## นิพนธ์ต้นฉบับ

# พยาธิวิทยาของมะเร็งรังไข่ชนิดเยื่อบุผิวที่โรงพยาบาลพระปกเกล้า: ศึกษาย้อนหลัง 5 ปี

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## บทคัดย่อ

**ที่มาของปัญหา :** มะเร็งรังไข่เป็นสาเหตุของการเสียชีวิตอันดับต้นๆ โดยที่พบมากที่สุดคือมะเร็งรังไข่ชนิดเยื่อบุผิว ซึ่งผลการรักษานั้นขึ้นอยู่กับระยะของโรค รอยโรคที่เหลืออยู่หลังการผ่าตัด

**วัตถุประสงค์ :** วัตถุประสงค์หลักคือ ศึกษาถึงพยาธิวิทยาของมะเร็งรังไข่ชนิดเยื่อบุผิว วัตถุประสงค์รองคือ ศึกษาถึงผลการผ่าตัด ปัจจัยที่มีผลต่อการผ่าตัดและวิธีการรักษาในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิว

**วัสดุและวิธีการ :** เป็นการศึกษาเชิงพรรณนาแบบย้อนหลังในผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่เข้ารับการรักษาในโรงพยาบาลพระปกเกล้าระหว่างเดือนมกราคม พ.ศ. 2554 ถึงเดือนธันวาคม พ.ศ. 2559 โดยเก็บจำนวนอุบัติการณ์จำแนกตามพยาธิวิทยา ระยะของโรค ผลการผ่าตัดรวมถึงการรักษาที่ได้รับหลังจากการผ่าตัด

**ผลการศึกษา :** มีผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวรายใหม่ทั้งหมด 172 คน พยาธิวิทยาที่พบมากที่สุดคือชนิด Serous (51 ราย, ร้อยละ 29.7) โดยพยาธิวิทยานั้นไม่ได้มีผลต่อผลการผ่าตัดอย่างมีนัยสำคัญทางสถิติ และเมื่อแบ่งพยาธิวิทยาตามความรุนแรงก็จะพบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ในเรื่องของการรักษาเพิ่มเติม ($p$ = 0.151) และตำแหน่งที่โรคกระจายไป ($p$ = 0.364) และพบว่า ความอ้วน (AOR = 2.37, 95%CI 1.09-5.15, $p$ = 0.03) และระยะของโรคที่เป็นระยะลุกลาม (AOR = 4.78, 95%CI 2.11-10.78, $p$ < 0.001) คือปัจจัยที่ส่งผลต่อการผ่าตัด

**สรุป :** พบว่ามะเร็งรังไข่ชนิดเยื่อบุผิวที่พบมากที่สุดคือชนิด serous และปัจจัยที่ส่งผลต่อผลการผ่าตัดคือ ความอ้วนและมะเร็งระยะลุกลาม

**คำสำคัญ :** มะเร็งรังไข่ชนิดเยื่อบุผิว; ผลการผ่าตัด; การรักษา; ปัจจัยเสี่ยง

## Original article

# Histopathological Patterns of Epithelial Ovarian Cancer at Prapokklao Hospital: A Five Years Retrospective Study

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## Abstract

**Background :** Ovarian cancer is a leading cause of death, primarily because of delays in diagnosis. Epithelial ovarian cancer (EOC) is the most common histological form of ovarian cancer. The results of treatment depend on the stage and the presence of a residual tumour after surgery.

**Objective:** The primary objective was to study the histopathological subtype of EOC in patients at Prapokklao Hospital. The secondary objectives included studying the outcomes and factors that affect the outcomes of surgery and treatment in EOC patients.

**Materials and methods:** This study is a hospital-based retrospective descriptive study which analysed the data of EOC patients in the Division of Obstetrics and Gynaecology at Prapokklao Hospital between January 2011 and December 2016. Incidences of EOC were counted, while the stage, results of surgery and adjuvant treatment after surgery were recorded.

