PREDICTORS OF LIMPH NODE METASTASIS IN ENDOMETRIAL CANCER

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Abstract

Introduction: Endometrial cancer is the most common gynecologic malignancy in developed countries. The adequate surgical staging proposed by FIGO (International Federation for Gynaecology and Obstetrics) advocates lymphadenectomy; however, it does not establish the indications, the type and the extent of lymphadenectomy, thus generating multiple controversies.

Methods: Retrospective, analytical study of patients treated surgically for endometrial adenocarcinoma in the Oncological Institute "Prof. Dr. Ion Chiricuţă" Cluj-Napoca (IOCN) between January 2008 and December 2012 – 709 cases eligible for the study.

Results: 206 pelvic and/or paraaortic lymphadenectomies were performed, the average number of excised lymph nodes being 15.6. Overall in 4.4% of patients the lymph nodes were affected by metastases. The presence of each risk factor analysed was statistically significantly associated with lymph node metastasis (p<0.05). Age above 55 years was statistically significantly associated (p<0.05) with the presence of negative prognostic factors in the study.

Conclusions: The analysed histopathological and clinical prognostic factors were statistically significantly associated with lymphatic dissemination in endometrial cancer. We recommend treating endometrial cancer in tertiary centres by surgeons or gynaecologists-oncologists with experience in extensive peritoneal and retroperitoneal surgery.

Keywords: endometrial cancer, prognosis, lymphadenectomy

Introduction

Endometrial cancer is the most common gynaecologic malignancy in developed countries with an estimated incidence of 49,560 new cases for 2013 and an estimated mortality of 8190 deaths for the same year in the U.S. [1]. European Cancer Observatory (ECO) – a project developed by the International Agency for Research on Cancer (IARC) in partnership with the European Network of Cancer Registries (ENCR) – reports for Europe an incidence of 98,919 new cases and a mortality of 23,723 deaths for the year 2012. The incidence is believed to grow in parallel with the increasing incidence of risk factors such as obesity, diabetes, use of Tamoxifen for breast cancer, prolonged oestrogen replacement therapy leading to late-onset menopause, as well as a higher lifeexpectancy in both developed and developing countries.

In general, endometrial cancer has a good prognosis, with a 5-year survival rate of 97.4% in Stage I patients, which is linked with early diagnosis in patients showing alarming symptoms – post-menopausal vaginal bleeding [2].

The staging proposed by FIGO in 1998 and modified in 2009, uses morpho-pathological factors (tumor grading, myometrial invasion, cervical stroma invasion, lymph node status, the intraperitoneal presence of disease), thus assigning surgery an important role in endometrial cancer staging, in addition to its therapeutic role [3,4].

Endometrial cancer surgery comprises total histerectomy and bilateral adnexectomy, procedures performed in the peritoneum and omentum – peritoneal biopsies, partial or total omentectomy, procedures performed in the retroperitoneum – lymph node biopsies, selective pelvic lymphadenectomy, paraaortic lymphadenectomy. Even though the FIGO staging system advocates lymphadenectomy, it does not mention the

indications, the type and the extent of lymphadenectomy, thus raising controversy, as evidenced in numerous studies [5-9].

The present study aims at evaluating the clinical and histopathological factors that are predictive for the lymphatic dissemination of endometrial cancer.

Patients and methods

The study is an analytical retrospective study of patients treated surgically for endometrial adenocarcinoma in the Oncological Institute "Prof. Dr. Ion Chiricuță" Cluj-Napoca (IOCN) between January 2008 and December 2012. The following data were analysed: Malignity register of IOCN, DRG register of IOCN and patient observation sheets, with the assessment of traditional prognostic factors – histological type, tumor grading (G), T parameter (myometrial invasion, cervical stromal invasion), intraperitoneal dissemination of disease but also lymphovascular space invasion (LVSI) and age at the time of diagnosis. All patients signed an informed consent form – institutional template and the study had the hospital's ethic committee approval.

Statistical analysis was performed using Microsoft Excel and Epiinfo software. After the descriptive indicators were calculated, the statistical tests Student and Chi-square were applied. The p-value was considered statistically significant if p<0.05.

Results

During the 5-year period of the study, 1227 new cases of endometrial cancer were registered in the territorial malignity register of IOCN and treated in various departments of our institute. Of these, 870 patients underwent surgery in the various departments of IOCN (cases reported in DRG Register). Cases presenting histological proof of sarcoma following the histopathological examination, cases of synchronous malignancies, uterine metastases of other tumors, tumor recurrence, cases that underwent neoadjuvant radiotherapy or cases featuring incomplete data were excluded from the study. A number of 709 cases were found eligible after applying the aforementioned exclusion criteria.

