Endometrioid Adenocarcinoma of the Uterus: Surgico-Pathological Correlations and Role of Pelvic Lymphadenectomy

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Abstract

***Introduction**: In 1988, FIGO added lymph node surgery to the staging system for endometrial cancer. This change remains controversial to date. From our study we aim to determine the significance of surgico-pathological parameters of endometrioid carcinoma for pelvic nodal metastases and survival, as well as to study the role of pelvic lymphadenectomy in the surgical treatment of this disease. **Materials and Methods**: A retrospective study was conducted in 198 women with endometrioid carcinoma who underwent full surgical staging including pelvic lymphadenectomy. The multiple variant regression analysis and the multi-variant logistic regression analysis were applied in the analysis of relationship. **Results**: A positive correlation between nodal metastases and grade, myometrial invasion, peritoneal cytology, adnexal involvement, lymphvascular space involvement and tumour size was found. For survival, significant prognosticators were grade, myometrial invasion, peritoneal cytology, lymphvascular space involvement, adnexal involvement, associated atypia and pelvic nodal metastases. Thirty-five per cent of the patients had high risk of recurrence based on uterine pathological factors but were node negative. They were spared external beam radiation and its associated morbidities, and were treated with adjuvant vault brachytherapy instead. Six per cent of the patients would have been understaged based on uterine factors alone if pelvic lymphadenectomy had not been done. **Conclusion**: We infer that routine pelvic lymphadenectomy should be considered for all surgically fit patients with endometrioid carcinoma. The accurate staging will allow individualised adjuvant therapy and prevent understaging and overtreatment.*

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Key words: Accurate staging, Individualised treatment, Morbidities, Nodal metastases, Pathological parameters

Introduction

Endometrial cancer is the most common female genital malignancy in industralised countries today. Despite the overall favourable prognosis in this neoplasia, survival is associated with several prognostic factors. In endometrial cancer, one of the most potent prognostic factors is nodal metastasis. Nodal metastasis, in turn, has been found to correlate with many histopathologic prognostic factors.

FIGO incorporated lymph node status into its staging system of endometrial cancer in 1988. The addition of routine lymphadenectomy to total abdominal hysterectomy bilateral salpingo-oopherectomy (TAHBSO) aims to provide accurate staging of the disease, so that patients may benefit from individualised postoperative adjuvant therapy. However, the therapeutic benefit and morbidity of lymphadenectomy remain controversial. Morbidities of the pelvic lymph node dissection include lymphoedema, lymphocyst, deep vein thrombosis and life-threatening pulmonary embolism. The addition of approximately 30 minutes of operating time, together with possible increase in intra- and postoperative complications must be offset against the morbidity of pelvic irradiation. The optimal management of lymph nodes remains to be established.

At the Gynaecological Cancer Centre (GCC) in the KK Women's and Children's Hospital (KKH), staging surgery for endometrial cancer has included TAHBSO, routine pelvic lymphadenectomy and peritoneal washings since 1996. Prospective pelvic lymphadenectomy was done because of the following assumptions:

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1) Lymph node status is the most important prognosticator in endometrial cancer.
2) Lymphadenectomy in the surgical staging can be performed quickly with minimal blood loss and morbidity.
3) Performing lymphadenectomy on all patients allows tailoring of postoperative adjuvant therapy by replacing external beam radiation with vaginal cuff brachytherapy for high-risk, early-stage node negative disease, and thereby avoiding the morbidity of external beam radiation on these selected group of patients.

Since 1998 our treatment protocol has been to divide stage 1 endometrioid cancer into a low-risk group and a high-risk group. The low-risk group comprises of Grade (G) 1 Stage 1a, 1b and G2 stage 1a; they are deemed to have low risk of recurrence and hence do not receive any adjuvant radiation. The rest of stage 1, i.e., G1 Stage1c, G2 Stage 1b, c and G3 Stage 1a, b, c and Stage 2a are at higher risk of recurrence and they receive vault brachytherapy as adjuvant therapy. External pelvic irradiation is omitted on the basis of negative pelvic lymph nodes.

