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Original Article

Clinical analysis of endometrial cancer patients with obesity, diabetes, and hypertension

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Abstract: The purpose of our study was to study the postoperation outcome and incidence of deep vein thrombosis (DVT) in endometrial cancer (EC) patients with or without hypertension, diabetes, and obesity. This analysis included 219 patients with endometrial carcinoma who were treated between 2002 and 2012 at the Department of Obstetrics and Gynecology, Yangzhou University Hospital. Patients were divided into five groups based on the comorbidities. Group 1 EC & Diabetes, Group 2 EC & Hypertension, Group 3 EC & Obesity, Group 4 EC Combined two, Group 5 no combined. Then the five groups were analyzed in postoperation outcomes and DVT incidence using one-way analysis of variance or Pearson χ^2 tests. we found that there was no significant difference in pelvic lymph node metastasis (P=0.102), aortic lymph node metastasis (P=0.221), and operative time (P=0.503). But there was significant difference in blood loss (P<0.01), hospital stay (P<0.01). No significant difference (P>0.05) in treatment outcome between surgical operation, surgical operation+ radiotherapy and radiotherapy. Deep vein thrombosis and pulmonary embolism have some significantly (P<0.01) (P<0.01), respectively. Compared to patients who simply suffer from endometrial cancer, diabetes make patients easy bleeding in surgery and increase hospitalization time in corresponding. VTE is a common complication of EC surgery with comorbidities, such as diabetes and hypertension, and it's a remarkable proportion of events occurring late after surgery.

Keywords: Endometrial carcinoma, diabetes mellitus, hypertension, obesity

Introduction

Endometrial carcinoma (EC) is one of the most common gynecologic malignancies. The incidence rate of EC is increasing surprisingly in both developing and developed countries [1]. Metabolic syndrome including obesity, hypertension, insulin resistance, diabetes, and dyslipidemia increases the risk of developing multiple types of cancer, particularly EC [2]. Observations linking blood pressure, glucose metabolism, and insulin resistance to endometrial cancer come mostly from retrospective studies. These retrospective studies have provided less conclusive results because of self-reported disease history and anthropometry or an absence of adjustment for body mass [3].

Many past studies showed that obesity was associated with an increased risk of endometrial cancer and that age may have confounded the obesity-EC stage association [4]. In fact, many metabolic disorders may influence estrogen/progesterone levels and expose women to a permanent hormonal imbalance, increasing the risk of endometrial malignant changes. Lifestyles associated with metabolic disorders play an important role in the development of this illness. It is considered that the increased number of EC cases in countries such as Mexico may be the result of lifestyles changes, which lead to obesity [5]. Metabolic dysfunction is a common consequence of obesity, a strong risk factor for endometrial cancer. Obesity causes disruptions in multiple metabolic pathways, including elevated levels of sex steroid hormones, insulin, and inflammatory mediators and lower levels of adiponectin [6]. Many studies suggested that higher BMI and inactivity was associated with a higher risk of developing endometrial cancer [7]. Babette S. Saltzman el at. [8] studied the data from a population-based case-control study (1,303 cases and 1,779 controls) conducted in western Washington

State during 1985-1999. It was found that type 2 diabetes was associated with endometrial cancer (odds ratio (OR): 1.7, 95% confidence interval (CI): 1.2, 2.3). Besides, patients with diabetes had a two-fold increased risk of endometrial cancer among hypertensive women.

Venous thromboembolism (VTE) is a common complication in patients undergoing surgery. Cancer surgery seems to have at least twice the risk of postoperative deep vein thrombosis (DVT) and more than three times the risk of fatal pulmonary embolism (PE) than similar procedures in noncancer patients. Though advances in the prevention of DVT and PE by sequential compression devices and perioperative anticoagulation, venous thromboembolic events remain a serious and common complication for women with endometrial cancer after primary surgical treatment. The relationship between thromboembolic events and underlying malignancy was first noted by Trousseau [9] in 1865. Further research noted that this relationship is especially strong for tumors of intra-abdominal or pelvic origin [10]. The exact mechanisms of cancer associated hypercoagulability are multi-faceted and controversial. Prandoni [11] suggested that tumor cells were pro-thrombotic. Neoplastic cells were known to activate the clotting system via thrombin and stimulation of mononuclear cells. Inflammatory cytokines released by tumor cells enhanced platelet aggregation. Whether different histologic subtypes of endometrial cancer are more or less prone to cause thrombosis remains undetermined, yet prior studies have suggested those with clear cell histology have the highest risk [12].

