DOI: 10.4081/aiua.2022.2.150

ORIGINAL PAPER

The effect of retroperitonealization of ureteroileal anastomosis on perioperative complications of radical cystectomy with ileal conduit urinary diversion

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Summary *Background: Radical cystectomy (RC) has been considered the standard management of muscle-invasive bladder cancer. Despite the improvements in surgical techniques and perioperative care, RC is still associated with high perioperative morbidity and mortality.*
Objective: This study aims to evaluate the effect of retroperitonealization of ureteroileal anastomosis on perioperative complications of RC with ileal conduit urinary diversion.
Patients and methods: This is a retrospective cohort study. We reviewed medical charts of 876 patients who underwent RC between 2016 and 2021. Based on the inclusion and exclusion criteria, 748 patients entered the study. According to retroperitonealization of the ureteroileal anastomosis, patients were categorized into two groups (group I without retroperitonealization of the ureteroileal anastomosis and group II with retroperitonealization of the ureteroileal anastomosis). Patients' characteristics and occurrences of any complications and high-grade complications were compared between these groups.
Results: In comparing the complication categories between the two groups, fewer patients in group II suffered from gastrointestinal, urinary, and cardiac events (p values were 0.018, 0.021, and 0.013, respectively). Moreover, fewer patients in group II experienced any complications and high-grade complications (p values were < 0.001 and < 0.001, respectively). The length of hospital stay was also significantly shorter in group II (p < 0.001).
Conclusions: RC is associated with comparatively high perioperative morbidity and mortality. In the present study, 61% of the patients experienced at least one complication postoperatively. Retroperitonealization of the ureterointestinal anastomosis may decrease perioperative adverse events of RC with ileal conduit urinary diversion.

KEY WORDS: *Radical cystectomy; Complication; Retroperitonealization.*

Submitted 6 May 2022; Accepted 19 May 2022

INTRODUCTION

Bladder cancer is a global disease, with 573.278 incident cases and 212.536 deaths in 2020 worldwide (1). About 25% of patients with bladder cancer are diagnosed with muscle-invasive bladder cancer (2). Since the early 1960s, *radical cystectomy* (RC) and pelvic lymphadenectomy have been considered the standard management of muscle-invasive bladder cancer and a valid option for selected patients with high-grade non-muscle invasive bladder cancer (3, 4).
Even with improvements in surgical techniques and perioperative care, RC is a technically challenging operation and is associated with comparatively high perioperative morbidity and mortality (5, 6). The incidence of complications after the surgery has been reported to be in the range of 11-70% and late morbidity in contemporary series has been 19 to 58% (6, 7). It has been shown that complications after RC and urinary diversion severely affect the patients' quality of life (8). Therefore, improving surgical techniques to reduce postoperative complications is required. In this study, we investigated the effect of ureteroileal anastomosis retroperitonealization on perioperative complications of radical cystectomy with ileal conduit urinary diversion.

PATIENTS AND METHODS

We retrospectively reviewed medical data of all patients who underwent RC between 2016 and 2021 at two high-volume referral urology centers. Three different expert surgeons had performed the operations.
Our inclusion criteria were 1. RC was performed to manage bladder urothelial carcinoma; 2. The ileal conduit was performed as urinary diversion; 3. The ureteroileal anastomosis was performed according to Wallace 1 technique.
Our exclusion criteria were 1. Patients with anatomical single kidney and ureter; 2. Those with incomplete medical charts which did not provide appropriate data about all of the variables that were investigated in this study. Patients who met all of the inclusion criteria and lacked the exclusion criteria were entered into the study.
We collected data regarding patients' characteristics and all of the postoperative complications within 90 days of surgery. Any deviations from the normal postoperative course were considered complications (9). Perioperative mortality was determined as death from any cause within 90 days of operation.

Procedure

Antiplatelet and anticoagulant medications were stopped at least 1 week before the operation. All patients received mechanical bowel preparation. We utilized elastic com-

No conflict of interest declared.

pressive stocking as mechanical prophylaxis for deep vein thrombosis. Ceftriaxone 1 gr, metronidazole 500 mg, and pantoprazole 40 mg were administered intravenously when anesthesia was initiated and maintained for the time of hospital admission postoperatively. The nasogastric tube was not inserted routinely.