**Results:** A total of 172 patients were included in the sampling. The most common form identified was serous cystadenocarcinoma (51 cases, 29.7%). The results of surgery were not statistically significant in terms of difference between histopathological subtypes ($p$ = 0.145). Further, there was no difference in treatment method ($p$ = 0.151), metastatic site of disease ($p$ = 0.364) between less and more aggressive histopathological subtypes. Obesity (AOR = 2.37, 95%CI 1.09-5.15, $p$ = 0.03) and advanced stage (AOR = 4.78, 95%CI 2.11-10.78, $p$ < 0.001) were factors that related to suboptimal surgery in EOC patients.

**Conclusions:** In this study, serous cystadenocarcinoma was found to be the most common of histopathological subtypes. Histopathological subtypes do not affect the outcome of surgery. Suboptimal surgery was found to be more prevalent in patients with obesity and advanced stages of illness.

**Keywords:** epithelial ovarian cancer; outcome of surgery; treatment; risk factor

## Introduction

Ovarian cancer is divided into two major subtypes: epithelial ovarian cancer [EOC], affecting 90% of sufferers, and non-epithelial ovarian cancer [germ cell, sex cord-stromal tumour], affecting 10%.[2] In the United States of America and Europe, EOC is the second most common gynaecologic malignancy. However, it has the highest mortality rate.[4,20] In Thailand, ovarian cancer is the sixth most common cancer in women[9] and the second most common gynaecologic cancer after cervical cancer (age-standardised incidence rate of 6.2 per 100,000 people)[11]. Ovarian malignancy is characterised by high mortality because roughly two-thirds of patients have advanced stages of the disease at diagnosis, with no accurate screening test and non-specific symptoms at the early stage. Thus, incidences of ovarian cancer are increasing, especially in Asia.[16]

The histopathologic subtype is one of the prognostic factors in EOC.[1,3,13] Serous cystadenocarcinoma and clear-cell carcinoma, especially in the advanced stage, offer poor prognosis, while endometrioid adenocarcinoma is detectable in the early stages, is chemo-sensitive and has a better prognosis.[21,23] Nevertheless, extensive cytoreductive surgical treatment includes hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy and infracolic omentectomy as primary treatment options for definite diagnosis, staging and tumour removal, which aim to alleviate symptoms and improve survival in all histopathologic subtypes.[2] Adjuvant chemotherapy is given to all patients except stage IA, IB grade 1 and 2. A combination of platinum and taxane is the standard regimen and aims to improve progression free survival as well as overall survival.[14,18]

From previous studies[22], the most common histopathologic subtype of EOC is serous cystadenocarcinoma (45%) followed by endometrioid carcinoma (12.6%). At King Chulalongkorn Memorial Hospital of Thailand[24], incidences of EOC were found to increase with age, with the peak being in the fifth decade of life. Proportions of endometrioid adenocarcinoma and clear cell carcinoma were increased with age. On the other hand, mucinous cystadenocarcinoma was decreased and serous cystadenocarcinoma remained constant across all age groups. The two most common histopathologic subtypes were endometrioid adenocarcinoma and clear cell carcinoma, different from other studies.

Prapokklao Hospital possessed no data concerning incidence and treatment of EOC, even in the case of ovarian cancer patients referred to the hospital for diagnosis and treatment.

In this study, the authors aim to evaluate rates of incidence according to histopathologic subtypes, treatment and surgical outcomes of EOC patients at Prapokklao Hospital from January 2011 to December 2016.

## Materials and methods

### Study design

This study was a retrospective case control study approved by the Prapokklao Hospital Institutional Review Board, No. CTIREC 021/61. This study was performed at Prapokklao Hospital, located in Chanthaburi Province, Thailand.

### Study population

The study utilised the recruitment of all medical records for EOC patients between January 2011 and December 2016. All new cases of EOC patients involving a gynaecologic oncologist team and medical records confirming diagnoses were enrolled to this study. All EOC cases were reviewed for pathological confirmation of diagnosis. Patients that were diagnosed with recurrent EOC were excluded.

### Data collection and Outcome measures

Medical records for new cases of EOC patients were reviewed and the data collected. Baseline characteristics, stage according to FIGO,25 histopathology based on WHO classification 2014[15], ultrasound findings, risk of malignancy index score, clinical presentation, treatment and surgical outcomes were recorded.

The primary outcome was the incidence of histopathologic subtypes of EOC. The secondary outcomes comprised treatment of EOC, surgical outcomes and the factors that affected those surgical outcomes.

