RESEARCH ARTICLE

Risk Factors of Lymph Node Metastases with Endometrial Carcinoma

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Abstract

Background: The purpose of this study was to investigate and evaluate risk factors for lymph node metastases (LNM) in cases of endometrial cancer (EC). Materials and Methods: A retrospective single institution analysis of patients surgically staged for EC at Ankara Oncology Education and Research Hospital from 1996 to 2010 was performed. Roles of prognostic factors, such as age, histological type, grade, depth of myometrial invasion, cervical involvement, peritoneal cytology, and tumor size, in the prediction of LNM were evaluated. Fisher's exact test and logistic regression analysis were used to assess the effects of various factors on LNM. Results: LNM was observed in 22 out of 247 patients (8.9%) and was significantly more common in the presence of tumors of higher grade, deep myometrial invasion (DMI), cervical involvement, size >2cm, and with positive peritoneal cytology. Logistic regression analysis revealed that DMI remained the only independent risk factor for LNM. NPV, PPV, sensitivity, and specificity for satisfying LNM risk were 98.0, 19.5, 86.3, and 65.3%, respectively for DMI. Conclusions: The incidence of LNM is influenced independently by DMI. If data support a conclusion of DMI, LND should be seriously considered.

Keywords: Endometrial carcinoma - risk factors - myometrial invasion - lymph node - metastasis

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Introduction

Among all patients diagnosed with endometrial cancer (EC), lymph node metastases (LNM) are observed in the form of pelvic and paraaortic node metastases with ratios of 9 and 5%, respectively (Creasman et al., 1987; Chan and Kapp 2007; Neubauer and Lurain 2011). Because of this, the risk assessment of lymph node metastasis before surgery has great importance (Kang et al., 2014). The method and extent of lymph node dissection (LND) have not been uniformly defined, and whether LND should be performed or not in EC patients remains controversial even among experts (Creasman et al., 1987; Case et al., 2006; Chan and Kapp 2007; Chi et al., 2008; Neubauer and Lurain 2011; Wilairat et al., 2012). It is not yet clearly known if LND should be performed in all patients (Case et al., 2006; Chi et al. 2008), or if it is unnecessary in early stages of the disease (Mariani et al., 2000; Zuurendonk et al., 2006; Benedetti et al., 2008).

Patients often present with postmenopausal uterine bleeding (Acmaz et al., 2014; Binesh et al., 2014), which allows for diagnosis in early stages, and those with stage I EC have an excellent survival rate of over 90% (Atalay et al., 2013), however, stage III patients have a 5-year survival rate of around 60-75% (Creasman et al., 1987; Chan and Kapp 2007; Neubauer and Lurain 2011). International Federation of Gynecology and Obstetrics (FIGO) recommends LND to be performed in all patients (Creasman, 2009). Surgical staging allows EC patients to determine the need for adjuvant therapies. Patients who have not been staged are more likely to receive postoperative radiation therapy (RT).

In current clinical practice, approximately 1 out of 10 patients that undergo LND are determined to have LNM. This approach unnecessarily increases LND morbidity and complication risk ratios (Cragun et al., 2005; Todo and Sakuragi, 2013). For optimal care in EC, the aim is to avoid both over-and under-treatment. Reported medical complications that develop with LND include ileum obstruction or extended ileus (2.6%), and deep venous thrombosis (2.6%). Surgical complications include lymphocyst formation that requires drainage (2.4%), ileum obstruction that requires exploration (1.8%), and damage to major vascular structures that requires repair. In addition, surgery and anesthesia (median, 220 *vs* 204 min), and hospitalization (8 *vs* 5 days) times are prolonged (Cragun et al., 2005). There are also comorbidities in many EC cases, particularly in the presence of diabetes mellitus, obesity and hypertension, and being 60 years of age or older. These comorbidities mean increased complication risks in abdominal surgeries. In order to reduce morbidity and complication risks, LND restrictions can be applied by identifying patients with low and high LNM risk. Patients are staged for LNM risk, and application of

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selective LND is recommended as an option (Dowdy et al., 2012). In recent years, the application of sentinel lymph node technique has emerged as a result of a similar effort (Abu-Rustum, 2014). However, clinical staging instead of surgical staging has been deemed insufficient, because it fails to identify all patients with advanced disease. This is important both for prognostic and therapeutic reasons. From the prognostic point of view, patients with LNM have worse outcomes.

In the present study, we aimed to retrospectively investigate EC patients previously treated at our clinic, identify the parameters that increase LNM risk, and determine which of these parameters carry a high risk for LNM.