RCs were performed according to the procedure suggested by the *International Consultation* on *Bladder Cancer* (10). Lymph node dissection included the removal of all lymphatic tissues around the external iliac and internal iliac arteries and from the obturator region bilaterally.

After completion of RC and lymph node dissection, a segment of 10-20 cm of ileum approximately 20 cm proximal to the ileocecal valve was isolated. The stapled ileoileal anastomosis was performed. The mesentery window was closed with interrupted sutures, and the conduit was flushed with saline and povidone-iodine until the irrigant is clear. Afterward, ureters were conjoined, with the left ureter transposed to the right side of the pelvis through a tunnel prepared at the base of the sigmoid mesentery in front of the common iliac vessels. Tension-free ureteroileal anastomosis was accomplished according to Wallace 1 technique (11) with 5-0 polydioxanone sutures and was stented intraoperatively for at least 30 days. In completing cutaneous rosebud stoma formation, in patients who were operated on from 2016 to mid-2018, we only brought the segment directly to the anterior abdominal wall (group I). In patients who were operated on from then to 2021, we placed a peritoneal flap over the ureteroileal anastomosis in that stage of surgery. The flap was sutured to the conduit and the lateral peritoneum so that the ureteroileal anastomosis was completely covered by the peritoneum and effectively retroperitonealized (group II). We performed this surgical technique with the purpose of separating the ureterointestinal anastomosis from the peritoneal cavity and decreasing intraperitoneal urine extravasation. Before wound closure, we placed an 18-24fr drain tube through the abdominal wall and a 24fr Foley catheter via the urethra into the pelvic cavity.

Postoperatively, patients were managed in the intensive care unit. Subcutaneous daily administration of low-molecular-weight heparin, or every 8 hours unfractionated heparin in patients with renal failure, was started 24 hours after surgery and maintained for at least 4 weeks postoperatively. Further postoperative management was continued in the urology ward according to our standardized clinical care pathways for cystectomy. A day after surgery, mobilization was initiated as soon as the patient could be ambulated. On the third postoperative day, if the patient had bowel movements, he/she was allowed to take sips of water. If the patient tolerated drinking water, the diet advanced gradually to a soft diet. We started a regular diet two weeks postoperatively. The amount of drained fluid out of the Foley catheter and the drain tube was measured continuously. If the creatinine concentration of drained fluid was 30% more than the concomitant serum creatinine concentration, the patient is presumed to have urine leakage.

More diagnostic studies including abdominopelvic sonography, supine and upright abdominopelvic X-rays, and intravenous contrast-enhanced abdominopelvic CT scan were requested in case of persistent postoperative azotemia, sepsis or symptoms and signs of peritonitis to rule out urinary extravasation or other possible intra-abdominal complications.

Statistical analysis

Mean ± standard deviation and range of quantitative variables and frequencies of the qualitative variables are presented. According to the characteristics of the variables, the Mann-Whitney U test or chi-square test were used to compare the two groups. P-value < 0.05 was considered

Table 1.
Patients' characteristics.

