

Prognostic Significance of Systematic Lymphadenectomy as Part of Primary Debulking Surgery in Patients with Ovarian Cancer

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ABSTRACT

Background: worldwide, ovarian cancer is diagnosed in more than 200,000 women yearly and accounts for over 125,000 deaths. Unfortunately, about 70% of cases are diagnosed in an advanced-stage with evidence of upper abdominal spread in approximately half of these.

Aim of the Work: was to review the surgical management of female patients with ovarian cancer including intraperitoneal complete cytoreduction and systematic lymphadenectomy to show prognosis, post operative morbidities, recurrence and follow up.

Patients and Methods: this study was conducted at Al-Azhar university hospitals and El Agousa police hospital – Ministry of interior - on 20 female patients who suffered from different stages of epithelial ovarian cancer with stage II, none bulky stage III, and only One patient with bilateral ovarian cancer stage Ic.

Results: This is study conducted on female patients with ovarian cancer the mean age of the studied patients was 51.35 years ranging from 37-64 years. 55% of patients represented with abdominal distension, 50% had abdominal pain, 40% abdominal discomfort, 15% had abnormal bleeding, 65% had nonspecific GIT manifestation, 20% had urinary symptoms and 10% had back pain.

Conclusion: Although the relationship between the retroperitoneal spread of lymph nodes and patient prognosis has been demonstrated in several studies. Lymphadenectomy, as a routine treatment procedure in ovarian cancer, remains controversial. Moreover, systematic lymphadenectomy often prolongs operation times, which may result in additional surgical complications such as lymphocele, lymphatic obstruction, lymphocysts and lymphedema, however these complications may be alleviated, and better outcome occurred by proper intra operative and post operative management by expert gynecological oncologist involvement and leveraging adequate instruments, which can eventually improve survival.

Keywords: Systematic Lymphadenectomy - Ovarian Cancer - Primary Debulking Surgery.

INTRODUCTION

Ovarian cancer is the second most lethal gynecologic malignancy worldwide, and the majority of women present with an advanced stage of the disease. Primary cytoreductive surgery followed by platinum and taxane combination chemotherapy is the standard treatment of this disease⁽¹⁾.

Peritoneal implantation by exfoliation of tumor cells and lymphatic dissemination are common routes of spread in ovarian cancer, so cytoreductive surgery should include both intraperitoneal and retroperitoneal surgical procedures. In recent years, there has been growing recognition that radical pelvic and abdominal cytoreductive procedures are associated with a favorable prognosis in patients with advanced ovarian cancer, and a

number of studies have demonstrated the importance of maximal cytoreductive surgical effort minimizing residual disease⁽²⁾.

However, the role of lymphadenectomy as part of maximal debulking surgery is still controversial. Some investigators have reported that systematic (complete) lymphadenectomy removes bulky or microscopic nodal diseases and might result in the improvement of survival in patients with advanced ovarian cancer⁽³⁾.

A meta-analysis from nine studies concluded that systematic lymphadenectomy might improve overall survival in advanced ovarian cancer⁽⁴⁾.

A recent retrospective review analyzing data from previous randomized

trials demonstrated that a survival Benefit may be associated with lymphadenectomy in advanced ovarian cancer patients ⁽⁵⁾.

However, other investigators have questioned the therapeutic efficacy of systematic lymphadenectomy ⁽⁶⁾.

AIM OF THE WORK

The aim of this work is to review the surgical management of female patients with ovarian cancer including intraperitoneal complete cytoreduction and systematic lymphadenectomy to explain prognosis, postoperative morbidities, recurrence and follow up.

PATIENTS AND METHODS

After approval of the local ethics committee, informed consent forms were signed by all participants.

This study was conducted at Al Azhar university hospitals and El Agousa police hospital – Ministry of interior on 20 female patients suffered from different stages of epithelial ovarian cancer with the following inclusion criteria:

Patients with stage II, non-bulky stage III and only One patient with bilateral ovarian cancer stage Ic. Preoperative evaluation included patient's history, age, comorbidities and clinical pictures.

Patients were clinically examined in the laboratory by taking blood samples for a complete blood picture, liver and kidney function tests, blood sugar, coagulation profile and tumor marker CA-125. Moreover, Radiological investigations followed including chest X-ray, pelviabdominal Ultrasound, transvaginal Ultrasound, CT abdomen and pelvis with contrast. Additionally, PET-CT, MRI and Endoscopic examination were performed when indicated by clinical findings.