### Statistical analysis

Data was analysed using Stata 12 (Stata Corp LLC, Texas, USA). Normal distribution of data was tested with the Kolmogorov-Smirnov test. Parametric descriptive data was expressed as mean ± SD or percentage and compared with Student t test and Chi-square test or Fisher Exact test, respectively. Nonparametric continuous data was shown as median (interquartile range; IQR) and compared with the Mann-Whitney U test. Statistical significance was considered if p value was less than 0.05.

## Results

A total of 172 new cases that were diagnosed with EOC between January 2011 and December 2016 were recruited. Mean age at time of EOC diagnosis was 52.3 years old. Baseline characteristics such as age, body mass index (BMI), menopausal status, parity, family history of cancer and RMI score were similar between less and more aggressive histopathological subtypes (table 1). The suboptimal surgery group tended to be older (53.4±12.7 versus 51.0±10.0, $p$ = 0.048). However, the optimal surgical group had more history of endometriosis [19 (24.4%) versus 12 (12.8%), $p$ = 0.049] and family history of cancer [14 (17.9%) versus 7 (7.4%), $p$ = 0.036] when compared to the suboptimal surgical group. The patients had advanced stages (stage 3 and stage 4) in both less and more aggressive pathological subtypes (64.5% and 59.3%) that were not statistically significant different between the 2 groups ($p$ = 0.266). However, when considering the results of surgery, early stage (stage 1 and 2) was ideal for surgery compared to suboptimal surgery (56.4% versus 18.1%). On the other hand, suboptimal surgery was ideal in advanced stages (stage 3 and 4) compared to optimal surgery (81.9% versus 43.6%), as shown in table 1.