	Total n = 748	Group I n = 362 (48.4%)	Group II n = 386 (51.6%)	P-value*
Age (years), mean ± SD (range)	64.97 ± 7.31 (44-84)	64.82 ± 6.88 (49-83)	65.11 ± 7.70 (44-84)	0.527
≥ 70 years old, n (%)	216 (28.9)	97 (26.8)	119 (30.8)	0.224
Sex Male, n (%) Female, n (%)	 586 (78.3) 162 (21.7)	 285 (78.7) 77 (21.3)	 301 (78.0) 85 (22.0)	0.803
Body mass index (kg/m^2), mean ± SD (range)	24.37 ± 4.92 (16.99-34.96)	24.42 ± 4.61 (17.09-34.96)	24.33 ± 5.19 (16.99-34.83)	0.435
Current smoking, n (%)	470 (62.8)	222 (61.3)	240 (62.2)	0.493
DM, n (%)	246 (32.9)	124 (34.3)	122 (31.6)	0.574
Cerebrovascular comorbidities, n (%)	40 (5.3)	19 (5.2)	23 (6.0)	0.673
Cardiovascular comorbidities, n (%)	185 (24.7)	113 (31.2)	112 (29.0)	0.512
Pulmonary comorbidities, n (%)	26 (3.5)	11 (3.0)	15 (3.9)	0.527
Routine dialysis, n (%)	50 (6.7)	12 (3.3)	18 (4.7)	0.348
Previous abdominopelvic surgery, n (%)	137 (18.3)	72 (19.9)	65 (16.8)	0.281
Neoadjuvant chemotherapy, n (%)	245 (32.8)	113 (31.2)	132 (34.2)	0.385
Poor (< 4 MET) functional capacity, n (%)	154 (20.6)	82 (22.7)	72 (18.7)	0.176
ASA score 1, n (%) 2, n (%) 3, n (%)	 78 (10.4) 511 (68.3) 159 (21.3)	 36 (9.9) 242 (66.9) 84 (23.2)	 42 (10.9) 269 (69.7) 75 (19.4)	0.443
Serum creatinine (mg/dl), mean ± SD (range)	1.86 ± 1.29 (0.8-8.1)	1.48 ± 1.00 (0.8-8.0)	1.57 ± 1.1 (0.7-8.0)	0.329
Hemoglobin concentration (g/dl), mean ± SD (range)	13.11 ± 1.78 (7.1-18.5)	13.10 ± 1.71 (10.0-16.0)	13.12 ± 1.85 (7.1-18.5)	0.708
Preoperative anemia, n (%)	323 (43.2)	156 (43.1)	167 (43.3)	0.963
NLR, mean ± SD (range)	5.80 ± 1.52 (2.10-8.99)	5.71 ± 1.56 (2.34-8.98)	5.78 ± 1.54 (2.10-8.99)	0.436
Hypoalbuminemia, n (%)	297 (39.7)	149 (41.2)	172 (44.6)	0.348
Clinical T stage 1, n (%) 2, n (%) 3, n (%) 4, n (%)	 18 (2.4) 569 (76.1) 135 (18) 26 (3.5)	 10 (2.8) 282 (77.9) 60 (16.6) 10 (2.8)	 8 (2.1) 287 (74.4) 75 (19.4) 16 (4.1)	0.466
Operative time (min), mean ± SD (range)	351.31 ± 99.93 (180-560)	351.33 ± 98.23 (180-540)	351.30 ± 101.63 (180-560)	0.918
Blood Loss (cc), mean ± SD (range)	803.93 ± 386.10 (200-5100)	825.03 ± 395.90 (200-5100)	784.15 ± 376.11 (210-4000)	0.141
Intraoperative Blood Transfusion, n (%)	394 (52.7)	202 (55.8)	192 (49.7)	0.097
Surgeons I, n (%) II, n (%) III, n (%)	 255 (34.1) 273 (36.5) 220 (29.4)	 118 (32.6) 137 (37.8) 107 (29.6)	 137 (35.5) 136 (35.2) 113 (29.3)	0.666

Group I without retroperitonealization of the ureteroileal anastomosis; group II with retroperitonealization of the ureteroileal anastomosis.
** Group I vs II.*
MET: Metabolic equivalent; ASA: American Society of Anesthesiology; NLR: Neutrophil to lymphocyte ratio; Hypoalbuminemia: serum albumin concentration < 3.5 g/dl.

as a significant level. Statistical analyses were performed using the *IBM SPSS Statistics for Windows*, version 24 (*IBM Corp., Armonk, N.Y., USA*).

Results

Out of 876 RCs that were performed in five years, 748 patients did not have the exclusion criteria and met all of the inclusion criteria; consequently, enrolled in the study. Table 1 shows the summary of the patients' characteristics. Men accounted for 586 (78.3%) of patients.

The mean age at RC was 64.97 ± 7.315 years, the mean *body mass index* (BMI) was 24.37 ± 4.92 kg/m^2, the mean operative time was 351.31 ± 99.93 minutes, and the mean estimated blood loss was 803.93 ± 386.1 ml.

The average length of stay after RC was 7.66 ± 4.26 days.

Table 2.
Summary of complication categories and types.