All 709 patients underwent simple total or radical histerectomy with bilateral adnexectomy, to which peritoneal staging procedures were added – peritoneal biopsies, total or infracolic omentectomy. A total of 206 pelvic and/or paraaortic lymphadenectomies were performed, with the average number of excised lymph nodes amounting to 15.6. The average age was 60 years, ranging between 35 and 83 years; 80% of patients were older than 55 years. Endometrioid adenocarcinoma histology was present in 85% of cases, the remaining 15% including other epithelial non-endometrioid histological types – clear-cell carcinoma, papillary serous carcinoma, adenoscuamos carcinoma, mucinous carcinoma, mixed adenocarcinoma. In most cases (77.5%), the disease was confined to the uterine body – T1a/T1b. Lymphovascular space invasion (LVSI)

was detected in 22.7% of cases, whereas the extrauterine, intraperitoneal disease was present only in 8.4% of cases. The overall metastatic lymph node involvement rate was 4.4% (Table I).

Table I. Demographic and histopathological characteristics of the 709 patients included in the study

Factor		No.	%
Age (years)	Median	60(35-83)	
	35-44	20	2.8
	45-54	123	17.3
	55-64	359	50.6
	>65	207	29.1
Histology	Endometrioid	604	85
	G1	237	33.5
	G2	282	40
	G3	85	11.5
	Non-endometrioid	105	15
Myometrial invasion	0	51	7
	<50%	281	39.5
	>50%	377	53.5
T	T1a	287	40.5
	T1b	262	37
	T2	100	14
	T3a	35	5
	T3b	23	3.2
	T4	2	0.3
LVSI	Present	161	22.7
	Absent	548	77.3
Intraperitoneal disease	Present	60	8.5
	Absent	649	91.5
Procedures	THBA	709	100
	Lymphadenectomy	206	29
	N+	31	4.4

Abbreviations: T = T parameter (tumor) from FIGO staging; LVSI = lymphovascular space invasion; THBA = total hysterectomy and bilateral adnexectomy; N+ = metastatic adenopathies

The influence of the histopathological parameters on lymph node involvement was statistically analysed. The presence of each risk factor was statistically significantly associated with lymph node metastasis (p<0.05) (Table II).

Special attention was given to preoperatively known risk factors – histological type, cell grading and patients' age. Thus, the influence of tumour differentiation degree on the lymphatic dissemination of endometrial cancer was demonstrated by univariate statistical analysis (p<0.05). The latter also showed a strong correlation between the lymphatic dissemination and the presence of histopathological negative prognostic factors (r^2>0.81). It also confirmed the negative influence of epithelial non-endometrioid histological types (NEEH) on these adverse prognostic factors, the lymph node invasion rate in these cases reaching 10.5% (Table III).

Table II Univariate statistical analysis of the histolopathological risk factor influence on lymph node invasion

Factor		N+ (%)	p
Myometrial invasion			
	<50%	0	
	>50%	8	<0.00001
LVSI	Absent	2	
	Present	12	<0.00001
Intraperitoneal disease	Absent	3	
	Present	18	<0.000001
T	T1a	0	
	T1b	5	<0.0001
	≥T2	10	<0.05

Abbreviations: LVSI = lymphovascular space invasion; N+ = metastatic adenopathies; T = T parameter (tumor) from FIGO staging

Table III Correlation between type and cell grading and the presence of negative prognostic histopathological factors

	G1	G2	G3	NEEH
Myometrial invasion >50%*	33%	60.5%	74%	60%
LVSI +*	6%	23%	45%	41%
Intraperitoneal disease +*	3.5%	4%	15%	23%
T ≥2*	12%	21%	33%	41%
N+**	2%	4%	5%	10.5%

* = correlation coefficient $r^2 > 0.81$

Table IV Correlation between age group and the presence of negative prognostic histopathological factors

	Age	
	<55 years	>55 years
Number	143	566
Myometrial invasion >50%*	31.5%	59%
LVSI +*	13%	25%
Intraperitoneal disease +*		
T ≥2*	16%	25.5%
N+*	1.5%	5%

* = p<0.05
Abbreviation: LVSI = lymphovascular space invasion; T = T parameter (tumor) from FIGO staging; N+ = metastatic adenopathies

The patients' age at the time of diagnosis was analysed as an independent factor affecting lymphatic dissemination: 5% lymph node involvement rate was detected in patients over 55 years, compared to 1.5% in younger patients. An age above 55 years was also statistically significantly (p<0.05) associated with the presence of the negative predictors covered in the study (Table IV).

Discussion

The review of special literature reveals the high diversity of indications, practices and beliefs of doctors regarding lymphadenectomy. The stance towards lymphadenectomy varies from being absent to being performed as a routine procedure in all surgically treated patients. The controversies arising are related to multiple areas such as role and indications of lymphadenectomy, preoperative patient evaluation and classification into risk groups for lymph node involvement, intraoperative assessment, type of surgery, extent of lymphadenectomy, its associated morbidity and cost-effectiveness of the procedure.

The first major study in this respect - GOG (Gynaecologic Oncology Group) Protocol 33 – was published in 1987 and mentioned a global nodal involvement rate of 9% for pelvic lymph nodes, and 5% for paraaortic lymph nodes respectively. The risk group stratification made by the authors at that time indicates different figures, that vary from 0 for low-risk patients (GI, no myometrial invasion) to 18% metastatic pelvic lymph nodes and 15% metastatic paraaortic lymph nodes in high-risk patients (deep myometrial invasion, intraperitoneal disease) [10]. GOG-33 led in 1998 to the modification of FIGO staging into surgical staging recommending lymphadenectomy. Subsequently, numerous authors supported lymphadenectomy in patients with endometrial cancer, claiming therapeutic benefits related to overall survival, disease-specific survival, as exact staging was found to impact clinical management through identification of adequate therapy and avoidance of overtreatment of certain cases, but also due to favourable cost-effectiveness reports [11-25].