The risk for thromboembolic complications in cancer surgery may have altered over the years as this particular surgery has witnessed a number of recent changes. Improvements in surgical techniques, more prompt mobilization, improved use of prophylaxis, and advances in perioperative care may have reduced the thromboembolic complications in the older and sicker patients. Furthermore, shorter hospital stay for surgery plus extended duration of prophylaxis could influence the occurrence of thromboembolic events today. The primary aim of our study is to assess the effect of obesity, diabetes, and hypertension on the operative time, blood loss, hospital stay, lymph node metastasis, and incidence of VTE in EC patients.

Materials and methods

Election and eligibility criteria

A total of 219 patients with endometrial carcinoma were selected from 2002 to 2012 at the Department of Obstetrics and Gynecology, Yangzhou University Hospital. The median age of the patients was 56.2 years (range 40-72 years). Patients were divided into five groups based on the comorbidities. Group 1 EC & Diabetes, Group 2 EC & Hypertension, Group 3 EC & Obesity, Group 4 EC Combined two (any two of Diabetes, Hypertension, or Obesity), Group 5 no combined. We selected all patients with FIGO stages I, II, and III, according to the International Federation of Gynecology and Obstetrics (FIGO, 2009). The study protocol was approved by the Ethics Committee of Clinical Medical College of Yangzhou University, and informed consent was obtained from each patient enrolled in the study. Data collected includes age at diagnosis, BMI (weight in kg/[height in m]^2), tumor grade, histology, surgical procedure, performance of lymphadenectomy, number of lymph nodes removed, and lymph node status.

Illustration: Grade, when reported, was described by a three-grade system; grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated and undifferentiated). Serous carcinomas, clear cell carcinomas, and carcinosarcomas were not graded, but were all considered as grade 3 [13].

Hypertension was diagnosed if the systolic blood pressure and diastolic blood pressure is persistently at or more than 140/90 mmHg. According to the World Health Organization (WHO) classification by BMI, women were assigned to be obese when their BMI exceeded 30 kg/m^2. The major diagnosis criteria of diabetes is according to the American Diabetes Association (ADA) classification criteria of diabetes in 2011 [14]. Diabetic patients were given oral metformin 0.25 g bid/tid or insulin protamine zinc insulin (PZI) 40U bid, and diabetic diet to make fasting plasma glucose be less than 5.6 mmol/L. Hypertensive patients took oral antihypertensive drugs, losartan 50-100 mg/d or telmisartan 40-80 mg/d. All patients' blood pressure was maintained steady <140/90 mmHg.

Table 1. Descriptive characteristics of hospitalization women in the study population

Demographic	Diabetes (n=33)	Hypertension (n=54)	Obesity (n=147)	Combined two (n=15)	None (n=72)	*P* value
Age (years)	56.8	56.5	55.9	55.6	56.0	0.32
BMI	29.8	29.6	28.7	28.7	28.6	0.65
Tumor Stage (n, %)						0.75
I	12 (36.36)	21 (38.89)	69 (46.94)	7 (46.67)	26 (36.11)	
II	5 (15.15)	11 (20.37)	32 (21.77)	3 (20.00)	12 (16.67)	
III	2 (6.06)	3 (5.56)	10 (6.80)	1 (6.67)	5 (6.94)	
Tumor Grade (n, %)						0.21
G1	8 (24.24)	13 (24.07)	41 (27.89)	4 (26.67)	20 (27.78)	
G2	5 (15.15)	10 (18.52)	28 (19.05)	3 (20.00)	12 (16.67)	
G3	6 (18.18)	10 (18.52)	30 (20.41)	3 (20.00)	14 (19.44)	
Tumor type (n, %)						0.34
Endometrioid	23 (12.10)	25 (13.16)	72 (37.89)	12 (6.32)	58 (30.53)	
Serous	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	0 (0.00)	
Clear cell	2 (40.00)	1 (20.00)	1 (20.00)	1 (20.00)	1 (20.00)	
Others	4 (18.18)	5 (22.73)	10 (45.45)	1 (4.55)	2 (9.09)	