Diagnosis of malignancy was done by considering:

(1) Radiological criteria for suspicious malignancy: complex mass with solid component involving pelvic structure, enlarged pelvic and/or para-aortic lymph nodes, omental masses, peritoneal nodules. Metabolically highly active by PET-CT

(2) Findings of omental mass or ascetic fluid cytology biopsy.

(3) Findings of Intra-operative frozen section of the ovarian masses in patients with uncertain malignancy.

Intra-operative method:

Patients underwent surgical staging in form of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, aspiration of ascites, biopsy from peritoneal surface, maximal cytoreduction. Except one unmarried patient refuse panhysterectomy so fertility preserving surgery was done. Bilateral pelvic lymphadenectomy was done by removal of lymph nodes overlying and medial to external iliac and internal iliac vessels, from the obturator fossa anterior to the obturator nerve, and overlying the common iliac arteries. Aortic lymph node dissection was done by stripping the nodal tissue from the vena cava and aorta including aortocavl group to the level of the renal vessels crossing the origin of inferior mesenteric artery from the abdominal aorta.

Pathological processing and follow up:

All lymph nodes dissections and primary tumors were examined as in a routine histologic examination. Pathologic analysis of primary tumor included assessment of tumor type, stage and histologic grad. histopathological investigations and surgical staging were according to the International Federation of Gynecology and Obstetrics (FIGO) system with follow up period was for at least 6 months postoperative including: operative complications, prognosis and adjuvant chemotherapy.

Statistical analysis

Descriptive statistics were used to describe different characteristic of age, history, symptoms, signs, laboratory investigation, radiological findings, histopathology, staging, surgical procedures, prognosis and postoperative follow up.

RESULTS

The present study was conducted on female patients with ovarian cancer.

The study outcomes are as follows:

Table (1): Distribution of studied patients according to age

Age/year	No. = 20
Mean ±SD	51.35 ± 8.16
Range	37 – 64

This table shows that the mean age of the studied patients was 51.35 years ranging from 37-64 years.

Table (2): Distribution of studied patients according to clinical pictures

Clinical picture	No.	%
Abdominal distention	No	9 45.0%
	Yes	11 55.0%
Abdominal pain	No	10 50.0%
	Yes	10 50.0%
Abdominal discomfort	No	12 60.0%
	Yes	8 40.0%
Abnormal bleeding	No	17 85.0%
	Yes	3 15.0%
Nonspecific GIT manifestation	No	7 35.0%
	Yes	13 65.0%
Urinary symptoms	No	16 80.0%
	Yes	4 20.0%
Back pain	No	18 90.0%
	Yes	2 10.0%

This table shows that 55% of patients represented with abdominal distention, 50% had abdominal pain, 40% abdominal discomfort, 15% had abnormal bleeding, 65% had nonspecific GIT manifestation, 20% had urinary symptoms and 10% had back pain.

Table (3): Distribution of studied patients according to radiological findings and Ca125 level

Radiological findings	No.	%
Pelvic mass	No	0 (0.0%)
	Yes	20 (100.0%)
Minimal to moderate ascites	No	14 (70.0%)
	Yes	6 (30.0%)
Omental nodules	No	12 (60.0%)
	Yes	8 (40.0%)
Peritoneal nodule/s	No	15 (75.0%)
	Yes	5 (25.0%)
Lymph node enlargement	No	11 (55.0%)
	Pelvic	2 (10.0%)
	Para-aortic	3 (15.0%)
	Pelvic and paraaortic	4 (20.0%)
Serum Ca125 levels		No. = 20
CA 125 level (N. 35 u/ml)	Mean	625.5
	Range	17 – 3706

This table shows that all patients had pelvic mass, 30% had minimal to moderate

ascites, 40% had omental nodules, 25% had peritoneal nodules

As regard lymph node enlargement 55% had no enlarged lymph nodes, 20% had pelvic and paraaortic, 15% had paraaortic lymphadenopathy and 10% had pelvic lymphadenopathy Mean level of CA125 was 625.5 with range 17 – 3706.