The objectives of this study were:

1) to study the correlation of the various surgico-pathologic prognostic factors with pelvic lymph node metastasis in endometrioid carcinoma of the uterus,
2) to determine the proportion of patients with high-risk early stage disease who avoided external beam radiation as a result of pelvic lymphadenectomy,
3) to study the role of pelvic lymphadenectomy in the surgical staging of endometrioid cancer of the uterus and the proportion of cases whose stage has been altered as a result of lymph node involvement,
4) to determine the association of the pathologic characteristics of pelvic lymph node involvement with disease recurrence and survival, and
5) to determine the long-term survival and late complication of high-risk early stage disease treated with pelvic lymphadenectomy and brachytherapy without external beam radiation.

Materials and Methods

This is a retrospective review of 223 patients who were diagnosed to have endometrioid carcinoma over the 4½-year period from January 1996 to June 2000. Of these, 198 underwent TAHBSO and pelvic lymphadenectomy and thus were eligible for our study. Patients with high-risk cell types, e.g., clear cell, serous carcinoma and undifferentiated, were omitted from the study. Data were obtained from case records and the GCC Tumour Registry.

All patients were operated on by gynaecological oncologists. Pelvic lymph nodes were removed in front of, behind, and between the iliac vessels up to the bifurcation of the aorta and down to the obturator fossa and the pelvic floor. All histopathology specimens were reviewed by the centre's gynaecological pathologist. All cases were managed at the centre in a multi-disciplinary manner.

Postoperative surveillance consisted of history, physical examination and vault smear every 3 months for the first year, every 4 months for the second year, and every 6 months for the third year through fifth year, and every year from then onwards.

To evaluate lymph node metastases, multiple variant regression analyses were carried out for 9 clinico-pathological factors including tumour grade, myometrial invasion, peritoneal cytology, site of tumour, adnexal involvement, cervical involvement, associated hyperplasia, lymphvascular space involvement and size of tumour. In addition, the multi-variant logistic regression test was applied in the analysis of relationship between these pathological factors and the prediction of recurrence.

Results

The age of the 198 patients ranged from 30 to 83 years (median 54 years). Majority (55%) were post menopausal and 45% were premenopausal.

The surgical staging included 139 (70.2%) patients with stage 1, 27 (13.6%) with stage 2, 31 (5.7%) with stage 3 and 1 (0.5%) with stage 4 disease (Table I). The number of lymph nodes removed ranged from 1 to 49 (mean 20).

Seventeen (9%) of the 198 women had positive lymph nodes (Table I). Disease characteristics of these women included greater than 50% myometrial invasion in 13 patients, grade 3 tumour in 7, lymphvascular space involvement in 15, cervical involvement in 2 and adnexal involvement in 5 patients. A review of these 17 patients with nodal disease showed 11 women would be understaged if pelvic lymphadenectomy had not been done. One will be clinical stage 1a, 2 will be stage 1b and 8 will be stage 1c. In other words, if pelvic lymphadenectomy had not been done, 2% (1/57) of stage 1a, 4% (2/57) of stage 1b and 22% (8/36) of stage 1c will be understaged and as a result undertreated.

Conversely, of the 181 patients with negative nodal status, 70 were considered to belong to high-risk, early-stage node negative disease (Table II). This group of patients are in the high-risk group for recurrence, and they would have been subjected to external beam radiation if the nodal status had not been known. Hence, 35% (70/198) of patients in this study were spared the effects of external beam radiation and its concomitant morbidity.

Conventionally, grade 1 tumour in a clinically stage 1 disease is assumed as low risk, and would have rendered lymphadenectomy unnecessary. In our series, however, out of 80 patients who belong to this category, 8 (10%)

TABLE I: SURGICO-PATHOLOGIC FINDINGS (n = 198)

Surgico-pathologic factor	No. of patients	%
Premenopausal	89	45
Postmenopausal	109	55
Stage 1a	56	28
1b	55	28
1c	28	14
2a	9	5
2b	18	9
3a	14	7
3b	0	0
3c*	17	9
4a	0	0
4b	1	1
Grade 1	104	53
2	57	29
3	37	19
Myometrial invasion		
No invasion	74	37
Less than half	71	36
More than half	53	27
Peritoneal cytology		
Positive	7	4
Negative	174	88
Not done	17	9
Lymphvascular space invasion		
Positive	73	37
Negative	125	63
Site of tumour		
Fundus	163	82
Isthmus	35	18
Adnexal involvement		
Positive	17	9
Negative	179	90
Synchronous tumour	2	1
Cervical involvement		
Endocervical	21	11
Stromal	11	6
Both	1	1
Negative	165	83
Pelvic lymph node Involvement		
Positive	17*	9
Negative	181	91
Associated hyperplasia		
None	132	67
Simple	4	2
Complex	16	8
Simple with atypia	1	1
Complex with atypia	45	23
Tumour size		
Not specified	25	13
<1 cm	13	7
1 - <2 cm	29	15
2 - <3 cm	37	19
3 - <4 cm	36	18
4 - <5 cm	22	11
5 - <10 cm	33	17
10 - <15 cm	2	1
≥15 cm	1	1

* These are the 17 patients with nodal disease.