Category	Complications	Total n (%) of patients	Group I n (%) of patients	Group II n (%) of patients	P-value*
Gastrointestinal		**147 (19.7)**	**84 (23.2)**	**63 (16.3)**	**0.018**
	Postoperative ileus	116 (15.5)	63 (17.4)	53 (13.7)	0.166
	Anastomotic bowel leakage	11 (1.5)	8 (2.2)	3 (0.8)	0.104
	Gastrointestinal bleeding	10 (1.3)	6 (1.7)	4 (1.0)	0.460
	Diarrhea	18 (2.4)	12 (3.3)	6 (1.6)	0.116
Infectious		**78 (10.4)**	**43 (11.9)**	**35 (9.1)**	**0.209**
	FUO	16 (2.1)	7 (1.9)	9 (2.3)	0.707
	UTI	39 (5.2)	15 (4.1)	24 (6.2)	0.202
	Sepsis	28 (3.7)	22 (6.1)	6 (1.6)	0.001
Wound		**133 (17.8)**	**70 (19.3)**	**63 (16.3)**	**0.281**
	SSI	112 (15.0)	53 (14.6)	59 (15.3)	0.805
	Wound dehiscence	23 (3.1)	19 (5.2)	4 (1.0)	0.001
Genitourinary		**81 (10.8)**	**49 (13.5)**	**32 (8.3)**	**0.021**
	Hydronephrosis	54 (7.2)	29 (8.0)	25 (6.5)	0.418
	Renal failure	7 (0.9)	6 (1.7)	1 (0.3)	0.047
	Urine leakage	39 (5.2)	30 (8.3)	9 (2.3)	< 0.001
Cardiac		**15 (2.0)**	**12 (3.3)**	**3 (0.8)**	**0.013**
	Arrhythmia	5 (0.7)	3 (0.8)	2 (0.5)	0.602
	Myocardial infarction	10 (1.3)	8 (2.2)	2 (0.5)	0.044
	Congestive heart failure	4 (0.5)	3 (0.8)	1 (0.3)	0.286
Pulmonary		**22 (2.9)**	**13 (3.6)**	**9 (2.3)**	**0.308**
	Pneumonia	12 (1.6)	6 (1.7)	6 (1.6)	0.911
	Pleural effusion	7 (0.9)	4 (1.1)	3 (0.8)	0.642
	Lung edema	3 (0.4)	3 (0.8)	0	0.073
Bleeding		**21 (2.8)**	**14 (3.9)**	**7 (1.8)**	**0.089**
	Anemia requiring transfusion	21 (2.8)	14 (3.9)	7 (1.8)	0.089
Thromboembolic		**10 (1.3)**	**7 (1.9)**	**3 (0.8)**	**0.169**
	Deep venous thrombosis	10 (1.3)	7 (1.9)	3 (0.8)	0.169
	Pulmonary embolism	3 (0.4)	2 (0.6)	1 (0.3)	0.526
Neurologic		**10 (1.3)**	**6 (1.7)**	**4 (1.0)**	**0.460**
	Cerebrovascular event	5 (0.7)	4 (1.1)	1 (0.3)	0.156
	Delirium	6 (0.8)	3 (0.8)	3 (0.8)	0.937
Surgical		**7 (0.9)**	**5 (1.4)**	**2 (0.5)**	**0.221**
	Rectal injury	6 (0.8)	3 (0.8)	2 (0.5)	0.602
	Obturator nerve injury	2 (0.3)	0	2 (0.5)	0.170
Miscellaneous		**7 (0.9)**	**3 (0.8)**	**4 (1.0)**	**0.768**
Death		**11 (1.5)**	**6 (1.7)**	**5 (1.3)**	**0.681**
All complications		**456 (61)**	**246 (68.0)**	**210 (54.4)**	**< 0.001**
High-grade complications		**115 (15.4)**	**93 (25.7)**	**22 (5.7)**	**< 0.001**
Hospital stay, mean ± SD (range)		**7.66 ± 4.26**	**8.54 ± 5.71 (5-73)**	**6.84 ± 1.78 (5-73)**	**< 0.001 (5-18)**

Group I without retroperitonealization of the ureteroileal anastomosis; group II with retroperitonealization of the ureteroileal anastomosis.
** Group I vs II.*
FUO: Fever of unknown origin; UTI: urinary tract infection; SSI: Surgical site infection.

Table 3.
Highest Clavien complication grade in each patient.