**Table 1.** Demographic characteristics of the study population (N = 172)

| Characteristics | All (N=172(%)) | Aggressive Epithelial ovarian cancer | | | Results of surgery | | |
|---|---|---|---|---|---|---|---|
| | | Less aggressive (113(65.7)) | More aggressive (59(34.3)) | *p-value* | Optimal Sx (78(45.3)) | Sub optimal Sx (70(40.7)) | *p-value* |
| Age | 52.3±0.9 | 53.2±11.1 | 50.6±12.4 | 0.168 | 51.0±10.0 | 53.4±12.7 | 0.048* |
| Ethics | | | | 0.744 | | | 0.157 |
| Thai | 165 (95.9) | 108 (95.6) | 57 (96.6) | | 73 (93.6) | 92 (97.5) | |
| Non-Thai | 7 (4.1) | 5 (4.4) | 2 (3.4) | | 5 (6.4) | 2 (2.1) | |
| Status | | | | 0.136 | | | 0.105 |
| Single | 49 (28.5) | 28 (24.8) | 21 (35.6) | | 27 (34.6) | 22 (23.4) | |
| Married | 123 (71.5) | 85 (75.2) | 38 (64.4) | | 51 (65.4) | 72 (76.6) | |
| Parity | | | | 0.171 | | | |
| Nulliparity | 61 (35.5) | 36 (31.9) | 25 (42.4) | | 32 (41.0) | 29 (30.9) | |
| Multiparity | 111 (64.5) | 77 (68.1) | 34 (57.6) | | 46 (59.1) | 65 (69.1) | |
| BMI | | | | 0.696 | | | 0.105 |
| Non-obesity | 117 (68.0) | 78 (69.0) | 39 (66.1) | | 58 (74.4) | 59 (62.8) | |
| Obesity* | 55 (32.0) | 35 (31.0) | 20 (33.9) | | 20 (25.6) | 35 (37.2) | |
| Smoking | | | | 0.494 | | | 0.504 |
| No | 167 (97.1) | 109 (96.5) | 58 (98.3) | | 75 (96.2) | 92 (97.9) | |
| Yes | 5 (2.9) | 4 (3.5) | 1 (1.7) | | 3 (3.8) | 2 (2.1) | |
| Contraception | | | | 0.071 | | | 0.086 |
| Non-Hormonal | 156 (90.7) | 101 (89.4) | 55 (93.2) | | 74 (94.9) | 82 (87.2) | |
| Hormonal | 16 (9.3) | 12 (10.6) | 4 (6.8) | | 4 (5.1) | 12 (12.8) | |
| Underlying disease | | | | 0.596 | | | 0.177 |
| No | 115 (66.9) | 74 (65.5) | 41 (69.5) | | 48 (61.5) | 67 (71.3) | |
| Yes | 57 (33.1) | 39 (34.5) | 18 (30.5) | | 30 (38.5) | 27 (28.7) | |
| History of endometriosis | | | | | | | 0.049* |
| No | 141 (82.0) | 96 (85.5) | 45 (76.3) | | 59 (75.6) | 82 (87.2) | |
| Yes | 31 (18.0) | 17 (15.0) | 14 (23.7) | | 19 (24.4) | 12 (12.8) | |
| Family history of cancer | | | | 0.116 | | | 0.036* |
| No | 151 (870.8) | 96 (85.0) | 55 (93.2) | | 64 (82.1) | 87 (92.6) | |
| Yes | 21 (12.2) | 17 (15.0) | 4 (6.8) | | 14 (17.9) | 7 (7.4) | |
| Menopausal status | | | | 0.681 | | | 0.514 |
| Premenopausal | 53 (30.8) | 36 (31.9) | 17 (28.8) | | 26 (33.3) | 27 (28.7) | |
| Postmenopausal | 119 (69.2) | 77 (68.1) | 42 (71.2) | | 52 (66.7) | 67 (71.3) | |
| Ca125(Mean ±SD) | 1713.35±410.1 | 1291.43±434.7 | 2521.44±854.1 | | 1362.8±420.8 | 2004±664.9 | 0.196 |
| Stage at surgery | | | | | | | |
| 1 | 49 (28.5) | 37 (32.7) | 12 (20.3) | 0.266 | 32 (41.0) | 17 (18.1) | <0.001 |
| 2 | 12 (7.0) | 9 (8.0) | 3 (5.1) | | 12 (15.4) | 0 (0) | |
| 3 | 43 (25.0) | 26 (23.0) | 17 (28.8) | | 22 (28.2) | 21 (22.3) | |
| 4 | 68 (39.5) | 41 (36.3) | 27 (45.8) | | 12 (15.4) | 56 (59.6) | |
| RMI | | | | 0.344 | | | 0.989 |
| <200 | 33 (19.2) | 24 (21.2) | 9 (15.3) | | 15 (19.2) | 18 (19.1) | |
| >200 | 139 (80.8) | 89 (78.8) | 50 (84.7) | | 63 (80.8) | 76 (80.9) | |

EOC-E= epithelial ovarian cancer coexisting with endometriosis; EOC-NE= epithelial ovarian cancer NOT coexisting with endometriosis; *Obesity defined as body mass index ( BMI= bodyweight(kgs)/ height(meter)$^2$) more than 24.9; † underlying disease defined as medical disease diagnosed before time of admission such as diabetes mellitus, chronic kidney disease, hypertension, syphilis, chronic lung disease etc.; Less aggressive subtype=serous, mucinous, Endometrioid, Brenner; more aggressive subtype=clear cell, mixed epithelium, undifferentiated.

Table 2 exhibits that the most common histopathological subtype was serous cystadenocarcinoma (51 cases, 29.7%), followed by unclassified (33 cases, 19.2%) and endometriod adenocarcinoma (32 cases, 18.6%). About two thirds of patients had advanced stages of disease at time of diagnosis [111(64.5%) versus 61(35.5%)]. The results of surgery showed no statistically significant differences between histopathological subtypes ($p$ = 0.145).

