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ORIGINAL ARTICLE

Concomitant endometriosis in malignant and borderline ovarian tumours*

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ABSTRACT

The aim of the study was to reveal the prevalence of concomitant endometriosis in malignant and borderline ovarian tumours. A retrospective analysis was performed of 530 patients with malignant ovarian tumours and 131 with borderline ovarian tumours, who underwent surgery in our hospital between 1995 and 2011. Forty-eight (7.3%) of 661 patients with malignant and borderline ovarian tumours were associated with endometriosis. Of the 48 endometriosis cases, 73% of those were atypical. Infertility was noted in 38% of patients with endometriosis-associated ovarian tumours. The most frequently endometriosis-associated subtypes were endometrioid (33%) and clear cell (18%) histologies. Of endometriosis-associated endometrioid and clear cell ovarian tumours, 70% were early stage and 60% were premenopausal. The prevalence of concomitant endometriosis in borderline tumours (12%) was found to be significantly higher than that found in the malignant ones (6%; $p = .02$). Of 32 endometriosis-associated malignant ovarian tumours, 69% were FIGO stages I and II. In conclusion, ovarian endometriosis is seen with both malignant and borderline ovarian tumours, the association being significant with borderline tumours. Fortunately, the endometriosis-associated malignant ovarian tumours are mostly early stage.

IMPACT STATEMENT

- **What is already known on this subject?** Epidemiologic data suggest that endometriosis has malignant potential. However, a subgroup of women with endometriosis at a high risk for ovarian cancer is yet to be clarified. Currently, endometriosis and ovarian cancer association does not seem to have a clinical implication.
- **What do the results of this study add?** The findings of this study revealed that nearly 75% of endometriosis-associated ovarian tumours were of atypical endometriosis. Half of endometriosis-associated ovarian tumour cases were of endometrioid/clear cell histology and 70% were early-stage. Endometriosis was significantly associated with borderline ovarian tumours and the endometriosis-associated malignant ovarian tumours were mostly early stage.
- **What are the implications of these findings for clinical practice and/or further research?** Additional studies need to be conducted to develop screening approaches for malignant transformation or an association in women with endometriosis. Till that time, a change of current clinical practices cannot be justified. However, counselling and treating women with endometriosis who are at high risk for cancer coexistence or conversion is encouraged.

KEYWORDS

Endometriosis-associated ovarian cancer; borderline ovarian tumour; malignant ovarian tumour; endometriosis

Introduction

Endometriosis is a chronic gynaecological disorder associated mainly with subfertility and pelvic pain. The prevalence of endometriosis is 6–10% in the general population and 35–50% in women with pelvic pain and infertility (Giudice and Kao 2004). It is seen in nearly 75% of adolescent girls with chronic pelvic pain resistant to drugs (Janssen et al. 2013). Endometriosis, although a benign disorder, is strongly linked to ovarian cancer in medical literature (Heidemann et al. 2014; Králíčková and Vetvicka 2014; Nezhat et al. 2014). In subfertile women, endometriosis patients have been found to have the highest risk of developing ovarian cancer (Ness et al. 2002; Brinton et al. 2004). The association between ovarian cancer and endometriosis persisted following an adjustment for confounding factors such as parity and oral contraceptive use (Ness et al. 2002). Many studies in the literature have reported specific subtypes of ovarian cancer predominated in women with endometriosis. In previous studies, the association of endometriosis with endometrioid ovarian cancer has ranged from 8 to 38% and with clear cell ovarian carcinoma from 21% to 55% (Buis et al. 2013). Accordingly, counselling and treating women with endometriosis who are at high risk for cancer coexistence or conversion is encouraged.

In women with endometriosis-associated subfertility, the probability of undergoing surgery with a coincidental finding of an ovarian neoplasm is higher (Buis et al. 2013).

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Therefore, endometriosis-associated ovarian cancer cases are more frequently diagnosed at an early stage compared with those without endometriosis (Noli et al. 2013). Endometriosis-associated ovarian cancer has been demonstrated to be of an early stage, low grade and of a specific histology which is endometrioid or clear cell carcinoma (Wang et al. 2013a; Kim et al. 2014). The presence of endometriosis tended to be associated with a higher 10-year survival rate; however, this effect is stage dependent. No association was found between the presence of endometriosis and survival after taking the potential confounding effect of stage into account (Noli et al. 2013). Similarly in another paper, endometriosis coexistence has been suggested not to confer an improved prognosis in clear cell and endometrioid tumours (Cuff and Longacre 2012).