Highest Clavien complication grade	Total n (%)	Group I n (%)	Group II n (%)
I	220 (29.4)	98 (27.1)	122 (31.6)
II	114 (15.2)	49 (13.5)	65 (16.8)
III	51 (6.8)	40 (11.0)	11 (2.8)
IV	53 (7.1)	47 (13.0)	6 (1.6)
V	11 (1.5)	6 (1.7)	5 (1.3)

Five hundred ninety-nine complications were recorded in 456 (61%) patients within 90 days of surgery.

To enhance the comparability among populations, we classified our complications using the modified Clavien grading system (9) and category grouping reported by *Shabsigh et al.* (12). In our study, the most common complication categories were gastrointestinal 147 (19.7%), wound-related 133 (17.8%), genitourinary 81 (10.8%), and infectious 78 (10.4%). Ileus 116 (15.5%), surgical site infection (SSI) 112 (15.0%), hydronephrosis 54 (7.2%), urine leakage 39 (5.2%), and urinary tract infections 39 (5.2%) were the most frequent complications. Table 2 represents a comprehensive breakdown of our complications. The highest complication grade in each patient was Clavien grade I in 220 (29.4%), grade II in 114 (15.2%), grade III in 51 (6.8%), grade IV in 53 (7.1%), and grade V in 11 (1.5%) patients (Table 3). Eleven (1.5%) deaths were recorded within 90 days of surgery. No patient died intraoperatively. Five patients died from gastrointestinal events, three from infectious events (sepsis), two from cardiovascular events, and one from a cerebrovascular event.

Group I and II consisted of 362 and 386 patients, respectively. Patients' characteristics were not significantly different between these groups. The number of patients who were operated on by each surgeon was not significantly different between the two groups (Table 1). Incidences of sepsis, wound dehiscence, renal failure, urine leakage, and myocardial infarction, were significantly lower in group II (p values were 0.001, 0.001, 0.047, < 0.001, and 0.044, respectively). In comparing the complication categories between the two groups, fewer patients in group II suffered from gastrointestinal, urinary, and cardiac events (p values were 0.018, 0.021, and 0.013, respectively). Moreover, fewer patients in group II experienced any complications and high-grade complications (p values were < 0.001 and < 0.001, respectively).

The length of hospital stay was also significantly shorter in group II (p < 0.001) (Table 2).

Discussion

Despite recent advances in surgical techniques, RC is still highly morbid with complications occurring in up to two-thirds of patients within 90 days (6, 7, 13-17). Various factors have been related to post-RC complications and prognosis. *Maffezzini et al.* have demonstrated that advanced age of more than 70 years and Charlson Comorbidity Index > 3 are associated with worse post-RC prognosis (18). It has been shown that in patients undergoing RC, low serum albumin concentration is a signifi-

cant predictor of mortality and serious adverse events (19). Other factors that are associated with adverse outcomes after RC include sarcopenia, an increased BMI, female gender, prior abdominopelvic surgery, extravesical disease, and prior pelvic radiotherapy (20-22).

Although the majority of the post-RC complications are minor, it has been reported that up to 20% of patients will experience a major complication (23, 24). Multiple studies reported that more common complication categories are gastrointestinal, infectious, wound-related, and genitourinary (12, 25). In our study, five hundred ninety-nine complications were recorded in 456 (61%) patients within 90 days of surgery. 15.4% of our patients experienced major (≥ grade III) complications.

Our observation was comparable with the study by *Shabsigh et al.* (12) reporting that the overall complication rate was 64% and the major complication rate was 13%. *Hautman et al.* (25) also reported complications in RC and ileal neobladder cases using the same standards. In their study, 58% of the patients experienced at least one complication within 90 days of surgery. In our cohort, the most common complication categories were gastrointestinal, wound-related, genitourinary, and infectious. Ileus, SSI, hydronephrosis, urine leakage, and urinary tract infections were the most frequent complications.

This distribution was similar to the results obtained from other studies (12, 25).