TABLE II: DISTRIBUTION OF HIGH-RISK, EARLY-STAGE NODE NEGATIVE ENDOMETRIOID CARCINOMA PATIENTS WHO RECEIVED ADJUVANT BRACHYTHERAPY POSTOPERATION, AND SPARED OF EXTERNAL BEAM RADIATION

Stage	Grade	No. of patients
1a	3	4
1b	2, 3	29
1c	1, 2, 3	28
2a	1, 2, 3	9
Total	-	70

TABLE III: CORRELATION BETWEEN HISTOLOGIC GRADE AND DEPTH OF INVASION IN STAGE 1 OF THE DISEASE

	Grade 1	Grade 2	Grade 3
No invasion	46 (58%)	6 (15%)	4 (20%)
Less than half	26 (33%)	18 (46%)	11 (55%)
More than half	8 (10%)	15 (39%)	5 (25%)
Total	80 (100%)	39 (100%)	20 (100%)

actually had more than 50% myometrial invasion on histology (Table III). The grade, size, myometrial invasion, peritoneal cytology, adnexal involvement and lymphvascular space involvement were significantly correlated with pelvic lymph node metastasis. On the other hand, site of tumour, cervical involvement and endometrial hyperplasia showed no correlation to pelvic lymph node metastasis (Table IV).

Six patients had defaulted and were lost to follow-up. Of the remaining 192 patients, 9 had died, leaving 183 survivors. One hundred seventy-three were well and alive with no evidence of disease, while the remaining 10 had documented evidence of recurrence. Five died of endometrioid carcinoma and 4 died of intercurrent disease. Of the 5 who died of the disease, 2 were considered to be high-risk, early stage.

Of the 10 of the patients with recurrences, the recurrence was only local in 2, distant in 5 and 3 women had both local and distant metastasis. Looking at the high-risk, early-stage node-negative group of patients, only 2 out of 70 had recurrences, 1 had distant recurrence whilst the other had both local and distant.

Using multi-variant logistic regression analysis, the various factors are correlated with prediction of recurrence. Positivity of peritoneal cytology and adnexal involvement were found to be significant. The odds ratio was 7.7 for peritoneal cytology (CI 1.2-47.9) ($P = 0.0286$), and 3.9 for adnexal involvement (CI 1.1-14.2) ($P = 0.0391$).

Using the Kaplan-Meier analysis, the mean length of follow-up was 65.8 months (confidence range 62.9 to 68.7). Of the 9 cases of death, the mean survival was 69.0 months. The surgico-pathological factors that were

TABLE IV: FREQUENCY OF PELVIC NODE METASTASES AMONG RISK FACTORS

Risk factor	No. of patients	No of positive nodes	Significance
Grade 1	104	5	Significant
2	57	5	Pearson correlation
3	37	7	0.181
Myometrial invasion			Significant
No invasion	74	1	Pearson correlation
Less than half	71	3	0.313
More than half	53	13	
Peritoneal cytology			Significant
Positive	7	2	Pearson correlation
Negative	174	11	0.166
Not done	17	4	
Site of tumour			Not significant
Fundus	163	14	Pearson correlation
Ishmus	35	3	0.000
Adnexal involvement			
Positive	17	5	Significant
Negative	179	11	Pearson correlation
Synchronous	2	1	0.239
Cervical involvement			Not significant
Endocervix	21	1	Pearson correlation
Stromal	11	1	0.030
Both	1	0	
Negative	165	15	
Associated hyperplasia			Not significant
None	132	15	Pearson correlation
Simple	4	0	0.138
Complex	16	1	
Simple with atypia	1	0	
Complex atypia	45	1	
Lymphvascular space involvement			Significant
Positive	73	2	Pearson correlation
Negative	125	15	0.326
Size of tumour			Significant
Not specified	25	3	Pearson correlation
<1 cm	13	0	0.166
1 - <2 cm	29	1	
2 - <3 cm	37	0	
3 - <4 cm	36	3	
4 - <5 cm	22	4	
5 - <10 cm	33	6	
10 - <15 cm	2	0	
≥15 cm	1	0	

significantly correlated with survival were grade of tumour, peritoneal cytology, lymphvascular space involvement and adnexal involvement (Table V).