Table 2. Operation outcome of hospitalization women in the study population

		Diabetes	Hypertension	Obesity	Combined two	No combined	*P* Value
N		33	54	147	15	72	
Operative time (min)		156	130.2	162.8	164.4	154.9	0.503
Blood loss (ml)		268.2	255.6	239.5	240	235	<0.01
Blood transfused (UI)		2	1	1	1	1	0.362
Hospital stay (d)		5.2	6.0	4.9	6.2	4.5	<0.01
Total number of	Pelvic lymph node	11.8	15.2	14.9	14.6	10.7	0.102
	Aortic lymph node	10.2	12.5	13.7	11.8	9.5	0.221

Surgical operation

The primary surgery was total abdominal hysterectomy, bilateral salpingo-oophorectomy, appendectomy, node sampling of enlarged lymph nodes, and peritoneal washing with cytology. All patients underwent preoperative bowel preparation with magnesium citrate, and were given preoperative prophylactic antibiotics and all patients were operated by the same surgeon using the same technique and instruments. A chief resident was the first assistant.

Mechanical methods to prevent DVT and pulmonary embolism (PE)

14 thrombosis patients in our research belong to high-risk group according to ACOG Committee on Practice Bulletins [15]. Available methods include graded elastic compression stockings starting 2 hours before surgery and continued 2 weeks postoperatively and low-molecular-weight heparins (LMWH) 0.4 ml daily continued discharged were applied.

Postoperative follow-up

In all instances of death or recurrence, the pertinent medical records were reviewed. Recurrence was confirmed with pathological diagnosis or imaging techniques. The overall survival was defined from the time of diagnosis to last contact with the patients. Among all the patients, the mean length of follow-up was 5 years (range 1.2 years-10 years). The standard follow-up is performed every 3 month in the first, second, and third year, every 6 month in the fourth and fifth year, and then yearly thereafter. During the follow-up period, a detailed history was obtained. Besides, pelvic examination (trimanual gynecological examination), vaginal cytology smears, pelvic ultrasound, CA-125 measurements, chest X-ray and CT scans were also included. MRI was also added when it was necessary.

Table 3. The comparison of intraoperative blood loss and hospital stay between the five groups

	Diabetes	Hypertension	Obesity	Combined two	no combined
Blood loss (ml)	268.2	255.6	239.5	240	235
F	14.23	13.78	13.24	13.25	
P	<0.01	0.27	0.254	0.253	

Table 4. The comparison of hospital stay between the five groups

	Diabetes	Hypertension	Obesity	combined two	no combined
hospital stay	5.2	6.0	4.9	6.2	4.5
χ^2	13.30	10.54	9.43	9.40	
P	<0.01	0.042	0.032	0.033	

Statistical analysis

All analysis were performed using commercially available software (SPSS version 17.0; SPSS, Inc., Chicago, IL). Continuous variables were analyzed using one-way analysis of variance (ANOVA) and evaluated with the standard F statistic. Categorical variables were analyzed with contingency tables and evaluated using the Pearson χ^2 test. A *P* value of <0.05 was considered to be statistically significant.