Table (4): Distribution of studied patients according to co-morbidities

Co morbidities	No.	%
D.M(Diabetes mellitus)	No	15 75.0%
	Yes	5 25.0%
HTN (Hypertension)	No	13 65.0%
	Yes	7 35.0%
Renal impairment	No	19 95.0%
	Yes	1 5.0%
HCV (hepatitis C virus)	No	17 85.0%
	Yes	3 15.0%
Asthmatic	No	19 95.0%
	Yes	1 5.0%

This table shows that 25% of patients had D.M, 35% had HTN, 5% had renal impairment, 15% had HCV positive and 5% had bronchial asthma .

Table (5): Distribution of studied patients according to operations done

Operation	No.	%
THBSO (total abdominal hysterectomy and bilateral salpingo-oophorectomy)	No	1 5.0%
	Yes	19 95.0%
Omentectomy	No	0 0.0%
	Yes	20 100.0%
Appendectomy	No	18 90.0%
	Yes	2 10.0%
Cholecystectomy	No	18 90.0%
	Chronic calcular cholecystitis	2 10.0%
Peritontonectomy	No	18 90.0%
	Right paracolic & right subdiaphragmatic	1 5.0%
	Pelvic peritonectomy	1 5.0%
Aspiration of ascites	No	14 70.0%
	Yes	6 30.0%
Fertility preserving	No	19 95.0%
	Yes	1 5.0%
Another procedures	No	15 75.0%
	Excision of peritoneal nodule	4 20.0%
	Falcifom ligament excision	1 5.0%

This table shows that 95% of patients undergo TAHBSO, all of patients had omentectomy, 10% had appendectomy, cholecystectomy, 30% had aspiration of ascities, 10% had peritonectomy in form of Right paracolic & right subdiaphragmatic in 5% and pelvic peritonectomy in 5%, 5% had fertility preserving and 25% of cases had another procedure in form of excision of peritoneal nodules in 20% and 5% had falciform ligament excision

Table (6): Distribution of studied patients as regard operative and postoperative complications

Operative and post-operative complication		No.	%
D.V.T	No	20	100%
	Yes	0	0%
Renal dialysis (P.T. with renal impairment)	No	19	95%
	Yes	1	5%
Right external iliac artery subacute thrombus with significant stenosis lead to lower limb ischemia controlled by medical treatment	No	19	95%
	Yes	1	5%
Ureteric injury	No	19	95%
	Yes	1	5%
Died (post dialysis)	No	19	95%
	Yes	1	5%
Wound debridement & secondary suturing)	No	18	90%
	Yes	2	10%
Bladder injury	No	18	90%
	Yes	2	10%
ICU admission	No	18	90%
	Yes	2	10%
Incisional hernia	No	18	90%
	Yes	2	10%
Lower limb oedema	No	16	80%
	Yes	4	20%
Wound infection	No	15	75%
	Yes	5	25%
Pelvic collection	No	15	75%
	Yes	5	25%
Wound dehiscence	No	12	75%
	Yes	8	40%
Blood transfusion	No	11	55%
	Yes	9	45%

This table shows that most common complication among studied patients was blood transfusion in 45% followed by wound dehiscence in 40%, 25% had wound infection and pelvic collection, 20% had lower limb edema, 10% had ICU admission, bladder injury, incisional hernia and wound debridement with secondary suturing, 5% had right external iliac artery subacute thrombus lead to lower limb ischemia, ureteric injury

and only one patient (5%) died post dialysis, no patient (0%) suffered from DVT.

Table (7): Distribution of studied patients as regard pathology

Pathology		No.	%
Laterality	Right	7	35.0%
	Left	8	40.0%
	Bilatera	5	25.0%
Microscopic (diagnosis)	Serous carcinoma	14	70.0%
	Endometrioid carcinoma	3	15.0%
	Mucinous carcinoma	2	10.0%
	Clear cell carcinoma	1	5.0%
Grade	2	9	45.0%
	3	11	55.0%
Positive omental nodules	No	12	60.0%
	Yes	8	40.0%

This table shows that 40% of patients had left masses, 35% right masses and 25% bilateral, most common pathology was serous carcinoma in 70% followed by endometrioid carcinoma in 15%, mucinous carcinoma in 10% and clear cell carcinoma in 5%

Most of cases were grade 3 in 55% and 45% was grade 2 with 40% of patients had positive omental nodules.