**Table 2.** Pathology report of early stage, advanced stage epithelial ovarian cancer and results of surgery

| Pathology | N=172 | **Early stage** | **Advanced stage** | **Results of surgery** | | ***p-value*** |
|---|---|---|---|---|---|---|
| | | | | **Optimal Sx** | **Sub optimal Sx** | |
| | | **61** | **111** | **78** | **94** | |
| Serous | 51 (29.7) | 16 (26.2) | 35 (31.5) | 26 (33.3) | 25 (26.6) | 0.145 |
| Endometrioid | 32 (18.6) | 18 (29.5) | 14 (12.6) | 19 (24.4) | 13 (13.8) | |
| Mucinous | 30 (17.4) | 12 (19.7) | 18 (16.2) | 10 (12.8) | 20 (21.3) | |
| Clear cell | 20 (11.6) | 9 (14.8) | 11 (9.9) | 10 (12.8) | 10 (10.6) | |
| Brenner | 0 | 0 | 0 | 0 | 0 | |
| Mixed EOC | 5 (2.9) | 0 | 5 (4.5) | 1 (1.3) | 4 (4.3) | |
| Unclassified | 33 (19.2) | 5 (8.2) | 28 (25.2) | 11 (14.1) | 22 (23.4) | |
| Undifferentiated | 1 (6.0) | 1 (1.6) | 0 | 1 (1.3) | 0 | |

Early=epithelial ovarian cancer stage I-II; Advanced= epithelial ovarian cancer stage III-IV; EOC-E=epithelial ovarian cancer coexisting with endometriosis, EOC-NE=epithelial ovarian cancer NOT coexisting with endometriosis; Sx= surgery; Optimal surgery= residual tumor nodules each measuring 1 cm or less in maximum diameter

There was no significant difference in treatment method ($p$ = 0.151), metastatic site of disease ($p$ = 0.364) between less and more aggressive histopathological subtypes. Most EOC patients underwent surgery and adjuvant chemotherapy (119 [69.2%]) followed by neo-adjuvant chemotherapy plus interval tumour debulking surgery (25 [14.5%]). The most metastatic sites included the pelvis and abdomen (84 [48.8%]), followed by only the pelvic region (83 [48.3%]), as shown in table 3.

**Table 3.** Comparison of treatment and between less & more aggressive

| Characteristics | All | Pathological subtype | | *p*-value |
|---|---|---|---|---|
| | | Less Aggressive | More Aggressive | |
| Treatment | 172 (100) | 113 (100) | 59 (100) | 0.151 |
| Surgery Only | 5 (2.9) | 4 (3.5) | 1 (1.7) | |
| Neoadjuvant CMT+Sx | 25 (14.5) | 12 (10.6) | 13 (22.0) | |
| Surgery before CMT | 119 (69.2) | 84 (74.3) | 35 (59.3) | |
| CMT alone | 14 (8.1) | 7 (6.2) | 7 (11.9) | |
| Palliative | 9 (5.2) | 6 (5.3) | 3 (5.1) | |
| Distribution | 172 (100) | 113 (100) | 59 (100) | 0.364 |
| Pelvis | 83 (48.3) | 58 (51.3) | 25 (42.4) | |
| Abdomen-pelvis | 84 (48.8) | 51 (45.1) | 33 (55.9) | |
| Distance | 5 (2.9) | 4 (3.5) | 1 (1.7) | |

Less aggressive subtype=serous, mucinous, Endometrioid, Brenner; more aggressive subtype=clear cell, mixed epithelium, undifferentiated

When calculated for crude odd and adjusted odd ratio, obesity (AOR=2.37, 95%CI 1.09-5.15, $p$ = 0.03) and advanced stage of disease at diagnosis (AOR = 4.78, 95%CI 2.11-10.78, $p$ < 0.001) were found to be factors that related to suboptimal surgery in EOC patients, as shown in table 4.

**Table 4.** Crude odd and adjusted odd ratios of factors related to suboptimal surgery (n=172)

| Factors | Crude odd ratio | 95%CI | *p*-value | Adjusted odd ratio | 95% CI | *p*-value |
|---|---|---|---|---|---|---|
| Age | 1.018 | 0.991 - 1.045 | 0.188 | 1.016 | 0.979 - 1.053 | 0.408 |
| Postmenopausal | 1.241 | 0.648 - 2.374 | 0.515 | 1.144 | 0.467 - 2.804 | 0.769 |
| Obese | 1.720 | 0.891 - 3.322 | 0.106 | 2.367 | 1.087 - 5.154 | 0.030* |
| Family history of cancer | 2.719 | 1.038 - 7.122 | 0.042* | 1.894 | 0.610 - 5.876 | 0.269 |
| RMI >200 | 1.005 | 0.469 - 2.154 | 0.989 | 1.989 | 0.741 - 5.336 | 0.172 |
| More aggressive pathology subtype | 1.484 | 0.783 - 2.815 | 0.227 | 1.405 | 0.651 - 3.035 | 0.387 |
| EOC-E | 0.454 | 0.205 - 1.008 | 0.052 | 0.470 | 0.181 - 1.218 | 0.120 |
| Advanced stage | 5.862 | 2.940 - 11.687 | < 0.001* | 4.775 | 2.114 - 10.784 | < 0.001* |

