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ORIGINAL ARTICLE

Feasibility of restorative proctocolectomy in patients with ulcerative colitis-associated lower rectal cancer: A retrospective study

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Summary *Background/Objective:* Restorative proctocolectomy (RP) may improve quality of life in patients with ulcerative colitis (UC)-associated lower rectal cancer to a greater extent than total proctocolectomy. However, patients with UC-associated cancer often have flat mucosal lesions that make it extremely difficult to endoscopically delineate the tumor margins. Therefore, there is a potential risk of residual tumor and local recurrence after RP in patients with UC-associated lower rectal cancer. The aim of this study was to assess the feasibility of RP in patients with UC-associated cancer of the lower rectum.
Methods: We retrospectively identified nine patients who had undergone RP for UC-associated lower rectal cancer at the Niigata University Medical and Dental Hospital between January 2000 and December 2016. The incidence of flat mucosal cancer, distal margin status, and oncologic outcomes were evaluated in the nine patients.
Results: Eight (89%) of the nine patients had flat mucosal cancer in the lower rectum. The median length of the distal margin was 22 mm (range 0–55 mm). No patient developed local or distant recurrence during follow-up. One patient had a positive distal margin. This patient underwent annual pouchoscopy, but had no local recurrence and died of pancreatic cancer 81 months after RP. The remaining eight patients were alive at the final observation. Five-year and 10-year overall survival rates in the nine patients were 100% and 66.7%, respectively.

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Conclusion: Patients with UC-associated lower rectal cancer often have lesions of the flat mucosal type. However, RP is feasible and not necessarily contraindicated in such patients.

1. Introduction

Restorative proctocolectomy (RP) is a well-established elective surgical treatment for ulcerative colitis (UC).[1–9] However, there is some controversy regarding the indication for this procedure. For patients with UC-associated cancer, total proctocolectomy (TP) is the standard of care. RP has the potential to improve quality of life, but there is a potential risk of residual tumor and local recurrence. The choice between TP and RP is based on patient preference and clinical criteria.

The risk of UC-associated cancer increases with the duration and extent of UC. The risk of UC-associated cancer after UC diagnosis is 2%, 8%, and 18% at 10, 20, and 30 years, respectively.[10] Therefore, surveillance colonoscopy is recommended in these patients. Development of UC-associated cancer is always accompanied (and probably preceded) by dysplastic change in the colorectal mucosa.[11] If high-grade dysplasia and/or adenocarcinoma are detected on surveillance colonoscopy, TP or RP is indicated.[12–17]

UC-associated cancer has distinct clinicopathologic features from sporadic colorectal cancer.[18] Flat mucosal cancer is one of the most common clinicopathologic characteristics of UC-associated cancer,[18,19] with the lesion margins generally difficult to identify endoscopically. Complete resection of the flat mucosal lesions is necessary to achieve R0 resection of these tumors. When RP is performed for UC-associated cancer in the lower rectum, there is a risk of a positive distal margin and subsequent residual cancer. However, there have been no studies to date that have investigated the distal margin in RP for UC-associated lower rectal cancer, and as such, the benefit of RP these patients remain unclear. In the present study, we aimed to clarify the feasibility of RP in patients with UC-associated cancer in the lower rectum.

2. Methods

2.1. Patients

The study was approved by the Ethics Committee of the School of Medicine at Niigata University (approval number 2218) and performed in accordance with the Declaration of Helsinki. The need for patient consent was waived due of the retrospective nature of the research. A review of the colorectal database at the Niigata University Medical and Dental Hospital between January 2000 and December 2016 identified 24 patients who had undergone surgery for UC-associated cancer. Patients were eligible for inclusion in the study if they had histologically confirmed UC-associated cancer in the lower rectum and had not received neoadjuvant chemotherapy and/or radiotherapy. Eleven of the 24 patients underwent surgery for UC-associated lower rectal cancer; nine patients underwent RP (Fig. 1) and two underwent TP (Fig. 2) for invasive cancer in the anal canal. The study population included the nine patients who underwent RP (Fig. 3, Table 1).