Major complications occurred in 4 patients. One patient with stage 3c disease developed deep vein thrombosis on the 36th postoperative day. Another patient with stage 1a had pulmonary embolism on the first postoperative day. One patient, who was staged as 1b, developed bilateral lower limb oedema a few months post-operation and post-

TABLE V: CORRELATION OF SURGICO-PATHOLOGIC FACTORS WITH SURVIVAL

Surgico-pathological factor	Mean survival Period (mo)	Significance
Grade of tumour		Significant
Grade 1	66.3	Log rank test
Grade 2	65.8	$P = 0.025$
Grade 3	54.4	
Myometrial invasion		Significant
No invasion	65.7	Log rank test
Less than half	67.2	$P = 0.107$
More than half	59.4	
Peritoneal cytology		Significant
Negative	66.9	Log rank test
Positive	41.9	$P = 0.002$
Lymphvascular space involvement		Significant
Negative	66.2	Log rank test
Positive	61.7	$P = 0.028$
Adnexal involvement		Significant
Negative	66.9	Log rank test
Positive	57.3	$P = 0.031$
Cervical involvement		Not significant
Negative	66.0	Log rank test
Positive	63.8	$P = 0.774$
Pelvic lymph nodes involvement		Significant
Negative	67.0	Log rank test
Positive	49.5	$P = 0.001$
Associated atypia		Significant
Negative	65.3	Log rank test
Positive	65.2	$P = 0.496$

brachytherapy. One patient, who was staged as 3c and received external beam radiation as well, developed intestinal obstruction a few months after the operation and radiation. All 4, however, are still alive with no evidence of disease.

Only 2 out of 4 patients with complications in our series can be considered as surgical related, i.e., deep vein thrombosis and pulmonary embolism. The other 2 patients had both surgery and radiotherapy; their complications cannot be accounted strictly by either modality of treatment alone.

Discussion

Surgico-Pathological Correlations

In concordance to many studies done todate,[1-5] lymphvascular space invasion, myometrial invasion, grade of tumour and peritoneal cytology are demonstrated to be important prognostic factors in the spread of endometrioid carcinoma of the uterus. Literature research suggests that, of these, lymphvascular space invasion appears to be the single most important prognosticator of nodal involvement.

Tumour diameter has been reported to be a prognostic factor in various malignancies. For endometrial cancer, however, reports on tumour diameter still remain sparse. From our study, tumour size had shown to be significantly correlated to nodal involvement. In our series, adnexal involvement too was demonstrated to be a significant prognosticator of nodal spread.

An intrinsic correlation between survival and lymphvascular space involvement, grade, peritoneal cytology, adnexal involvement and pelvic lymph node involvement was found.

Role of Pelvic Lymphadenectomy

The role of routine lymphadenectomy in the surgical treatment of endometrial carcinoma has not been fully defined. The potential benefits of lymph node dissection must be weighed against the possible complications associated with the procedure. One definite benefit of lymphadenectomy is the availability of accurate staging of the disease, thereby allowing individualised adjuvant therapy. Without it, there is always the risk of unnecessarily subjecting clinically high-risk patients to external radiotherapy and its concomitant complications. Conversely, apparent stage 1 disease with subclinical lymph node metastases may be missed, resulting in higher recurrence rate. Another debatable advantage of this procedure is its therapeutic value. However, complications of lymph node dissection, such as deep vein thrombosis, lymphocysts, febrile morbidity, extraperitoneal site infections, wound dehiscence, relaparotomy and deaths, cannot be ignored either.

There are two main schools of thought on this subject: one camp advocates routine lymphadenectomy as part of surgical staging for all endometrial cancer patients, while the other prefers to select and subject only the high-risk group of patients to retroperitoneal lymph node dissection.

