every 5 will have a surgical stage higher than I due to metastasis in the pelvic lymph nodes or other extraterine sites. Complete pelvic lymphadenectomy may increase the chances of detecting single nodal metastasis and should be considered in all patients undergoing lymph node dissection for endometrial cancer.

References


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