2.2. Surveillance program for detecting UC-associated cancer

A surveillance program was applied to UC patients (left-sided colitis and pancolitis) for whom seven years or more had passed since the onset of disease. Typically, in our institution, an annual surveillance colonoscopy was performed, with a targeted biopsy performed if the patient had area suspected for UC-associated cancer.[20]

2.3. Treatment and follow-up schedule

Selection of operative procedure was determined by the clinical features of the disease and patient preference. RP was performed if the distal tumor edge was located at least 2 cm from the dentate line in the preoperative diagnosis. Conversely, TP was performed if the distal tumor edge was within 2 cm of the dentate line. As an exception, RP with intersphincteric resection (ISR) was performed for a tumor located within 2 cm of the dentate line and the tumor was diagnosed as clinical Tis/T1. The criteria of RP with ISR for UC-associated cancer was based on the criteria of ISR for sporadic lower rectal cancer,[21] and the procedure was performed following rigorous informed consent. During the study period, the RP procedure at our institution consisted of mucosectomy with a hand-sewn ileal pouch-anal anastomosis. No patient underwent RP with a double-stapled anastomosis,[22] and we did not perform any lateral pelvic lymph node dissection, as no patients fulfilled the criteria for this procedure.[21] Additionally, no patients underwent any preoperative chemoradiation for UC-associated cancer during the study period. Patients with stage III disease received adjuvant chemotherapy (5-fluorouracil or one of its derivatives) for approximately six months. Patients were observed postoperatively according to the follow-up schedule outlined in the Japanese Society for Cancer of the Colon and Rectum guidelines.[21] Carcinoembryonic antigen and carbohydrate antigen 19-9 levels were monitored periodically. Disease recurrence was mainly determined by chest-abdominal-pelvic computed tomography scans. Proctoscopy and/or pouchoscopy was performed on an annual basis where possible. Median follow-up duration was 60 (range 17—159) months.

2.4. Operative procedure for RP

The operative procedure for RP with mucosectomy and a hand-sewn anastomosis was as follows: the entire colon was