Our study objective was to investigate the prevalence of concomitant endometriosis in a large sample of patients with malignant and borderline ovarian tumours. The clinical characteristics of the patients with endometriosis-associated borderline ovarian tumours were compared to those of the ones with endometriosis-associated malignant ovarian tumours. The clinical features of endometrioid and clear cell ovarian tumour cases with and without concomitant endometriosis were further evaluated.

Materials and methods

All of the patients with malignant or borderline ovarian tumours (BOT) who were operated on between 1995 and 2011 in a university hospital were retrospectively evaluated. The authors published a preliminary data on this issue in 2003 and further data from a larger patient cohort was added and analysed (Oral et al. 2003). As the study was purely retrospective and non-interventional, it was not necessary to declare it to any Ethics Committee. Informed consent was obtained from all of the patients, allowing the use of their blinded clinical data for research purposes.

Each case was staged according to the FIGO staging system (Denny et al. 2012). Histologic classification was based on the WHO classification of ovarian tumours (Kurman et al. 2014). The tumours were assigned to the mixed epithelial category only when a second component represented 10% or greater of the sampled tumour tissue. The presence of endometriosis was determined both surgically and histologically. In the present study, endometriosis-associated ovarian cancer was described as follows: (1) the coexistence of carcinoma and endometriosis identified histopathologically in the same ovary; (2) the presence of endometriosis in one ovary and of ovarian cancer in the contralateral ovary, or the presence of ovarian cancer and pelvic endometriosis (Oral et al. 2003; Králíčková and Vetvicka 2014).

The diagnosis of *atypical endometriosis* was based on the histopathological criteria (Czernobilsky and Morris 1979; LaGrenade and Silverberg 1988; Ali-Fehmi et al. 2006). Endometriosis was defined as the presence of endometrial glands and stroma. *Atypical endometriosis* was defined as the presence of the architectural and cytological atypia. In *architectural atypia*, the cells show crowding and stratification. *Cytological atypia* was defined as an increased nuclear/cytoplasmic ratio, an enlarged hyperchromatic nucleus with moderate or marked pleomorphism, and an abundant pale cytoplasm. The slides of endometriosis lesions were evaluated according to these definitions (Figure 1(A,B)).

The clinical characteristics of patients with endometriosis-associated BOT were compared to those of ones with endometriosis-associated malignant ovarian tumours. Age, fertility status, parity and menopausal status were evaluated between the groups.

The data on patients with endometrioid and clear cell ovarian tumours, with and without concomitant endometriosis were then further analysed. We evaluated whether the age, fertility status, parity, menopausal status and the stage of the tumour were different between the groups.

The analysis of the data was performed using the SPSS software for Windows 21 (SPSS Inc., Chicago, IL). The data were expressed as numbers and percentages. For the comparison of the data, the Chi-square test and Students' *t*-test were used. The normality of the variables distribution was tested in using the Kolmogorov–Smirnov test. A p value of less than .05 was considered to be statistically significant.

Results

During the years 1995–2011, a total of 661 women with ovarian tumours (530 malignant ovarian tumour and 131 BOT)