Materials and Methods

This study was approved by the ethic committee of Ankara Oncology Education and Research Hospital (AOERH). Records of patients operated at AOERH between 1996 and 2010 were retrospectively reviewed. EC patients, whose histopathological diagnosis were confirmed at AOERH, were started on treatment. Washing cytology was performed following midline laparotomy, and patients who had undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, LND, and staging surgery were included in the study. Patients, who had preoperative radiotherapy, and those with a secondary malignity, were excluded from the study.

All cases were staged according to the FIGO 09 system, and analyzed for survival. Presence of correlation between clinical parameters and LNM were examined in order to evaluate the risk for LNM. Clinical parameters that were evaluated were as follows: age, histological type, grade, depth of myomaterial invasion, cervical stromal invasion, peritoneal cytology, and tumor size for the prediction of lymph node metastases. These factors were evaluated using Fisher's exact test and univariate analysis. Parameters with significance in the univariate analysis were re-calculated with multivariate logistic regression analysis. Significance level was set at $p<0.05$.

Results

LNM was observed in 22 out of 247 (8.9%), while LNM was not observed in 225 patients (91.1%). Of the factors with potential effects on LNM, the following were analyzed using the Fisher's exact test: age, grade, histological type, myometrial invasion, cervical stromal invasion, tumor size and malign peritoneal cytology (Table 1). Lymph node involvement was significantly more common in the presence of tumors of higher grades, deep myometrial invasion, cervical stromal involvement, and positive peritoneal cytology.

Factors with a level of significance were subject to multivariate logistic regression analysis. Myometrial invasion with a depth of over 1/2 was determined to have increased the risk of LNM by 8.6 fold, and was identified as an independent prognostic factor. The%95 confidence interval values were 1.8-40.4. P value was calculated as 0.006.

Table 1. Risk Factors for Lymph Node Metastases.

	Absent LNM n=225 (%)	Present LNM n=22 (%)	p[a]
Age (y)			0.441
< 60	97 (92.8)	7 (7.2)	
≥ 60	80 (89.9)	9 (10.1)	
Grade			0.003
Grade I	95 (97.9)	2 (2.1)	
Grade II-III	123 (87.3)	18 (12.7)	
Myometrial invasion			<0.001
<1/2	147 (98.0)	3 (2.0)	
≥1/2	78 (80.5)	19 (19.5)	
Cervical stromal invasion			0.001
Absent	207 (93.7)	14 (6.3)	
Present	18 (69.3)	8 (30.7)	
Tumor size			0.001
<2 cm	121 (96.8)	4 (3.2)	
≥2 cm	104 (85.3)	18 (14.7)	
Histological type			0.095
Endometrioid	197 (92.5)	16 (7.5)	
Others	28 (82.4)	6 (17.6)	
Positive Peritoneal Cytology			0.002
Absent	213 (93.5)	15 (6.5)	
Present	12 (76.7)	6 (33.3)	

*[a]Fisher's exact probability

When calculated by grade III and/or deep myometrial invasion in pelvic lymph node involvement; the negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity in high risk patients were 97.7, 17.1, 86.3, and 59.1%, respectively. When myometrial invasion with a depth of over 1/2 was considered alone as high risk, NPV, PPV, sensitivity, and specificity for satisfying LNM risk were 98.0, 19.5, 86.3, and 65.3%, respectively.

Median age was 59 years (range, 27-80 years). FIGO 09 stages were distributed as; stage I, 82.7%, stage II, 4.6%, stage III, 10.9%, and stage IV, 1.8%. Majority of the cases were diagnosed as FIGO stage I. The overall survival rates in stage I, II, and III cases in the present study were 94.3, 83.3, and 71.7%, respectively. 5-year overall survival for the entire cohort was determined to be 91.3%.

Discussion

Vaginal bleeding allows for a diagnosis in the early stages in 70-80% of EC patients (Binesh et al., 2014). The 5-year survival rates reported in early stage cases were around 80-95% (Creasman et al., 1987; Chan and Kapp, 2007; Neubauer and Lurain 2011; Atalay et al., 2013). In the present study, observed rates of stages I, II, and III were 82.7, 4.6, and 10.9%, respectively, and the overall survival rates were 94.3, 83.3, and 72.7%, respectively. Presence of LNM negatively affects survival, and the prevalence of LNM in EC has been reported to be 5-18% (Creasman et al., 1987; Chan and Kapp 2007; Neubauer and Lurain 2011). Lymph node dissection was performed 88.5% of patients and lymph node involvement was observed at a rate of 8.9% in the current study.

