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Original Article

Clinicopathological characteristics and survival outcomes of patients with coexistence of adenomyosis and endometrial carcinoma

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Abstract: Objective: To examine the association of coexistence of adenomyosis and endometrial carcinoma on tumor characteristics and survival outcome of patients. Methods: Clinical and pathological data were retrospectively reviewed from 1584 patients who underwent surgical treatment of endometrial carcinoma. Statistical analyses were performed to evaluate associations of the presence or absence of adenomyosis with demographics, clinical parameters, histopathological factors, and survival outcomes. Results: Adenomyosis was found in 150/1584 patients, and was significantly associated with premenopausal status (46% vs. 35.15%, *P* = 0.008), younger age (60.67% vs. 41.92% < 55 years old, *P* < 0.001), lower positive p53 expression (53.36% vs. 63.32%, *P* = 0.034), earlier disease stage (I-II) (92.67% vs. 85.56%, *P* = 0.016), lower grade of the tumors (1-2) (91.33% vs. 84.52%, P = 0.025), lower likelihood of outer-half myometrial invasion (10% vs. 22.25%, P < 0.001), and absence of pelvic lymph node metastasis (97.04% vs. 92.09%, P = 0.037). The presence of adenomyosis was also associated with better survival outcomes, with a higher 5-year survival rate (92.1% vs. 84.1%, P = 0.045). In multivariate analysis, age, BMI, stage/grade of tumors, and myometrial invasion were independent prognostic factors associated with survival outcomes. Conclusion: The presence of adenomyosis was associated with less aggressive behavior of endometrial cancer and is a protective factor associated with better outcomes of patients.

Keywords: Endometrial carcinoma, adenomyosis, prognostic factors, survival outcome

Introduction

Endometrial carcinoma is the most common gynecological cancer among women in developed countries. In the USA an estimated 49,560 women were diagnosed with endometrial cancer in 2013 [1]. Some of the risk factors of endometrial carcinoma include obesity, diabetes, and cumulative exposure to estrogen. The majority of patients with endometrial cancer are diagnosed in an early stage, in which the disease is curable with surgical treatment. Adenomyosis is a condition of the uterus, where the endometrial tissue in the uterine myometrial layers also grows outside the endometrial lining [2]. Typical symptoms include dysmenorrhea, chronic pelvic pain, and menorrhagia. It has been reported that adenomyosis coexists with endometrial carcinoma in 16-34% of hysterectomy specimens obtained from the surgical treatment of endometrial carcinoma [3-8]. The role of adenomyosis in pathogenesis and clinical behavior of endometrial carcinoma remains unclear, despite evidence of a frequent association between adenomyosis and endometrial carcinoma.

Studies have been performed to investigate whether the presence of adenomyosis is associated with tumor progression of endometrial cancer, and the results appeared controversial. While there are studies that observed a relationship between adenomyosis and deep myometrial invasion [4, 9-11], other studies suggested the presence of adenomyosis may be considered as an enabling factor that allows malignant cells to invade the myometrium by increasing the contact area [5, 8, 12]. Some of these studies are based on case reports or relatively small sample size cohort studies.

Table 1. Associations of clinical characteristics with the incidence of adenomyosis co-existence in patients with endometrial carcinoma

	Total	With Adenomyosis	Without Adenomyosis	χ^2	*P*
Menopausal Status					
Premenopausal	573	69 (46%)	504 (35.15%)		
Postmenopausal	1011	81 (54%)	930 (64.86%)	6.928	0.008
Age, years					
Median	55	53	55		
< 55	745	91 (60.67%)	654 (41.92%)		
≥ 55	839	59 (39.33%)	780 (58.08%)	12.363	< 0.001
BMI					
Median	26.07	27	26.65		
< 25	488	42 (28.38%)	446 (31.23%)		
≥ 25	1088	106 (71.62%)	982 (68.77%)	0.511	0.475

The present study retrospectively reviewed a relatively large cohort and evaluated the association of adenomyosis with tumor and clinical characteristics of patients, as well as the survival outcome of patients in a large-scale comprehensive analysis.