## Discussion

In this study, the incidence of EOC over 5 years (January 2011 - December 2016) was 172. The most prevalent histopathological subtype was serous cystadenocarcinoma, which is correspondent to global previous studies,[5,17,22] but different from previous study in Thailand,[24] which found that endometrioid

adenocarcinoma was the most histopathological subtype. The mean age of EOC was 52.3 years old, which was similar to a recent study in Thailand,[24] which showed patients were affected by reproductive factors. Further, most patients were menopausal, possibly due to estrogen transducing the pro-metastatic pathways via nuclear estrogen receptors (ER) and conforms to epidemiological study[8,19] that shows elevation incidence of ovarian cancer in postmenopausal women who received estrogen. The stage at diagnosis was advanced (64.5%), which could be due to EOC patients displaying no symptoms in the early stage. The risk factors for EOC include low parity, age, early menarche and late menopause.[2] In the current study, however, most patients were married and multiparity, but showed no statistically significant difference. In previous cohort studies and meta-analysis, it was found that cigarette smoking increased the risk of ovarian mucinous cystadenocarcinoma, but did not increase the risk of serious or endometrioid adenocarcinoma.[6,10] This was correlated with a previous study by the authors that found low prevalence of cigarette smoking as a reason for low incidence of mucinous cystadenocarcinoma. At present, the population of Chanthaburi Province and Thailand in general has adapted more westernised forms of diet and lifestyles, leading to earlier menarche, decreased parity, increased obesity associated with compounded exposure of estrogen and endometriosis resulting in increased endometrioid and clear cell carcinoma.[7]

Histopathologic subtype was one of the prognostic factors for patients with EOC. In this study, however, histopathological subtype was not influential on the stage at diagnosis, treatment strategies or results of surgery. Standard treatment strategy for EOC is surgery for definite diagnosis, staging and tumour removal aimed at alleviating symptoms.[2] In this study, most patients received surgery and adjuvant chemotherapy for primary treatment, followed by neoadjuvant chemotherapy plus debulking surgery.

This study demonstrated the univariate and multivariate analysis of factors that are associated with the results of surgery in table 4. It was found that obesity and advanced stage of disease at diagnosis were factors that related to suboptimal surgery in EOC patients. The results were matched with knowledge that advanced stage of disease, more residual disease after primary surgery had inferior outcomes for treatment.[2] Moreover, obesity may be associated with higher estrogen levels, which increase the risk for clear cell carcinoma (poorly differentiated, very aggressive subtype). Prognosis is worse than for other histological subtypes and advanced stage at diagnosis, meaning this may affect the results of surgery.

One limitation of this study was the small

sample population used. This was due to the fact that the hospital only recently had gynaecologic oncology. Further, this study was retrospective, so could not establish overall and disease-free survival statistics for EOC patients. A larger sample size and extended follow-up period is needed to determine these outcomes. Furthermore, the hospital is a tertiary care centre in Eastern Thailand. As such, the sample might not be representative of all Thai female patients.

To the best of the authors' knowledge, this study was the first to report the incidence, histological subtypes and surgical outcomes of EOC patients in Chanthaburi Province, Thailand.

In conclusion, the incidence of EOC at Prapokklao Hospital was 172 between January 2011 and December 2016. Serous cystadenocarcinoma was the most common histopathological subtype, expressing different distribution from previous studies in Thailand. Nevertheless, histopathological subtype did not affect the outcomes of surgery in this study. Most patients received surgery and adjuvant chemotherapy for first-line treatment. The factors that caused suboptimal surgery included obesity and advanced stage of disease at diagnosis.

**Conflicts of interest:**

The authors declare that there are no conflicts of interest regarding this study.

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