Results

Table 1 displays the distribution of 219 cases of endometrial cancer according to selected variables. 120 (60%, 120/200) cases received hysterectomy and bilateral salpingo-oophorectomy. 48 (24%, 48/200) cases received hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection. Among these patients 30 (15%, 30/200) cases also have appendectomy and 3 (1.5%, 3/200) cases also had omentum resection. 50 (25%, 50/200) patients received hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node biopsy; 3 (1.5%, 3/200) cases had high ligation of infundibulopelvic ligament. There are 6 (3%, 6/200) cases intraoperative massive hemorrhage and given concentrated erythrocytes 6U and plasma 200 ml, concentrated erythrocytes 3U respectively. The average operative time was 1.8 hours, blood loss was 265.7 ml, and hospitalization was 9 days. Postoperative radiotherapy was added in 50 (22.8%) patients because of local recurrence and distant metastasis. Because radiotherapy is suitable for advanced cancer or patients who are not suitable for surgery, 19 (8.7%) patients required single radiation therapy.

There were no significant differences among EC patients regarding the mean age, body mass index, tumor grade, histology (**Table 1**). As demonstrated in **Table 2**, there were no significant differences between the five groups with respect to operative time, and lymph metastasis. The mean numbers of removed pelvic lymph nodes in groups 1 to 5 were 11.8, 15.2, 14.9, 14.6, and 10.7, respectively (p=0.102). And the mean numbers of removed aortic lymph nodes in groups 1 to 5 were 10.2, 12.5, 13.7, 11.8, and 9.5, respectively (*p*=0.221). Furthermore there was a significant difference in estimated amount of blood loss between group 1 and group 5 (p<0.01) (**Table 3**). Similarly, the length of hospital stay significantly increased among the four groups with comorbidities compared to that of the group without comorbidities. A significant difference was found between group 4 and group 5 (p<0.01) (**Table 4**).

We further studied the incidence of postoperative complication, VTE in the five groups. **Table 5** demonstrates that VTE occurred in 25 patients. DVT occurred in 22 patients, 5 (11.42%) patients in group 1, 6 (2.74%) patient in group 2, 2 (0.91%) patients in group 3, 8 (3.65%) patients in group 4, and 1 patient (0.46%) in group 5, respectively. There was a significant difference in the incidence of DVT among the 5 groups (p<0.01) (**Table 6**). Furthermore, significant differences were found between group 5 and group 1, group 2 and group 4, respectively. The incidence of PE was 1 (4.5%) patient in group 1, 2 (13.3%) patients in group 4, and none in group 2, 3, and 5. There was a significant difference in the incidence of PE between group 5 and group 4. All the three PE patients were dead because of acute onset.

Discussion

Endometrial cancer is the most common gynecologic malignancy worldwide. This study was retrospective to compare the treatment methods, postoperation outcomes and deep vein thrombosis of patients with endometrial cancer

Table 5. Incidence of postoperative venous thromboembolism in the patients with endometrial cancer

	Diabetes (n=22)	Hypertension (n=69)	Obesity (n=82)	Combined two (n=15)	No combined (n=31)	N	P
DVT (n, %)	5 (9.1%)	6 (1.4%)	2 (2.4%)	8 (40%)	1	22	<0.01
PE (n, %)	1 (4.5%)	0	0	2 (13.3%)	0	3	<0.01

Table 6. Postoperative complications in the patients with endometrial cancer

	Diabetes (n=33)	Hypertension (n=54)	Obesity (n=147)	Combined two (n=15)	None (n=72)	P
Survival rate (%)						0.21
3-year survival rate	92.31	91.45	92.17	90.30	92.36	
5-year survival rate	79.12	79.63	81.06	82.00	79.07	
Median time to	15.3	15.5	16.0	17.1	15.0	
Recurrence (mouths)						0.24
3-year recurrence rate	10.8	11.2	11.7	11.8	10.5	
5-year recurrence rate	16.5	15.4	16.7	16.8	16.4	
Site of recurrence						
Vagina	1	2	4	1	2	
Pelvis	1	1	2	0	1	
Para-aortic lymph node	1	1	1	1	1	
Lung	1	0	0	0	0	
Others	0	0	0	0	0	