Patients and methods

Patients

Clinical data were retrospectively reviewed from patients who were admitted to the hospital during the period from January 2008 to December 2014. These patients were diagnosed with endometrial carcinoma and no other primary malignancies were found. The patients received surgical treatment. Among the endometrial cancer cohort, adenomyosis was found in 150/1584 cases.

Clinical information

Clinical information was collected, including patient demographics (e.g. age, body mass index), menopausal status, histopathologic characteristics (e.g. histologic subtype, tumor grade, invasion, lymph node metastasis), and the immunohistochemistry findings on protein expression in cancer specimens (e.g. estrogen-receptor, progesterone-receptor, p53, Ki-67, survivin, and CA125). The surgical treatment information and treatment outcome on survival time were also reviewed.

Statistical analysis

Statistical analyses were performed using SPSS 16.0. Survival curves were constructed with the Kaplan-Meier method. Significance of adenomyosis on survival outcome was examined with the log-rank test in univariate analysis. Cox regression was used to identify the independent prognostic factors of survival. Nonparametric test was used for data not following normal distribution. Categorical variables were evaluated with Chi-square test. *p* values of less than 0.05 were considered statistically significant.

Results

Clinical and pathological data from 1584 patients with endometrial carcinoma were reviewed. Among them, 1434 patients had no adenomyosis and 150 patients had adenomyosis. The incidence rate of adenomyosis co-existence was 9.47%. The endometrial carcinoma patients were divided into two groups: 1) with adenomyosis; and 2) without adenomyosis.

We compared various clinical parameters and demographics between the two groups. There were no statistically significant differences between the two groups in terms of the types of hysterectomy, whether or not adnexectomy was performed, and excision of pelvic lymph node or aortic lymph node (Table S1). Patients with adenomyosis were younger in age (higher percentage of patients with age < 55 years old, $P < 0.001$) (**Table 1**). In addition, a higher percentage of patients was in a premenopausal state (46% in the adenomyosis group vs. 35.15% in the group without adenomyosis, $P = 0.008$). There were no significant differences in BMI between the two groups.

Pathological characteristics of endometrial cancer were also examined (**Table 2**). The majority of the patients (> 90%) in this study had endometrioid histology. The presence of adenomyosis was significantly associated with a higher likelihood of early stage (I-II) disease (92.67% vs. 85.56%, $P = 0.016$) and Grade 1-2 tumors (91.33% vs. 84.52%, $P = 0.025$), when compared with non-adenomyosis cases. When the tumor details were compared, the presence of adenomyosis was significantly associated with a lower likelihood of invasion of ≥ 1/2

Table 2. Association of histopathological characteristics with the incidence of adenomyosis co-existence in patients with endometrial carcinoma

	With Adenomyosis n = 150	Without Adenomyosis n = 1434	χ^2	*P*
Histology				
Endometrioid cancer	140 (93.33%)	1294 (90.23%)		
Non-endometrioid cancer	10 (6.67%)	140 (9.76%)	1.519	0.218
Stage				
I-II	139 (92.67%)	1227 (85.56%)		
III-IV	11 (7.33%)	207 (14.44%)	5.771	0.016
Grade				
1-2	137 (91.33%)	1212 (84.52%)		
3	13 (8.67%)	222 (15.48%)	4.991	0.025
Myometrial invasion				
< 1/2	135 (90%)	1115 (77.75%)		
≥ 1/2	15 (10%)	319 (22.25%)	12.237	< 0.001
LVSI				
No	144 (96%)	1341 (93.51%)		
Yes	6 (4%)	93 (6.49%)	1.513	0.219
Cervical invasion				
No	124 (82.67%)	1105 (77.06%)		
Yes	26 (17.33%)	329 (22.94%)	2.457	0.117
Adnexa invasion				
No	144 (96.64%)	1330 (93.46%)		
Yes	5 (3.36%)	93 (6.54%)	2.333	0.127
Pelvic LN metastasis				
No	131 (97.04%)	1176 (92.09%)		
Yes	4 (2.96%)	101 (7.91%)	4.339	0.037
Aortic LN metastasis				
No	96 (100%)	767 (95.64%)		
Yes	0	35 (4.36%)	-	-

LVSI: Lymphovascular space invasion.