Table (8): Distribution of studied patients as regard criteria of lymph node dissected for 20 patients

lymph nodes dissected	Median (IQR)		No	%
Total number L.Ns	30 (26.5 - 35)	Total	605	
		Positive	45	7.44%
Paraortic L.Ns	11 (9 - 13.5)	Total	229	
		Positive	16	6.99%
Lt. pelvic L.Ns	10.0 (8.5 - 11)	Total	188	
		Positive	17	9.04%
Rt. Pelvic L.Ns	9.5 (7.5 - 11)	Total	188	
		Positive	12	6.38%
Total pelvic L.Ns	19.5 (17- 22)	Total	376	
		Positive	29	7.71%

This table shows that the total number of lymph node dissected was 605, the median (IQR) was 30 (26.5 - 35), including 45(7.44%) positive nodes.

Total para aortic L.Ns dissected was 229, the median (IQR) was 11 (9 - 13.5), including 16 (6.99%) positive nodes in 5 patients.

Total Lt. pelvic L.Ns dissected was 188, the median (IQR) was 10.0 (8.5 - 11), including 17 (9.04%) positive nodes in 4 patients.

Total Rt. pelvic L.Ns dissected was 188, the median (IQR) was 9.5 (7.5 - 11), including 12 (6.38%) positive nodes in 3 patients.

Total pelvic L.Ns dissected was 376, the median (IQR) was 19.5 (17-22), including 29 (7.71%) positive nodes.

Table (9): Distribution of studied patients as regard stages

		No. = 20
Stage	IIIa	5 (25.0%)
	IIB	5 (25.0%)
	IIIb	6 (30.0%)
	IC	1 (5.0%)
	IIIc	3 (15.0%)

The most of patients was stage IIIb in 30% followed by IIIa, IIB 25%, IIIc in 15% and IC % in 5%.

Table (10): Distribution of studied patients as regard adjuvant chemotherapy

Adjuvant chemotherapy		No. = 20
Regemin	Taxol/carboplatin/avastin	2 (10.5%)
	Taxol/carboplatin	17 (89.5%)
Recurrences	No	16 (84.2%)
	Local recurrence	1 (5.3%)
	Peritoneal nodule	1 (5.3%)
	Aorto-caval	1 (5.3%)
Total follow up time from /-month)	Mean±SD	8.68 ± 3.33
	Range	6 – 20

This table shows that 89.5% of patients received Taxol/carboplatin, 10.5% received Taxol/carboplatin/avastin.

84.2% had no recurrence, 5.3% had local recurrence or peritoneal nodules or aorto-caval recurrence. Mean follow up time was 8.68 months.

DISCUSSION

Ovarian cancer is the seventh cause of cancer death worldwide, and the sixth most common cancer in women. The disease is most often diagnosed at an advanced stage because there are no effective measures for early detection, and as a result, the long-term

survival of patients with ovarian cancer ranges from 30% to 40% (7).

While long-term outcomes remain less than desirable, the survival of patients with advanced ovarian cancer has improved with the introduction of platinum and paclitaxel as standard front-line chemotherapy, and maximal cytoreductive surgery. The value of lymphadenectomy, however, in early and late stage ovarian cancer remains the subject of research (8).

Although systematic lymphadenectomy has been shown to be feasible and safe in the treatment of advanced ovarian cancer, its therapeutic role remains controversial. The core issue of the controversy is whether removal of the lymph nodes should be performed only to stage the disease or whether removal improves survival. In the former case, lymph node regions at risk would only be sampled, whereas in the latter case there would be a systematic effort to remove all accessible lymph node-bearing tissue (9).

In the current study we aimed to review the surgical management of female patients with ovarian cancer including intraperitoneal complete cytoreduction and systematic lymphadenectomy to show prognosis, post operative morbidities, recurrence and follow up. 20 patients were involved with mean age of the studied patients was 51.35 years ranging from 37-64 years.

In a study by *Chang et al.* (10) 203 patients were included in the study The median age was 54 years (range 30–78 years) on other study by *Iwase et al.* (11) 124 patients were included with median age was 58 years (range, 29 to 83 years). With the same age range in *Gasimli et al.* (12) study found that the median age at date of first diagnosis was 57 years (range 27–85).