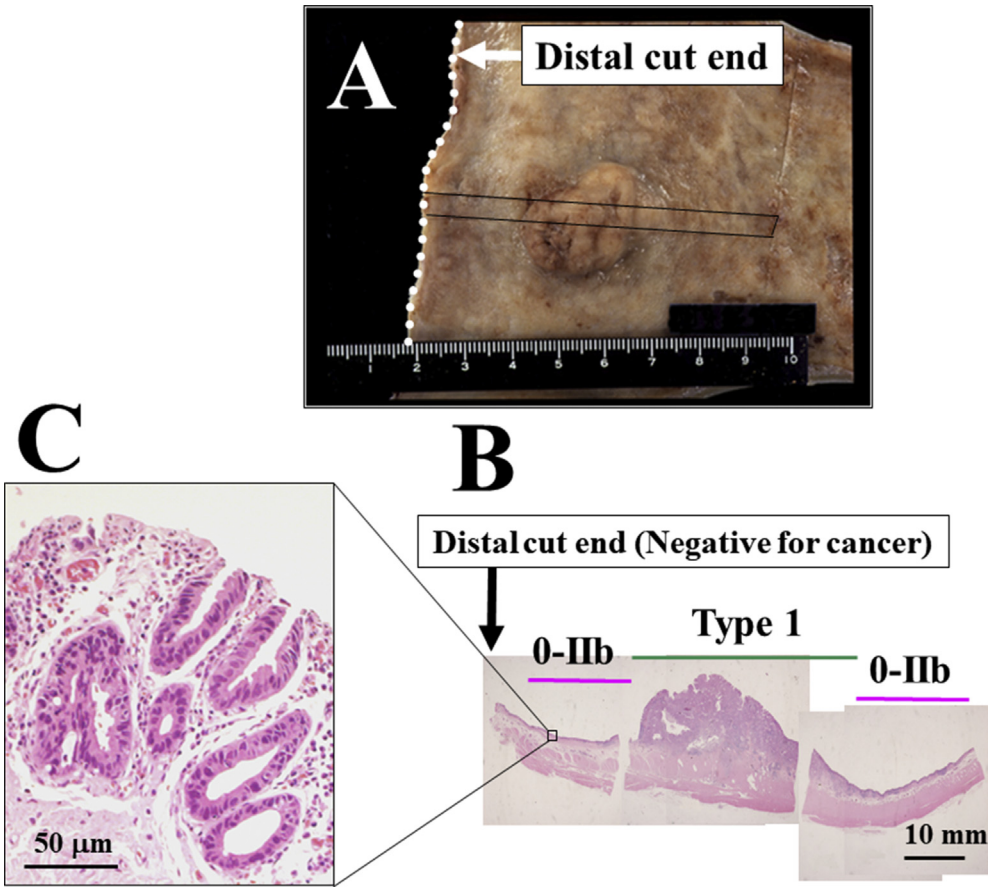

Figure 1 Representative case of restorative proctocolectomy for ulcerative colitis-associated cancer in the lower rectum. This case had T2 cancer with flat mucosal lesion, and the distal margin was 10 mm (Case 7 in Table 2). Macroscopic picture (A). Hematoxylin and eosin staining, ×1 objective lens (B). Hematoxylin and eosin staining, ×20 objective lens (C).

mobilized and the ileum was divided just proximal to the ileocecal valve. The mesenteric artery feeding the UC-associated neoplastic lesion was ligated and cut at the root of the artery. When there was no cancer in the cecum or ascending colon, the ileocecal artery and vein were preserved to maintain blood supply to the ileal pouch. The dissection of the rectum was extended to the level of the superior border of the puborectalis muscle. The dissection was kept close to the mesorectal fascia to avoid damaging the pelvic autonomic nerves. The mucosa in the anal transitional zone was resected proximal to the dentate line via the anus. The rectum was transected about 2 cm proximal to the dentate line, and the colon and rectum were removed. A W-shaped or J-shaped ileal pouch was created and attached to the anus by a hand-sewn anastomosis. A temporary loop ileostomy was created to protect the anastomosis.

2.5. Rectal anatomic division and macroscopic tumor classification

The anatomic division of the rectum and the macroscopic tumor type were defined according to the Japanese Classification of Colorectal Carcinoma.[23] The rectum was defined as the portion of the large intestine located between the inferior border of the second sacral vertebra and the superior border of the puborectalis muscle. The rectum was divided into upper and lower portions, and the border between these two portions was defined as the peritoneal reflection. Hence, the lower rectum was defined as the large intestine between the peritoneal reflection and the superior border of the puborectalis muscle.

The tumors were classified macroscopically as type 0 (superficial), type 1 (polypoid), type 2 (ulcerated with a clear margin), type 3 (ulcerated with infiltration), and type 4 (diffusely infiltrating). Type 0 tumors were further subdivided into 5 categories: 0-Ip (pedunculated), 0-Is (sessile), 0-IIa (elevated), 0-IIb (flat), and 0-IIc (depressed). In the present study, UC-associated flat mucosal cancers were categorized as 0-IIb lesions.

2.6. Pathologic examination

The excised specimen was opened along the antimesenteric border and macroscopically evaluated. Mesenteric lymph nodes were dissected out for histologic examination immediately after the resection by removing the mesenteric fatty tissue. The bowel specimen was then fixed in 10% formalin and sent for pathologic examination where paraffin-embedded sections of the entire tumor mass were prepared and whole-mount sections of the rectum were