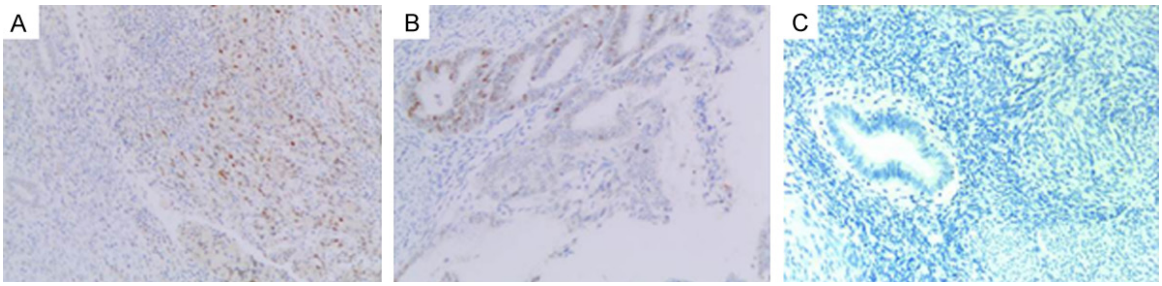

Figure 1. Representative IHC images of p53 in tissues. A: With adenomyois group; B: Without adnomyosis group; C: Negative control.

of the thickness of the myometrium (10% vs. 22.25%, $P < 0.001$). Also, the adenomyosis group was more likely to have an absence of pelvic lymph node metastasis (97.04% vs. 92.09%, $P = 0.037$). Other tumor characteristics, including cervical invasion, adnexa invasion, had no significantly difference between the two groups. All of the patients in the adenomyosis group had the absence of aortic lymph node metastasis (100% vs. 95.64%).

Table 3. Immunohistochemistry results of endometrial cancer

	Total	With Adenomyosis	Without Adenomyosis	χ^2	*P*
ER					
Positive	1174	112 (94.87%)	1062 (90.14%)		
Negative	123	6 (5.13%)	117 (9.86%)	2.926	0.087
PR					
Positive	1111	101 (86.32%)	1010 (85.88%)		
Negative	182	16 (13.67%)	166 (14.12%)	0.117	0.896
P53					
Positive	807	63 (53.39%)	744 (63.32%)		
Negative	486	55 (46.61%)	431 (36.68%)	4.507	0.034
Ki-67					
Positive	1230	111 (94.87%)	1119 (96.97%)		
Negative	41	6 (5.13%)	35 (3.03%)	1.494	0.222
Survivn					
Positive	687	58 (59.79%)	629 (62.59%)		
Negative	415	39 (40.21%)	376 (37.41%)	0.294	0.588
CA125					
Positive	794	72 (65.45%)	722 (66.54%)		
Negative	401	38 (34.55%)	363 (33.46%)	0.053	0.818

ER: Estrogen-receptor; PR: progesterone-receptor.

At the molecular level, we examined expression of several proteins using immunohistochemistry on available tissue samples. The percentage of positive staining of p53 was lower in the adenomyosis group (53.39% vs. 63.32%, $P = 0.034$) (**Figure 1**). Other tumor markers including ER, PR, Ki-67, survivin, and CA125 had no significant differences between the two groups (**Table 3**).

Survival analysis was also performed. Endometrial cancer cases with adenomyosis had a significantly higher 5-year survival rate (92.1% vs. 84.1%, $P = 0.045$) (**Table 4** and **Figure 2**). However, the presence of adenomyosis was not an independent prognostic factor. The risk factors for survival (in the univariate analysis) listed in **Table 4**, include: age, BMI, menopausal status, histology, stage of disease, grade of tumor, myometrial invasion, cervical invasion, adnexa invasion, pelvic lymph node metastasis, aortic lymph node metastasis, and LVSI. On multivariate analysis, after considering all the significant variables from univariate analysis, the age, BMI, disease stage, tumor grade, and myometrial invasion remained independent significant factors associated with survival, but not adenomyosis.

Discussion

The key findings of our study include that the presence of adenomyosis in patients with endometrial carcinoma was associated with 1) the less aggressive properties of the tumors and 2) better prognosis of patients.