Recently, two multicentre randomized trials - ASTEC (A Study in the Treatment of Endometrial Cancer) and an Italian trial managed by Benedetti Panici – have concluded that lymphadectomy does not engender benefits in the sense of enhancing the survival rate in patients with endometrial cancer [26-27]. Many practitioners have accepted these results and stopped performing lymphadenectomies. Others, however, have called into question the two trials, dismissing them as biased with regard to the heterogeneity of patient cohorts, institutions involved, surgical procedures performed and adjuvant therapies administered [28-30].

The present study evaluates the negative prognostic histopathological factors used for classifying into risk groups patients with incipient endometrial cancer that are

eligible for surgery, and demonstrates the correlation between these factors and the presence of lymph node invasion. Most clinical guides such as the Romanian Society for Obstetrics and Gynaecology guide, use the classical histopathological factors – tumor grading (G), T parameter (myometrial invasion, cervical stromal invasion), intraperitoneal dissemination of the disease.

Some specialised clinics use in the risk group stratification protocols also the patients' age – a parameter that is investigated also in the present study and statistically significantly correlated with the presence of other negative prognostic factors analysed in the study.(31) The 55-years threshold was chosen on account of the high incidence of the disease above this age, notably 80% in the analysed patient lot.

Some institutions use imaging to establish the risk of lymph node involvement. Thus, the Mayo clinic proves a very low lymphatic dissemination risk for tumors below 2 cm in diameter, even defining a parameter – PTD ("primary tumour diameter") that is generally used in this institution [32]. In our study, the imaging results were difficult to interpret due to a variety of sources and especially because in most cases, the imaging investigations were performed after the diagnostic curettage that reduced the initial dimensions of the tumors.

The surgical tactics in endometrial cancer is based on preoperative awareness of risk factors (histological type, differentiation degree, useful imaging investigations, age), but intraoperative evaluation is just as essential. The classical interaoperative evaluation comprises the exhaustive exploration of the peritoneal cavity by inspection and palpation, the palpation of retroperitoneal lymph node areas, the post-resection dissection of the uterus and visual evaluation of tumor size and myometrial or cervical stromal invasion. These procedures were studied by different authors who reported false negative result rates between 26 and 36% for lymph node site palpation [33,34]. The increased rate of false negative results may be explained to a great extent by small size lymph node metastases, a fact demonstrated in 1993 by Girardi et al., who report that 37% of lymph nodes presenting malignancies are smaller than 2 mm [35]. Currently, frozen-section examination is accepted for an adequate intraoperative evaluation, and various institutions set up efforts in order to perfect this investigation. Thus, if in 2006 Case et al. [36] claim that compared to frozen-section examination the final histopathological analysis modifies the clinical management of the patient in 18% of cases, in 2011 Mariani et al. [37] set forth that the frozen-section examination was modified by the final histopathological analysis in a way that would affect surgical approach in only 1.4% of cases, whereby the importance of this investigation is clearly highlighted. In the present study the decision of performing a lymphadenectomy as well as its extent were established by the surgeon, based on preoperatively known risk factors

and intraoperative classical evaluation, but also by taking into account idiosyncrasies, in particular with regard to associated morbidities. The study is however limited, in that it does not employ sophisticated frozen-section examination techniques for establishing intraoperatively the degree of myometrial invasion, cervical stromal invasion, the presence of small-size lymph node metastases or the histological type and the degree of cell differentiation in the entire tumor mass. The correspondence between the data on global lymph node invasion obtained from the study and from literature, the correlation between the presence of histopathological and clinical risk factors and lymphatic metastasis, as well as the strong statistical significance of these correlations demonstrate that the decision to perform lymphadenectomy was taken sensibly, to the full benefit of the patients.

Conclusions

The histopathological and clinical risk factors evaluated in the study (histological type, degree of cell differentiation, miometrial invasion, T FIGO parameter, lymphovascular space invasion, intraperitoneal disease and age were statistically significantly associated with lymphatic dissemination in endometrial cancer.

Pelvic and/or paraaortic lymphadenectomy is justified in cases of increased lymph node invasion risk, with decision to be made on a case by case basis, in order to avoid surgical overtreatment of incipient cases and the morbidities associated with extensive surgery, respectively to avoid undertreatment of advanced cases for which the therapeutic benefit of this surgical procedure is evident.

We recommend that the national therapy guideline for endometrial cancer be adapted according to FIGO 2009 staging and to include additional factors like "lymphovascular space invasion" and "age" for the risk group stratification of patients with endometrial cancer.

We recommend the treatment of endometrial cancer in specialised centres where preoperative and intraoperative risk factors evaluation is available and can be performed by a surgeon or gynaecologist-oncologist with experience in extensive peritoneal and retroperitoneal surgery.

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