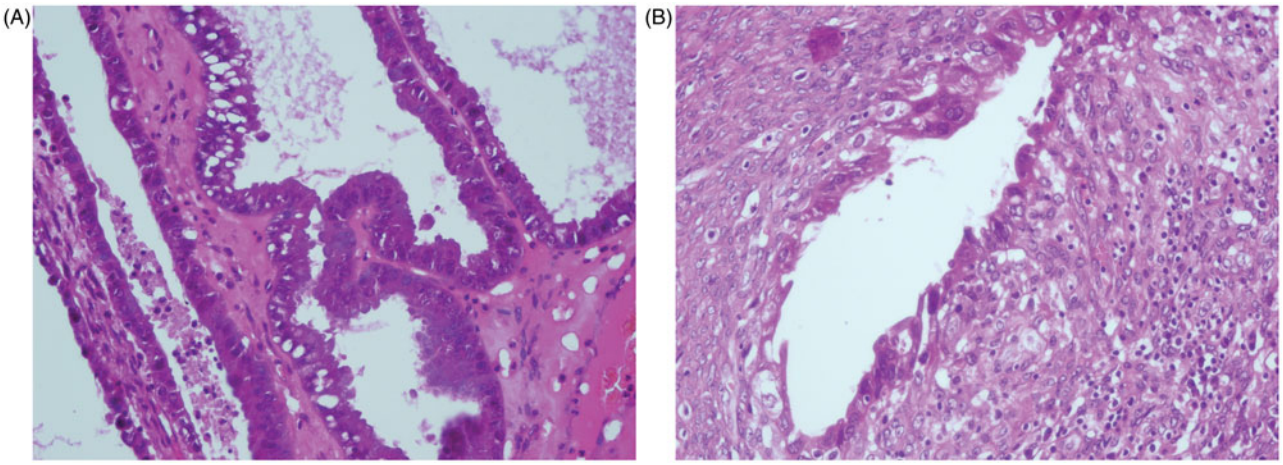

Figure 1. (A) Architectural atypia in atypical endometriosis. HE ×40. (B) Cytological atypia in atypical endometriosis.

were retrospectively analysed. Serous adenocarcinoma was the most frequently encountered histological subtype (233 women, 35%). The other histologies were mixed tumours (87 women, 13%), endometrioid carcinoma (55 women, 8%), mucinous carcinoma (42 women, 6%), clear cell carcinoma (27 women, 4%), borderline mucinous tumour (68 women, 10%), borderline serous tumour (54 women, 8%), borderline endometrioid tumour (five women, 0.8%), borderline clear cell tumour (one woman, 0.2%), borderline mixed type tumour (three women, 0.5%) and others (86 women, 13%).

Endometriosis was found in 48 of 661 cases (7.3%). The mean age of women with endometriosis-associated ovarian tumour was 44 years (range 22–70). Thirteen of 48 cases (27%) were nulliparous and sixteen (33%) were postmenopausal. Of those 48 cases, 15 (31%) were right-sided, 19 (40%) were left-sided and 14 (29%) were bilateral. Of 48 endometriosis-associated ovarian tumour cases, 35 (73%) were atypical (Table 1). Of 35 atypical endometriosis cases, 17 (49%) were found to be associated with endometrioid carcinoma and 11 (31.4%) with BOT. Of 32 endometriosis-associated malignant ovarian tumours, 22 cases (69%) were FIGO stages I and II. The prevalence of endometriosis in each histological subtype of ovarian cancer is demonstrated in Table 1. Half of the cases were endometrioid and clear cell types.

The prevalence of endometriosis in women with BOT was found to be significantly higher than that in women with malignant ovarian tumours (12% versus 6%; $p = .02$).

Table 1. Prevalence of concomitant endometriosis in each histological subtype of ovarian tumours.

Histological type (*n*)	Atypical endometriosis (*n*)	Typical endometriosis (*n*)	Total *n* (%)
Endometrioid[a] (60)	17	3	20 (33.3)
Clear cell[a] (28)	3	2	5 (18)
Mixed[a] (90)	5	1	6 (6.7)
Mucinous[a] (110)	4	3	7 (6.4)
Serous[a] (287)	6	3	9 (3.1)
Others (86)	0	1	1 (1)
Total (661)	35	13	48 (7.3)

[a]Malignant and borderline tumours.
Of 32 endometriosis-associated malignant ovarian tumours; 15 were endometrioid adenocarcinoma, four were clear cell adenocarcinoma, three were mixed carcinoma (one serous + mucinous + clear cell, one endometrioid + mucinous + serous, one serous + mucinous), two were mucinous adenocarcinoma, seven were serous adenocarcinoma and one was carcinosarcoma.
Of 16 endometirosis-associated borderline ovarian tumours; six were mucinous, five were endometrioid, two were serous, one was clear cell and two were mixed type (one clear cell + serous, one clear cell + endometrioid).