In the current study we found that mean level of CA125 was 625.5with range 17 – 3706 which was near to the level in a study by *Chang et al.* (10) the median preoperative serum CA-125 level was 603.8 U/mL **and lower than in Iwase et al.** (11) the median serum cancer antigen 125 (CA-125) level was 1,569.4 U/mL (range, 13.5 to 24,821 U/mL) before NACT and 15.8 U/mL (range, 2.3 to 1,965.1 U/mL) after NACT. Another study by *Gasimli et al.* (12) found

that the median serum concentration of CA125 was 576.5 U/ml (range 7–30,000).

In the present study we found that 25% of patients had D.M, 35% had HTN, 5% had renal impairment, 15% had HCV positive and 5% had bronchial asthma, all patients had pelvic mass, 30% had minimal to moderate ascites, 40% had omental nodules, 25% had peritoneal nodules.

Gasimli et al. ⁽¹²⁾ found that ascites was present in 69.3 % of patients, with 40.4 % of patients presenting with less than, and 28.9 % of patients presenting with more than, 500 ml of ascites. In 30.7 % of patients, no ascites was present at all.

Moreover, we found that 95% of patients have undergone TAHBSO, all of patients had omentectomy, 10% had appendectomy, cholecystectomy, 30% had aspiration of ascities, 10% had peritonectomy in form of Right paracolic & right subdiaphragmatic in 5% and pelvic peritonectomy in 5%, 5% had fertility preserving and 25% of cases had another procedure in the form of excision of peritoneal nodules in 20% and 5% had falciform ligament excision.

Chang et al. ⁽¹⁰⁾ found that of 84 patients who underwent radical procedures, radical oophorectomy was performed in 72 patients (85.7 %), and 37 patients (44.0 %) had extensive upper abdominal surgery.

Iwase et al. ⁽¹¹⁾ showed that exploratory laparotomy was performed in 11 patients, TAH+BSO+OM (minimum) in 10 patients, TAH+BSO+ OM+excision of other organs (radical-1) such as the sigmoid colon, rectum, liver, and small intestine in 16 patients, TAH+BSO+OM+retroperitoneal lymphadenectomy (radical-2) in 38 patients, and TAH+BSO+OM+excision of other organs and retroperitoneal lymphadenectomy (radical-3) in 48 patients

In the present study we found that most common complication among studied patients was blood transfusion (45%) followed by wound dehiscence (40%).

Furthermore, 25% of the patients had wound infection and pelvic collection, 20% had lower limb edema, 10% had ICU admission, bladder injury, incisional hernia and wound debridement with secondary

suturing, 5% had right external iliac artery subacute thrombus lead to lower limb ischemia, ureteric injury and only one patient (5%) died post dialysis.

In comparison to other studies *Chang et al.* ⁽¹⁰⁾ involved two groups with simple or radical surgery found that radical surgery had more complications in form of intraoperative and Postoperative blood transfusion in n25%, 39.3% of patients respectively Infected lymphocyst in 12 patients, Wound infection in 6 patients, Intestinal obstruction in 4 patients, Thromboembolism, Anastomotic leakage, Ureteral injury, Sepsis in 3 patients and Intra-abdominal abscess, Pneumothorax in 1 patients and Postoperative death \30 d in 1 patients.

In the current study we found that 40% of patients had left masses, 35% right masses and 25% bilateral, most common pathology was Serous adenocarcinoma in 70% followed by Endometrioid carcinoma in 15%, Mucinous adenocarcinoma in 10%, and Clear cell carcinoma in 5%.

Regarding histologic subtypes in *Iwase et al.* ⁽¹¹⁾ study, serous adenocarcinoma accounted for 85.0% (105/124) of cases; furthermore, 92.7% (115/124) of cases if 10 cases with mixed adenocarcinoma and carcinosarcoma with serous components were included.

In consistent with our result *Gasimli et al.* ⁽¹²⁾ found that the vast majority of patients (93.6 %) presented a serous histological subtype.

Moreover *Cuylan et al.* ⁽¹³⁾ found that of 218 women who met the inclusion criteria, 64 (29.4%) patients had endometrioid, 61 (28%) had mucinous, 54 (24.8%) had clear-cell and 39 (17.9%) had mixed epithelial tumors and bilaterality in 49.1%.