Several characteristics of the tumors were investigated in this study, such as cancer invasion, lymph node metastasis, stage and grade of the tumors. We found decreased myometrial invasion (≥ 1/2) in the adenomyosis group, which is consistent with another study [13]. It was reported that the increased thickness of endometrial stroma in adenomyosis is associated with rapid cell proliferation under stimulation of estrogen or inflammatory cytokines [14], and the thickened endometrial stroma may contribute to a mechanical blockage of the endometrial cancer invasion in the myometrium. Both the current study and other finding support this hypothesis [13].

In the present study, the presence of adenomyosis was also associated with reduced incidence of aortic/pelvic lymph node metastasis, as well as lower grade and stage of endometrial carcinoma. Indeed, the lower incidences of aortic/pelvic lymph node metastasis in patients with adenomyosis were also observed in other studies [13, 15]. Among the 150 patients who had adenomyosis in our study, none of them had aortic lymph node metastasis. This was much lower than the incidence observed in the patients without adenomyosis (4.36%), although statistical analysis could not be performed.

At the molecular level, expression of mutated p53 in endometrial cancer was associated with patients lacking adenomyosis. The wild-type p53 usually has a shorter half-life when compared to the mutated p53; therefore, the posi-

Table 4. Risk factors for survival in endometrial cancer patients

	5-year survival proportion (%)	Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Adenomyosis					
No	84.1	1			
Yes	92.1	0.375 (0.13-1.01)	0.045		
Age, years					
< 55	90.3	1			
≥ 55	80.1	2.15 (1.43-3.22)	< 0.001	2.65 (1.24-5.64)	0.011
BMI					
< 25	86.2	1			
≥ 25	87.3	0.642 (0.44-0.93)	0.019	0.392 (0.20-0.75)	0.005
Menopausal Status					
Premenopausal	92.6	1			
Postmenopausal	81.7	3.14 (1.90-5.22)	< 0.001		
Laparoscopic					
No	83.1	1			
Yes	86.4	0.68 (0.43-1.06)	0.088		
Histology					
Endometrioid cancer	88	1			
Non-endometrioid cancer	59.8	5.451 (3.71-8.00)	< 0.001		
Stage					
I-II	91.8	1			
III-IV	47.7	12.01 (8.2-17.60)	< 0.001	7.26 (3.51-15.00)	< 0.001
Grade					
1-2	89.8	1			
3	58.3	4.44 (3.057-10.967)	< 0.001	2.51 (1.28-4.92)	0.007
Myometrial invasion					
< 1/2	92.4	1			
≥ 1/2	62.3	7.45 (5.06-10.96)	< 0.001	2.77 (1.30-5.89)	0.008
Cervical invasion					
No	87.9	1			
Yes	74.8	2.93 (2.01-4.23)	< 0.001		
Adnexa invasion					
No	87.5	1			
Yes	50.1	7.79 (5.24-11.58)	< 0.001		
Pelvic lymph nodemetastasis					
No	87.9	1			
Yes	55.2	10.37 (5.50-19.56)	< 0.001		
Aortic lymph nodemetastasis					
No	86.6	1			
Yes	40.5	13.09 (6.59-25.99)	< 0.001		
LVSI					
No	87.5	1			
Yes	50.1	6.19 (4.09-9.38)	< 0.001		

tive expression of p53 detected in IHC of the present study represented predominately the mutated p53. It was reported that the high expression of p53 was associated with poor

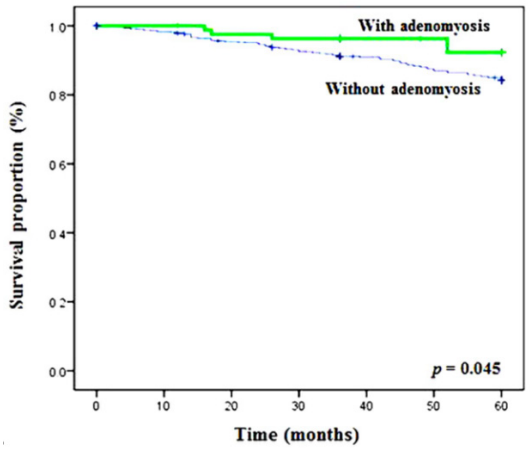

Figure 2. Survival outcomes of endometrial cancer patients, with or without adenomyosis. The *p* value was calculated based on log-rank test.

prognosis of endometrial carcinoma patients [16]. In the present cohort, positive expression of p53 was found in 53.39% of patients with adenomyosis (who had better prognosis), and 63.32% of patients without adenomyosis. The link between the presence of adenomyosis and the positive expression of p53 remains unclear and warrants further investigation.