The clinical characteristics of endometriosis-associated BOT and malignant ovarian tumours were evaluated. No significant difference was noted with respect to fertility status and parity (Table 2). The patients with endometriosis-associated BOT were significantly younger and premenopausal compared with those with endometriosis-associated malignant ovarian tumours (Table 2). Infertility was noted in nearly half of the patients with endometriosis-associated BOT and 1/3 of the patients with endometriosis-associated malignant ovarian tumours (Table 2).

Of 48 endometriosis-associated ovarian tumour cases, 52% were of endometrioid and clear cell types. Of all endometrioid ovarian tumour (EOT) cases, 20 (33.3%) were associated with endometriosis. Of all clear cell ovarian tumour (CCOT) cases, five (18%) were associated with endometriosis. When the clinical characteristics of endometriosis-associated EOT/CCOT (25 cases) were compared with those of non-endometriosis-associated EOT/CCOT (63 cases), the patients with endometriosis tended to be significantly younger than those without endometriosis, and the parity was statistically lower in those with endometriosis (Table 3). Infertility was noted in 1/3 of the endometriosis-associated EOT/CCOT cases.

Discussion

Clear evidence exists in the literature revealing that endometriosis is linked to ovarian cancer (Králíčková and Vetvicka 2014). However, risk factors and clinical utility of this association are ill defined. In the current study, endometriosis is coexistent in 7.3% of ovarian tumours. Specifically, 50% of endometrioid (33%) and clear cell tumours (18%) are associated with endometriosis. Endometriosis is associated more

Table 3. Clinical characteristics of endometrioid and clear cell ovarian tumour cases with or without endometriosis.

	Endometriosis-associated EOT/CCOT ($n = 25$)	Non-endometriosis-associated EOT/CCOT ($n = 63$)	*p*
Age (years)	**45.1 ± 9.4**	**52.6 ± 11.8**	**.02**
Infertility (%)	33.3	15.2	.16
Parity (*n*)	**1.1 ± 0.2**	**1.9 ± 0.4**	**.05**
Tumour stages I and II (%)	72	61	.5
Borderline (%)	17	3	.1
Postmenopausal period (%)	39	61	.2
Endometrioid tumour (%)	78	60	
Clear cell tumour (%)	22	40	

EOT: endometrioid ovarian tumour; CCOT: clear cell ovarian tumour. Bold values signifies $p < 0.5$.

Table 2. Clinical characteristics of patients with borderline and malignant ovarian tumours classified according to endometriosis coexistence.

	EAMOT ($n = 32$)	EABOT ($n = 16$)	nEAMOT ($n = 498$)	nEABOT ($n = 115$)
Age (years)	49.2 ± 10.4[a]	37.3 ± 8.2[a]	54.3 ± 14.8[c]	42.3 ± 15.5[c]
Infertility (%)	31.3	46.2	[d]	[d]
Parity (*n*)	1.9 ± 0.7	1.7 ± 0.5	1.9 ± 0.4	1.2 ± 1.1
Postmenopausal period (%)	47.6[b]	7.7[b]	78.5	74.8
Atypical endometriosis (%)	75	69	–	–

EAMOT: endometriosis-associated malignant ovarian tumour; EABOT: endometriosis-associated borderline ovarian tumour; nEAMOT: non-endometriosis-associated malignant ovarian tumour; nEABOT: non-endometriosis-associated borderline ovarian tumour.
[a]$p < .001$.
[b]$p = .02$.
[c]$p < .0001$.
[d]Data not existent.

with BOT (12%) compared with malignant ones (6%), and endometriosis-associated malignant ovarian tumours are mostly early stage (70%).

The relationship between endometriosis and ovarian cancer has been sought for a long time. It is strongly established that endometriosis is associated with an increased risk of ovarian cancer, especially with endometrioid and clear cell types (Vlahos et al. 2010; Pearce et al. 2012; Buis et al. 2013; Kim et al. 2014). Kurman and Shih (2004, 2016) proposed a dualistic model of ovarian tumorigenesis (type I and type II tumours) integrating histopathologic characteristics with the molecular features and biological behaviour. Type I tumours include endometriosis-related tumours which are endometrioid, clear-cell, and seromucinous carcinoma. The type I tumours were found to develop from borderline or atypical proliferative tumours, be frequently at early stage, low grade, slow growing, had good overall clinical outcome and an early detection was thought might be possible. Endometriosis was reported to be a risk factor for type I ovarian carcinomas, specifically a potential precursor lesion of endometrioid and clear cell tumours (Kurman and Shih 2016). The prevalence of ovarian cancer in women with endometriosis was reported to be 2–17% (Heidemann et al. 2014). The prevalence of endometriosis in women with ovarian cancer was reported to be 3.4–52.6% (Heidemann et al. 2014). In the current study, the prevalence of endometriosis in patients with ovarian cancer was found to be 7.3%.