who combined with hypertension, diabetes, obesity and who simply suffers from endometrial cancer. This analysis was feasible because all patients were operated by the same surgeon using the same technique and instruments. Epidemiologic studies have identified several risk factors for endometrial cancer. Overweight/obesity and diabetes mellitus (Types 1 and 2) are associated with endometrial cancer risk. Hypertension increases the risk of endometrial cancer among obese women [16]. The most prominent risk factors include obesity, endogenous and exogenous estrogens, and related reproductive factors: nulliparity, early menarche, and late menopause. Other risk factors, including type 2 diabetes, hypertension, greater alcohol intake, and sedentary lifestyle, showed an association with endometrial cancer, but the causality is debated. No dietary factor is strongly associated with endometrial cancer, but according to a recent review, vegetables and fruits 'possibly decrease' the risk and saturated/animal fat 'possibly increases' the risk. The association between diabetes and endometrial cancer may largely be explained through correlations with other risk factors for endometrial cancer, particularly obesity. However, there may be an independent association between diabetes and endometrial cancer. Another possibility could be that a high dietary glycemic index or load is a common risk factor for both diabetes and endometrial cancer [17].

Adiposity may be part of a metabolic syndrome involving insulin resistance and compensatory hyperinsulinemia, which may increase endometrial cancer risk through estrogenic or growth factor pathways. In Weiderpass's study, the overall prevalence of diabetes mellitus (Types 1 or 2) was significantly higher among case patients (12%) than among control women (6%), and the age-adjusted OR was 2.0 (95% CI 1.5±2.7). Subjects with probable Type 1 diabetes mellitus had a markedly higher risk (OR 13.3, 95% CI 3.1±56.4) than those with probable Type 2 diabetes mellitus (OR 1.5, 95% CI 1.0±2.1) [8]. TAs for diabetes, women with hypertension had a significantly higher mean BMI (27.7 kg/m^2, s.d. 5.3) than women without hypertension (mean BMI 25.1 kg/m^2, s.d. 4.0). Less degrees of overweight (less than 29 kg/m^2) are not associated with an increased risk. Diabetes mellitus was clearly linked to an increased risk but hypertension conferred an increased risk only among obese women [16]. These data suggest that diabetes mellitus is

associated with endometrial cancer risk independently of obesity. Babette et al [18] suggested that type 2 diabetes is associated with endometrial cancer irrespective of the presence of other risk factors for this disease, except possibly hypertension and extreme obesity.

The literature regarding the association between hypertension and endometrial cancer is inconclusive. There are some reports of a positive association and others of no association. In Elisabete's study [8] they did not find any overall effect of hypertension after adjustment for BMI. However, they did observe an effect of hypertension among obese women, compatible with the hypothesis that a metabolic syndrome including obesity, hypertension and insulin resistance is a risk factor for endometrial cancer.

Stage is the most important prognostic factor, and surgical staging offers the most accurate prognostic information. Surgical staging facilitates adjuvant therapeutic recommendations. There is no agreement on the standard treatment for women with advanced endometrial cancer. Typically, a combination of surgery, radiotherapy and/or chemotherapy is employed. Laparotomy has traditionally been the surgical approach for the treatment of endometrial cancer. Now, minimally invasive techniques are widely accepted by many authors, such as laparoscope, robotic approach [19]. Anyway, no matter which method has been chose, lymph node metastasis is one of the most important prognostic factors of endometrial carcinoma. The prognosis of advanced endometrial carcinoma with lymph node metastasis (IIIc/IV) is poor. Choose laparoscopic surgery or laparotomy based on clinical stage and histological grade.