The inflammatory signals were not investigated in this study, but other reports showed that the unique cytokine profile in patients with adenomyosis may alleviate the endometrial cancer progression. It is known that patients with adenomyosis have increased interferon (IFN)-α, IFN-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-10 [17, 18]. The increase of these cytokines may amplify the host anti-tumor immune activities [19-22]. On the other hand, adenomyosis is known to have decreased secretions of cytokines, such as IL-8, IL-1β, and epidermal growth factor (EGF) that have an important role in tumor progression [18, 23, 24]. In summary, both the clinical and molecular studies from current and previous findings suggested the protective role of adenomyosis in the progression of endometrial carcinoma.

In this study, patients with adenomyosis had a significantly higher 5-year survival rate than patients without adenomyosis (92.1% vs. 84.1%), which is consistent with other reports [13, 25]. This may be partly attributed to the lower expression of p53 in endometrial carcinoma. The presence of adenomyosis, however, was not an independent prognostic factor of patients' survival. In addition to the expression of p53, patients with adenomyosis are generally younger, had earlier stage and lower grade of tumor, reduced myometrial invasion, and lymph node metastasis.

In conclusion, patients with adenomyosis were associated with less aggressive behavior of the tumors and the presence of adenomyosis may be a protective factor of endometrial carcinoma that is associated with better prognosis.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.
[2] Garcia L and Isaacson K. Adenomyosis: review of the literature. J Minim Invasive Gynecol 2011; 18: 428-37.
[3] Benagiano G, Habiba M and Brosens I. The pathophysiology of uterine adenomyosis: an update. Fertil Steril 2012; 98: 572-9.
[4] Kucera E, Hejda V, Dankovcik R, Valha P, Dudas M, Feyereisl J. Malignant changes in adenomyosis in patients with endometrioid adenocarcinoma. Eur J Gynaecol Oncol 2011; 32: 182-4.
[5] Ismiil N, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Ackerman I, Thomas G, Covens A, Khalifa MA. Adenomyosis involved by endometrial adenocarcinoma is a significant risk factor for deep myometrial invasion. Ann Diagn Pathol 2007; 11: 252-7.
[6] Mittal KR and Barwick KW. Endometrial adenocarcinoma involving adenomyosis without true myometrial invasion is characterized by frequent preceding estrogen therapy, low histologic grades, and excellent prognosis. Gynecol Oncol 1993; 49: 197-201.