Endometriosis-associated tumorigenesis may involve multiple biochemical pathways, dominance of certain cytokines, hyper-estrogenic hormonal milieu, genetic mutations including PTEN, PIK3CA, ARID1A, Wnt/β-catenin, microsatellite instability, Src, and KRAS and free iron-induced oxidative stress due to repeated haemorrhaging, causing iron accumulation (Higashiura et al. 2012; Munksgaard and Blaakaer 2012; Ruderman and Pavone 2017). Hypothesis for the contribution of endometriosis to the development of ovarian cancer was proposed based on the information that the cause of endometriosis was retrograde menstruation; that is the backward flow of menstrual fluid through the fallopian tubes into the pelvis (Paulson 1997). This is supported by the decreased prevalence of ovarian cancer in women with tubal ligation or hysterectomy (Cibula et al. 2011; Rice et al. 2012; Saraswat et al. 2018). Similarly, a high parity and oral contraceptive use decrease the ovarian cancer risk in women with endometriosis, most probably reducing inflammation, the number of menstruel cycles and the amount of menstrual flow (Ness 2003; Giudice and Kao 2004; Saraswat et al. 2018). In the current study, the parity was significantly lower and the infertility rate was two-fold in endometriosis-associated EOT/CCOT cases compared to those without endometriosis.

Epithelial ovarian cancer includes five major histological subtypes classified based on molecular, clinical and pathological features: low-grade serous, high-grade serous, mucinous, endometrioid and clear cell (Gilks et al. 2008; Gilks 2010). Endometriosis co-occurence varies according to the histological subtype. The ovarian neoplasms associated with endometriosis may be classified as follows: (1) epithelial ovarian cancers (endometrioid adenocarcinoma and clear cell carcinoma), (2) other müllerian tumours (müllerian-type mucinous borderline tumours, serous borderline tumours) and (3) sarcomas (adenosarcoma, endometrial stromal sarcoma) (Higashiura et al. 2012). In the present study, 50% of endometriosis-associated ovarian tumours was of endometrioid (33%) and clear cell (18%) subtype. Women with endometriosis-associated EOT/CCOT were significantly younger, the parity was lower, 70% early-stage and 60% premenopausal compared with those without endometriosis. Similarly, in a recent study in 188 women with EOT, concurrent endometriosis was identified in 17% and those cases were 5 years younger; more likely to have early-stage disease compared with those without endometriosis (Wang et al. 2013b). However, a significant prognostic effect of concurrent endometriosis for disease-free survival disappeared in multivariate analysis (Wang et al. 2013b).

Female infertility was found to be associated with increased risk of endometrioid/clear cell tumours but not any of other histological types (Merritt et al. 2013). Similarly, a history of endometriosis increased the risk for endometrioid/clear cell tumours with the greatest risk increase for clear cell histology (Pearce et al. 2012; Merritt et al. 2013). In the study by Merritt et al. (2013), having at least one child was shown to decrease the risk of developing CCOT. High parity and thus an increased number of children also was shown to protect against the development of EOT and an additional risk reduction was observed with each subsequent pregnancy (Merritt et al. 2013). Previous tubal ligation or hysterectomy was also protective for EOT/CCOT (Merritt et al. 2013). Finding of protective effect of tubal ligation for EOT adds to the hypothesis that the retrograde flow of endometrium through the tubes may lead to the development of EOT (Gates et al. 2010; Cibula et al. 2011; Rice et al. 2012). Maybe in the future, tubal ligation will be recommended to women with endometriosis as a measure to decrease the risk of EOT development. In the current study, the infertility rate is high both in endometriosis-associated malignant ovarian tumours (33%) and BOT (46%). Similarly, one-third of endometriosis-associated EOT/CCOT are infertile.