In the present study, patients were divided into five groups based on the comorbidities. We adopt surgical operation, surgical operation+ radiotherapy and radiotherapy+ chemotherapy methods according to 2009 FIGO EC staging criteria. Approximately 75% of women was stage I disease curable by surgery alone. Among those who combined comorbidities (hypertension, diabetes, obesity), in our research, we find that there is no significant difference in pelvic lymph node metastasis (P=0.102), aortic lymph node (P=0.221), and operative time (P=0.503). But there is significant difference in blood loss (P<0.01), and hospital stay (P<0.05). Those with more advanced disease may require chemotherapy or radiation therapy. Pelvic washings are no longer part of FIGO staging but may be reported separately. Some authors have reported pelvic and paraaortic lymphadenectomy to be associated with improved survival. The postoperative radiation therapy in endometrial carcinoma patients confirmed the value of radiation therapy in women after surgical therapy without comprehensive surgical staging. The absolute benefit of external beam radiation therapy in preventing isolated local recurrence was small and was not without toxicity. Vaginal brachytherapy can reduce the incidence of vaginal vault recurrence. Using high-dose therapy, treatment can be on an outpatient basis with low morbidity. Treatment of recurrent disease depends on the original stage, the location of the recurrence, and previous treatments. The most common site for recurrence of stage I disease is the vagina. Chemotherapy is now used as the primary therapy for advanced and metastatic disease [20].

VTE encompasses both DVT and PE. Clinical features of DVT include swelling, pain, pitting edema, increased warmth, and superficial venous dilation of the lower limb. PE may present with or without symptoms of a DVT in addition to chest pain, breathlessness, hemoptysis, syncope, hypotension, tachycardia, and hypoxia [8]. The incidence of VTE among patients with stroke is high, and PE remains the third-highest cause of case fatality in stroke [16]. The prevalence of DVT in patients undergoing major gynecologic surgery ranges from 15% to 40% in the absence of thromboprophylaxis [4]. In our research there are 22 cases of DVT and 3 cases of PE. The presence of an asymptomatic DVT is highly linked to the development of a clinically significant pulmonary embolism. Most patients who die from a pulmonary embolism succumb within 30 minutes of the event, leaving little time for therapeutic interventions [15]. Hospitalization and surgery are associated with an increased thrombosis risk, with odds ratios of 11.1 and 5.9, respectively. Patients undergoing bed rest are nearly nine times more likely to develop a VTE [23]. Our operational patients belong to high-risk group according to ACOG Committee on practice Bulletins, and graded elastic compression stockings are used

from 2 hours before surgery to 2 weeks postoperatively and low-molecular-weight heparins (LMWH) 0.4 ml daily continued discharged were applied.

Recurrence was detected via symptoms, physical examination, or CA-125 measurements and so on. Approximately 70% of endometrial cancer recurrences happen within the first three years after primary surgery. Based on our experience, we find that there is no significant difference at pelvic lymph node metastasis (P=0.102), aortic lymph node (P=0.221), survival rate (P=0.21), and recurrence rate (P=0.24). But there is significant difference in blood loss (P<0.01), hospital stay (P<0.05). This may be because diabetes mellitus leads to microvascular lesions, which makes operative time be long, easy bleeding in surgery. At the same time, hospitalization time is also increase in corresponding.

In Arvind Bakhru' study [24], 10.8% of all subjects were diagnosed with DVT and 7.2% were diagnosed with PE. Borderline tumors and mucinous showed a strikingly low rate of both DVT and PE. Clear cell and high-grade undifferentiated adenocarcinomas were the most likely to result in VTE. In a multivariate model, pathologic subtype was not only a significant predictor of VTE, but also was the single best predictor of VTE. Giancarlo Agnelli [25] found that VTE remains a common complication of cancer surgery, with a remarkable proportion of events occurring late after surgery. In patients undergoing cancer surgery, VTE is the most common cause of death at 30 days after surgery. As to our results, deep vein thrombosis and pulmonary embolism were significantly different (P<0.01, P<0.01), respectively. The underlying reason for this may related to differences in comorbidities.

Compared to patients who simply suffer from endometrial cancer, diabetes make patients easy bleeding in surgery and increase hospitalization time in corresponding. VTE is a common complication of EC surgery with comorbidities, such as diabetes and hypertension, and it's a remarkable proportion of events occurring late after surgery.

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Disclosure of conflict of interest

None.

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