Most of cases in the current study were grade 3 in 55% and 45% was grade 2 with 40% of patients had positive omental nodules and 30% had abdominal peritonea metastasis

In consistent with our result Bachmann C et al include 108 patients and found that most of patients was grade 3 (55.5%) and (44.44%) were grade G1/2 (Bachmann C et al., 2016) also *Gasimli et al.*

⁽¹²⁾ found that most patients had grade III (70.6 %), followed by grade II (24.3 %) and grade I (5 %).

In the current study we found that as regard lymph node enlargement 55% had no enlarged lymph nodes, 20% had pelvic and paraaortic, 15% had paraaortic lymphadenopathy and 10% had pelvic lymphadenopathy, the median (IQR) of lymph nodes dissected from right pelvic was 9.5 (7.5 - 11), left pelvic was 10.00 (8.5 - 11), para aortic was 11 (9 - 13.5) and the total (para-aortic and pelvic) was 30 (26.5 - 35)

Regarding dissected lymph node *Iwase et al.* ⁽¹¹⁾ 86 patients underwent systematic retroperitoneal lymphadenectomy, and the mean number of dissected pelvic and para-aortic nodes was 46 (range, 19 to 96). Positive lymph nodes (LNs) were detected in 49 patients, including two patients for whom we only sampled bulky LNs. While negative LNs were detected 41 patients, also including two patients for whom we only sampled bulky LNs.

In another study by *Cuylan et al.* ⁽¹³⁾ found that the median number of pelvic LNs removed and number of para-aortic LNs removed was 25 (10–93), 12 (5–66) respectively and 55.5% had retroperitoneal LN metastases, 64.7% had Peritoneal involvement and, 60.1% had Omental involvement.

In the current study we found that the most of patients was stage IIIb in 30% followed by IIIa, IIb 25%, IIc in 15% and IC % in 5%.

This differ than other studies as in *Chang et al.* ⁽¹⁰⁾ the majority of patients had FIGO stage IIIC disease (93.1 %) and serous histology (82.3 %) and in *Iwase et al.* ⁽¹¹⁾ six cases (4.8%), stage IIIB; 77 cases (62.1%), stage IIIC; and 41 cases (33.1%), stage IV.

Another study by *Cuylan et al.* ⁽¹³⁾ found that there were 55 (25.2%) women with stage IIIA1, 14 (6.4%) with stage IIIA2, 34 (15.6%) with stage IIIB and 115 (52.8%) with stage IIIC disease.

In the current study after mean follow up time was 8.68 months 84.2% had no recurrence, 5.3% had local recurrence or peritoneal nodules or aorto caval recurrence.

On the other hand, *Iwase et al.* ⁽¹¹⁾ study showed that Recurrence occurred in 91 of 113 patients, and irrespective of surgical procedure, recurrence rates were high, ranging from 75% to 94%. Peritoneal dissemination was detected in about 62% of cases. LN recurrence was detected in 8/27 patients (29.6%) in the non-lymphadenectomy group (minimum and radical-1) and 17/86 patients (19.8%) in the lymphadenectomy group (radical-2 and radical-3); this difference was not statistically significant (p=0.534).

Iwase et al. ⁽¹¹⁾ found that median follow-up period was 39.5 months (range, 5 to 142 months). In *Cuylan et al.* ⁽¹³⁾ the median duration of follow-up was 31.5 (range, 1–120) months.

The relative differences in results between this study and the other studies may be due to the smaller sample size, short follow up period, lack of follow up of patients, differences in surgical procedures, postoperative management, histopathological examination and different stages of disease.

CONCLUSION:

- Lymphadenectomy, as a routine treatment procedure in ovarian cancer, remains controversial. Moreover, systematic lymphadenectomy often prolongs operation times, which may result in additional surgical complications such as lymphocele, lymphatic obstruction, lymphocysts and lymphedema, however these complications may be alleviated, and better outcome occurred by proper intra operative and post operative management by expert gynecological oncologist involvement and leveraging adequate instruments, which can eventually improve survival.
- The surgical community should consider adopting the terms complete cytoreduction, optimal (for cases with RD<1 cm) and suboptimal (residual >1 cm) given the survival benefits of less than complete cytoreduction.

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