Several histopathological and clinical risk factors have been identified that predict the likelihood of LNM (Chan and Kapp 2007). In the current study, presences of the following factors were observed to be significant when individually evaluated for the occurrence of LNM: >1/2 myometrial invasion (MI), positive peritoneal cytology, high grade, >2cm tumor size, and cervical stromal invasion.

The ideal approach would be to identify the disease that has spread outside the uterus and reached the lymph nodes using non-invasive techniques, and determine the appropriate surgical intervention accordingly. However, preoperative clinical staging has been deemed insufficient and failed to identify all patients with LNM. In two studies conducted with 291 and 181 EC patients, endometrial biopsy findings were upgraded to 18 and 19%, respectively, following final pathology reports (Goudge et al., 2004; Ben-Shachar et al., 2005). Several techniques can be used for the preoperative assessment disease invasion. Magnetic resonance imaging (MRI) has a sensitivity of 57.9% in determining deep myometrial invasion, and an accuracy of 80.4% (Gallego et al., 2014). In another study, sensitivity, specificity, NPV, PPV and accuracy for diagnosing deep MI were 69.0%, 93.1%, 91.3%, 74.1%, and 87.8%, respectively, for MRI (Hahn et al., 2013). It was demonstrated that positron-emission tomography/computed tomography (PET/CT) has a sensitivity of 69.2%, specificity of 90.3%, PPV of 42.9%, and NPV of 96.6% (Park et al., 2008). None of the current preoperative techniques have adequate predictive success rates to prevent unnecessary LND. It is our hope that the success rates of preoperative non-invasive techniques for determining MI depth will increase with technological advancements, contributing to the prevention of unnecessary LND.

Intra-operative inspection and palpation techniques were also used in a study to determine the presence of LNM. It was reported a false-negative rate of 36% for intraoperative palpation in 126 women with gynecologic cancers undergoing LND, with a palpation sensitivity and specificity of 72 and 81%, respectively (Arango et al., 2000). Even with experienced hands, 36% of pelvic lymph nodes could not be determined using palpation. In addition, abnormal palpation findings for metastatic nodes remained below 30% (Mariani et al., 2000). In one study, 37% of metastatic nodes in EC cases were observed to have diameters below 2mm (Girardi et al., 1993).

It was reported that intra-operative frozen sections for histologic depth of MI correlated with final pathology in EC. Sensitivity, specificity, NPV, PPV and accuracy for diagnosing deep MI were 85.7%, 96.8%, 95.8%, 88.9%, and 94.3% for intraoperative frozen section (IFS) (Hahn et al., 2013). In another study the accuracy, sensitivity, specificity, PPV, and NPV for detecting deep invasion of the myometrium were 90.2%, 73.7%, 100%, 100%, and 86.5%, respectively (Gallego et al., 2014).

In GOG Protocol 33, it was reported that the overall incidence of LNM in EC was around 3, 9, and 18% in grades I, II and III, respectively (Creasman et al., 1987). The incidence of LNM in the current study was 1.9, 9.0, and 25.0% in grades I, II and III, respectively. Less than 5% of the patients with <1/2 MI had LMN compared to around 20% of patients with >1/2 MI (Creasman et al., 1987). In the current study, the incidence of LNM was 2.0 and 19.5% in patients with <1/2 and >1/2 MI, respectively.

In the current group of patients, when calculated by taking the GOG study (Creasman et al., 1987) criteria into account, NPV, PPV, sensitivity, and specificity in high risk patients with grade III and/or deep myometrial invasion (DMI) in pelvic lymph node involvement and compare myometrial invasion with a depth of over 1/2 was considered alone as high risk, it is seen that DMI alone predicts more accurately the pelvic lymph nodal involvement.

In the current study, LNM ratio was determined to be 8.9%, and thus, the necessity of LND in all EC patients was unknown. The goals were sparing the patient an unnecessary surgery or radiotherapy, and also sparing not treating a patient with occult nodal involvement.

In conclusion, the risk of LNM significantly increases in EC patients, particularly with higher grade, PPC, deep MI, cervical stromal involvement, tumor size of >2 cm, and stage of disease. MI depth was identified as an independent prognostic factor in the risk of LMN. When MI depth for the prediction of LNM was considered a high risk criterion, NPV, PPV, sensitivity, and specificity were determined to be as high as 98.0, 19.5, 86.3, and 65.3%, respectively. DMI alone predicts LNM really accurately. In clinical practice it may be conclude that, if data supports the DMI, LND should not be omitted.

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