[7] Jacques SM and Lawrence WD. Endometrial adenocarcinoma with variable-level myometrial involvement limited to adenomyosis: a clinicopathologic study of 23 cases. Gynecol Oncol 1990; 37: 401-7.
[8] Seidman JD and Kjerulff KH. Pathologic findings from the Maryland Women's health study: practice patterns in the diagnosis of adenomyosis. Int J Gynecol Pathol 1996; 15: 217-21.
[9] Boes AS, Tousseyn T, Vandenput I, Timmerman D, Vergote I, Moerman P, Amant F. Pitfall in the diagnosis of endometrial cancer: case report of an endometrioid adenocarcinoma arising from uterine adenomyosis. Eur J Gynaecol Oncol 2011; 32: 431-4.
[10] Abushahin N, Zhang T, Chiang S, Zhang X, Hatch K, Zheng W. Serous endometrial intraepithelial carcinoma arising in adenomyosis: a report of 5 cases. Int J Gynecol Pathol 2011; 30: 271-81.
[11] Quick CM, May T, Horowitz NS, Nucci MR. Low-grade, low-stage endometrioid endometrial adenocarcinoma: a clinicopathologic analysis of 324 cases focusing on frequency and pattern of myoinvasion. Int J Gynecol Pathol 2012; 31: 337-43.
[12] Ismiil ND, Rasty G, Ghorab Z, Nofech-Mozes S, Bernardini M, Thomas G, Ackerman I, Covens A, Khalifa MA. Adenomyosis is associated with myometrial invasion by FIGO 1 endometrial adenocarcinoma. Int J Gynecol Pathol 2007; 26: 278-83.
[13] Matsuo K, Cahoon SS, Gualtieri M, Scannell CA, Jung CE, Takano T, Paulson RJ, Muderspach LI, Roman LD. Significance of adenomyosis on tumor progression and survival outcome of endometrial cancer. Ann Surg Oncol 2014; 21: 4246-55.
[14] Mehasseb MK, Bell SC, Brown L, Pringle JH, Habiba M. Phenotypic characterisation of the inner and outer myometrium in normal and adenomyotic uteri. Gynecol Obstet Invest 2011; 71: 217-24.
[15] Musa F, Frey MK, Im HB, Chekmareva M, Ellenson LH, Holcomb K. Does the presence of adenomyosis and lymphovascular space invasion affect lymph node status in patients with endometrioid adenocarcinoma of the endometrium? Am J Obstet Gynecol 2012; 207: 417 e1-6.
[16] Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer 2000; 88: 814-24.
[17] Wang F, Li H, Yang Z, Du X, Cui M, Wen Z. Expression of interleukin-10 in patients with adenomyosis. Fertil Steril 2009; 91: 1681-5.
[18] Sotnikova N, Antsiferova I and Malyshkina A. Cytokine network of eutopic and ectopic endometrium in women with adenomyosis. Am J Reprod Immunol 2002; 47: 251-5.
[19] Ikeda H, Old LJ and Schreiber RD. The roles of IFN gamma in protection against tumor development and cancer immunoediting. Cytokine Growth Factor Rev 2002; 13: 95-109.
[20] Ferrantini M, Capone I and Belardelli F. Interferon-alpha and cancer: mechanisms of action and new perspectives of clinical use. Biochimie 2007; 89: 884-93.
[21] Tagashira Y, Taniguchi F, Harada T, Ikeda A, Watanabe A, Terakawa N. Interleukin-10 attenuates TNF-alpha-induced interleukin-6 production in endometriotic stromal cells. Fertil Steril 2009; 91 Suppl: 2185-92.
[22] van Horssen R, Ten Hagen TL and Eggermont AM. TNF-alpha in cancer treatment: molecular insights, antitumor effects, and clinical utility. Oncologist 2006; 11: 397-408.
[23] Zitvogel L, Kepp O, Galluzzi L, Kroemer G. Inflammasomes in carcinogenesis and anticancer immune responses. Nat Immunol 2012; 13: 343-51.
[24] Palena C, Hamilton DH and Fernando RI. Influence of IL-8 on the epithelial-mesenchymal transition and the tumor microenvironment. Future Oncol 2012; 8: 713-22.
[25] Gizzo S, Patrelli TS, Dall'asta A, Di Gangi S, Giordano G, Migliavacca C, Monica M, Merisio C, Nardelli GB, Quaranta M, Noventa M, Berretta R. Coexistence of adenomyosis and endometrioid endometrial cancer: role in surgical guidance and prognosis estimation. Oncol Lett 2016; 11: 1213-1219.

Table S1. The characteristics of the surgical procedures

	Total N = 1584	With Adenomyosis N = 150	Without Adenomyosis N = 1434	χ^2	*P*
Hysterectomy type					
Adbominal/vaginal	56.50%	45.33%	57.67%		
Laparoscopic	43.5%	54.67%	42.33%	0.501	0.479
Hysterectomy	89.84%	95.33%	89.26%		
Radical Hysterectomy	2.53%	1.33%	2.65%		
Modified radical hysterectomy	7.64%	3.33%	8.09%	5.433	0.066
Adnexectomy					
Yes	99.24%	99.33%	199.23%		
No	0.76%	0.67%	0.77%	0.018	0.893
Pelvic lymph node excision					
Yes	89.14%	90%	89.05%		
No	10.86%	10%	10.95%	0.126	0.722
Aortic lymph node excision					
Yes	56.76%	64%	55.93%		
No	43.24%	36%	44.07%	3.604	0.058
Number of LN					
Median	20	20	20		0.514