Ovarian endometriotic foci showing *epithelial cytologic atypia* may be precursors of cancer (Bedaiwy et al. 2009). Based on this assumption, the surgical excision of these *foci* should be considered rather than their simple cauterisation. Women diagnosed with atypical endometriosis were recommended to be referred to a gynaecologic oncologist because of their possible risk of progression to endometriosis-associated ovarian carcinoma (Wilbur et al. 2017). The authors advocated that ovarian surgery in women with endometriosis may lower the risk of invasive cancer (Rossing et al. 2008). In the present study, of 48 endometriosis-associated ovarian tumour cases, 73% were atypical and of those atypical endometriosis cases, 49% were associated with EOT. Atypical endometriosis was identified in 5.3% of ovarian tumours, 10.7% of CCOT and 28.3% of EOT. The literature regards to the prevalence of atypical endometriosis in ovarian tumours is shown in Table 4. It varies in different papers. It could be the result of genetic and immunologic differences in different ethnic groups. Furthermore, atypical endometriosis has not been

Table 4. Prevalence of atypical endometriosis in women with ovarian tumours.

Fukunaga et al. (1997)	15% (33/224)
Ogawa et al. (2000)	23% (29/127)
Guo et al. (2001)	42% (5/12 endometrioid ovarian ca)
Oral et al. (2003)	4% (8/183)
Zhao et al. (2011)	35% (28/79 clear cell tm)
Terada (2012)	54% (7/13 clear cell tm)

Table 5. Prevalence of endometriosis in women with borderline ovarian tumours.

Bell and Scully (1985)	15% (3/20)
Rutgers and Scully (1988)	53% (19/36 müllerian-type BOT)
Snyder et al. (1988)	52% (16/31 endometrioid BOT)
Fukunaga et al. (1997)	9.5% (4/42)
Bell and Kurman (2000)	42% (14/33 endometrioid BOT)
Oral et al. (2003)	13% (3/23)
Roth et al. (2003)	63% (19/30 endometrioid BOT)
Zhao et al. (2011)	34% (14/41 clear cell BOT)
Pearce et al. (2012)	8.8% (168/1907)
Uzan et al. (2012)	19% (3/16 endometrioid BOT)

properly defined among pathologists. Therefore, variations in the definition might be another reason for different ratios in previous studies.

The association between endometriosis and BOT is of clinical significance. In the present study, the prevalence of endometriosis in women with BOT is 12%; significantly higher than that in malignant ovarian tumours (6%). In a large cohort, no association was found between a history of endometriosis and BOT (Pearce et al. 2012). However, in that study only serous and mucinous borderline tumours were analysed. In our study, all BOT, including rarely seen endometrioid and clear cell histologies, were included. BOT are usually of serous or mucinous subtype; clear cell and endometrioid BOT are rare (Acs 2005). Endometriosis, on the other hand, is more commonly associated with clear cell and endometrioid subtype of invasive ovarian cancer (Pearce et al. 2012). In the present study, nearly half of the patients with endometriosis-associated BOT are infertile. A recent study demonstrated an increased rate of BOT in women who underwent IVF treatment (Stewart et al. 2013a). However, in that study, BOT risk was not increased in women with endometriosis. This result is contradictory to the situation with invasive epithelial ovarian cancer, that is history of endometriosis was associated with an increased risk of invasive ovarian cancer (Pearce et al. 2012). This result is also contradictory to the findings of Stewart et al. (2013b), who demonstrated that both parous and nulliparous women with endometriosis had an increased risk of ovarian cancer, a slight increase in parous but a marked increase, three-fold, in nulliparous women. The literature with regard to the prevalence of endometriosis in women with BOT is shown in Table 5.

To conclude, endometriosis coexists in 7.3% of patients with ovarian tumours. Half of endometriosis-associated ovarian tumour cases are of endometrioid/clear cell histology and 70% are at an early-stage. Endometriosis is significantly associated with borderline ovarian tumours, and endometriosis-associated malignant ovarian tumours are usually early stage. Future genetic and immunologic studies are warranted to identify the clinical tools for ovarian cancer development or association with the endometriosis cases.

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Disclosure statement

The authors have declared that no conflict of interest exists.

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