Acknowledging the profound information that nodal status provides, gynaecological oncologists favouring routine lymphadenectomy believe that prediction of nodal disease based only on conventional preoperative investigations is inaccurate. Therefore, they argue that all patients should undergo full surgical staging until a reliable system is found to identify those with negligible risks.[1,2,5-8] Candiani et al[7] evaluated patients as a function of both different surgical treatment and of risk factors by histology. They concluded that lymphadenectomy for pelvic lymph nodes was necessary in all endometrial cancer patients, since they found lymph node metastasis in 5% of the disease with grade 1 and no myometrial invasion.

Furthermore, lymphadenectomy by experienced gynaecological oncologists is thought not to significantly add to morbidity from hysterectomy.[3,9-12] Homesley et al[9] compared the morbidity of patients with endometrial cancer who were surgically staged by standardised protocol in which they received TAHBSO either alone or with pelvic lymph node dissection. They found there was no difference in intra or postoperative morbidity except in operating time.

On the other hand, those who recommend selective lymphadenectomy only in cases with high risk of recurrence, argue that its use can only be justified provided that there is no significant increase in morbidity or mortality, both from malignant and non-malignant causes. They argue that pelvic lymphadenectomy is not necessary in stage 1 endometrial carcinoma due to the low incidence of node positivity. Moreover, not only does nodal dissection increase morbidity, it does not improve prognosis in patients with early stage disease.[13-15] In patients with low-risk, stage 1 endometrial cancer (G1-2, <50% myometrial invasion), hysterectomy alone with postoperative vaginal brachy-therapy provide excellent long-term survival and are not associated with significant complications.[16]

The ability to differentiate between high-risk cases and low-risk ones preoperatively or intraoperatively will be of great advantage. For this purpose, ascertaining the grade of tumour, degree of invasion, tumour diameter, peritoneal cytology, adnexal involvement and lymphvascular space involvement either preoperatively or intraoperatively will be useful. In particular, further studies investigating accuracy of potential significant correlators of nodal spread like DNA ploidy, CA125 level, p53 overexpression, Bcl-2 or myometrial invasion with either magnetic resonance (MR) imaging or transvaginal ultrasonography should be explored.[17-21] Intraoperative evaluation of myometrial invasion and lymphvascular space involvement using frozen section should also be investigated.[22,23] If it is possible to accurately identify preoperative patients with low risk of nodal metastasis, not only can we avoid lymphadenectomy and its complications, alternative surgical approaches like vaginal hysterectomy can be considered.

During the study period, a significant proportion of our patients avoided over- and under-treatment because the correct staging was available after pelvic lymphadenectomy. Seventy out of 198 patients (35%) were spared external beam radiation and its associated morbidities, such as acute and late cystitis and proctitis,[24-26] because a full surgical staging including pelvic lymph node dissection showed nodal negativity for tumour. On the other hand, 11 out of 198 (6%) patients would have been understaged and, hence, undertreated if pelvic lymph node dissection had not been carried out. While 2 out of 4 complications encountered in our series were all subsequent to operation and presumably pelvic lymph node dissection, none of the complications

were fatal. It cannot be determined if the complication in the other 2 patients were due to surgery or radiotherapy.

Of the 70 patients who were node negative but considered at high risk of recurrence and, hence, given only adjuvant vault brachytherapy, only 2 developed recurrences and an additional 2 died of their disease. The safety of this approach can only be confirmed by randomised controlled trials comparing brachytherapy with external beam radiation in this group of patients.

Conclusion

Surgico-pathological factors that are correlated to pelvic lymph node metastasis are the grade, degree of myometrial invasion, peritoneal cytology, adnexal involvement, lymphvascular space involvement and size of tumour. Of these, only grade, peritoneal cytology, lymphvascular space involvement, adnexal involvement and pelvic lymph node metastasis are correlated to survival.

In our series of 198 patients undergoing full surgical staging with pelvic lymph node dissection, associated complications appear minimal (1%).

We acknowledge that at the current state of understanding, routine pelvic lymphadenectomy for all patients with endometrioid carcinoma remains controversial. The ongoing MRC-ASTEC trial is a prospective randomised phase III trial to compare the effectiveness of conventional surgery with or without lymphadenectomy and/or radiation therapy in treating patients with endometrial cancer. When completed, the MRC-ASTEC trial will hopefully shed more light on this issue.

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