Retroperitonealization of the ureteroileal anastomosis during RC is mainly performed to prevent the herniation of the small bowel lateral to the conduit and the effect of performing this maneuver on perioperative complications has not been thoroughly studied. In this concept, *Soleimani et al.* compared the postoperative complications of transperitoneal vs extraperitoneal RC. They reported that early gastrointestinal complications including oral intake intolerance, ileus, intestinal obstruction, and anastomosis leakage were lower in the extraperitoneal RC group. Also in this group, the rate of postoperative urine leakage and wound-related complications were lower (26). *Kulkarni et al.* investigated the transperitoneal and extraperitoneal RC complications and reported that the rates of gastrointestinal complications, reoperation, and intestinal obstruction were significantly lower in the extraperitoneal approach. They noted that extraperitonealization of the neobladder or conduit may make postoperative urinary leakages amenable to less invasive managements such as simple extraperitoneal drainage or transurethral catheterization alone (27). In our study, the incidences of sepsis, wound dehiscence, renal failure, urine leakage, and myocardial infarction, were significantly lower in group II (p values were 0.001, 0.001, 0.047, < 0.001, and 0.044, respectively). In comparing the complication categories between the two groups, fewer patients in group II suffered from gastrointestinal, genitourinary, and cardiac events (p values were 0.018, 0.021, and 0.013, respectively). Overall, fewer patients in group II experienced any complications (246 (68.0%) *vs* 210 (54.4%), $p < 0.001$) and high-grade complications (93 (25.7) *vs* 22 (5.7%), $p < 0.001$). The length of hospital stay was also significantly shorter in group II (8.54 ± 5.71 *vs* 6.84 ± 1.78, $p < 0.001$).

One of the possible reasons for these findings, which according to the nature of our intervention seems to be rational, might be a decrease in the rate of postoperative urine leakage from ureteroileal anastomosis. It has been reported that post-RC urinary extravasation may lead to a prolonged hospital stay, chemical peritonitis, and ureteroileal anastomosis stricture (28), which in turn may result in renal deterioration. Also, severe urinary leakage has been associated with perioperative mortality (29). In our investigation, hospital stay was significantly longer in patients with postoperative urine leakage than in those who did not suffer from this complication (12.38 ± 4.16 *vs* 7.22 ± 3.99, $p < 0.001$). Besides, the rate of urine leakage was significantly lower in group II (30 (8.3%) *vs* 9 (2.3%), $p < 0.001$).

However, it must be stated that only a limited number of studies with controversial results investigated the effect of retroperitonealization of the ureterointestinal anastomosis on post-RC urine leakage. *Kavaric et al.*, as a part of their modification of the Wallace technique, retroperitonealized the conduit by suturing the serosa of the conduit to the posterior peritoneum above the anastomosis, thus placing the ureterointestinal anastomosis in the retroperitoneum. They reported that their technique significantly decreased postoperative urine leakage (30). As mentioned earlier, *Soleimani et al.* reported that the rate of postoperative urine leakage was lower in the extraperitoneal than transperitoneal RC group (26). Contrary to these findings and our assumption, in *Kulkarni et al.'s* study, although the rate of post-RC urine extravasation was not significantly different in the extraperitoneal *vs* transperitoneal approach, the rates of gastrointestinal complications, reoperation, and intestinal obstruction were lower in the former group (27). This suggests that other causative factors might have a role in the decrease in perioperative adverse events. Due to our study design, we could not assess whether the decrease in the rate of urine leakage is a true cause of lower complications occurrence in the group with retroperitonealization of the ureteroileal anastomosis or not. Further investigations to clarify the pathophysiology of these findings are required.

The present study is among the few investigations that have assessed the effect of retroperitonealization of ureteroileal anastomosis on the perioperative complications of RC. Albeit, the current study has several shortcomings including its retrospective design and the short duration of follow-up. In addition, it is possible that some minor adverse events were not recorded. However, major adverse events or deaths were probably not overlooked. Also in this study, we only enrolled patients with ileal conduit diversion and ureteroileal anastomosis that was performed according to the Wallace technique; other types of urinary diversions and ureterointestinal anastomoses were not covered.

Finally, based on the study design, we were not able to factor out time and experience in the earlier group rather than the latter group. However, it must be noted that the operations were performed by surgeons with more than a decade of experience in radical cystectomy in high-volume urology centers and we have not changed our postoperative care during the five-year period of the study. Thus, it seems that these factors might have a negligible effect on our comparison and interpretation.

Conclusions

RC is associated with comparatively high perioperative morbidity and mortality. In the present study, 61% of the patients experienced at least one complication postoperatively. During RC with ileal conduit urinary diversion, retroperitonealization of the ureterointestinal anastomosis may decrease urine extravasation and some of the other adverse events and shorten the length of hospital stay.

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