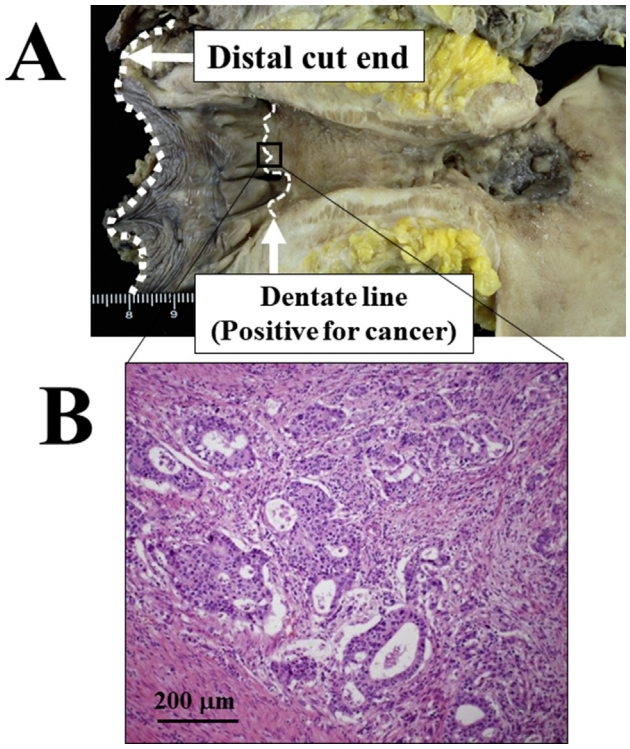

Figure 2 Representative case of total proctocolectomy for ulcerative colitis-associated cancer in the lower rectum. This case had T3 cancer that invaded to the dentate line. Macroscopic picture (A). Hematoxylin and eosin staining, ×10 objective lens (B).

prepared to detect cancer in the lower rectum in all the patients with UC-associated cancer.

3. Results

3.1. UC-associated lower rectal cancers of the flat mucosal type

The median size of the nine lower rectal cancers was 55 (range 5—120) mm. On microscopic examination, eight (89%) of the nine patients had a flat mucosal type of cancer, that is, a 0-IIb lesion, which was either solitary or coexisting with an elevated lesion. In all cases, the flat mucosal lesion was in an area of chronically inflamed mucosa where the border between neoplastic tissue and non-neoplastic tissue was not clear. As such, the distal margin of the lesion could not be endoscopically diagnosed in any of these eight patients.

3.2. Distal margins in specimens obtained by RP

On microscopic examination for diagnostic purposes, the flat mucosal type of lower rectal cancer was often found to have spread near to the dentate line. The median length of the distal margin was 22 (range 0—55) mm. The distal margin was negative in eight (89%) of the nine patients and positive in one patient with a flat mucosal cancer (Table 2).

3.3. Oncologic outcome after RP for UC-associated lower rectal cancer

All patients underwent closure of the temporary ileostomy approximately 2—3 months after RP. No patient developed local or distant recurrence. The one patient with a positive distal margin was annually examined using pouchoscopy with or without biopsy near the anastomosis, but had no local recurrence during follow-up and died of pancreatic cancer 81 months after RP. The remaining eight patients were all alive at the final observation. Five-year and 10-year overall survival rates for the nine patients were 100% and 66.7%, respectively. Five-year and 10-year cancer-specific survival rates for the nine patients were both 100%.

4. Discussion

In this study we demonstrated that patients with UC-associated lower rectal cancer often have a flat type of mucosal cancer that spreads close to the distal margin. The oncologic outcome of RP in these patients was mostly favorable, which suggests RP is feasible in patients with UC-associated cancer of the lower rectum.

While RP is often performed in patients with UC-associated colorectal cancer, there has been limited published research on the benefit of RP in UC-associated cancer of the lower rectum.[12—17] Merchea et al investigated the oncologic outcomes and function of the pouch in 11 patients who underwent RP for UC-associated rectal cancer, and suggested that the presence of early-stage UC-associated neoplasia in the rectum should not be considered a contraindication for RP.[16] Similarly, Remzi et al reported the oncologic outcomes and functioning of the pouch in 22 patients who underwent RP for UC-associated rectal cancer, and considered RP to be successful in these patients.[17] However, unlike our present study, the previous studies did not focus on UC-associated lower rectal cancer, and did not investigate pathologic features or distal margins.

RP with mucosectomy and a hand-sewn anastomosis is a radical procedure that includes mucosectomy of the anal transitional zone (which extends proximally from the dentate line),[23] and a hand-sewn ileal pouch-anal anastomosis.[22] In contrast, RP with a double-stapled anastomosis retains the mucosa of the anal transitional zone and is superior in terms of postoperative defecation function.[22] Previous studies have shown that patients who undergo RP with a double-stapled anastomosis have a superior functional outcome and better quality of life than those who undergo RP with mucosectomy and a hand-sewn anastomosis.[24—26] Both techniques have similar early postoperative functional outcomes; however, RP with a double-stapled anastomosis provides improved nocturnal continence.[24] However, there is a risk of residual tumor in the retained rectal mucosa when RP with a double-stapled anastomosis is used in a patient with UC-associated lower rectal cancer. Hence, we recommend a detailed preoperative assessment including biopsy near the dentate line to rule out a flat mucosal cancer that might extend to this line, which would be a contraindication to RP with a double-stapled anastomosis.

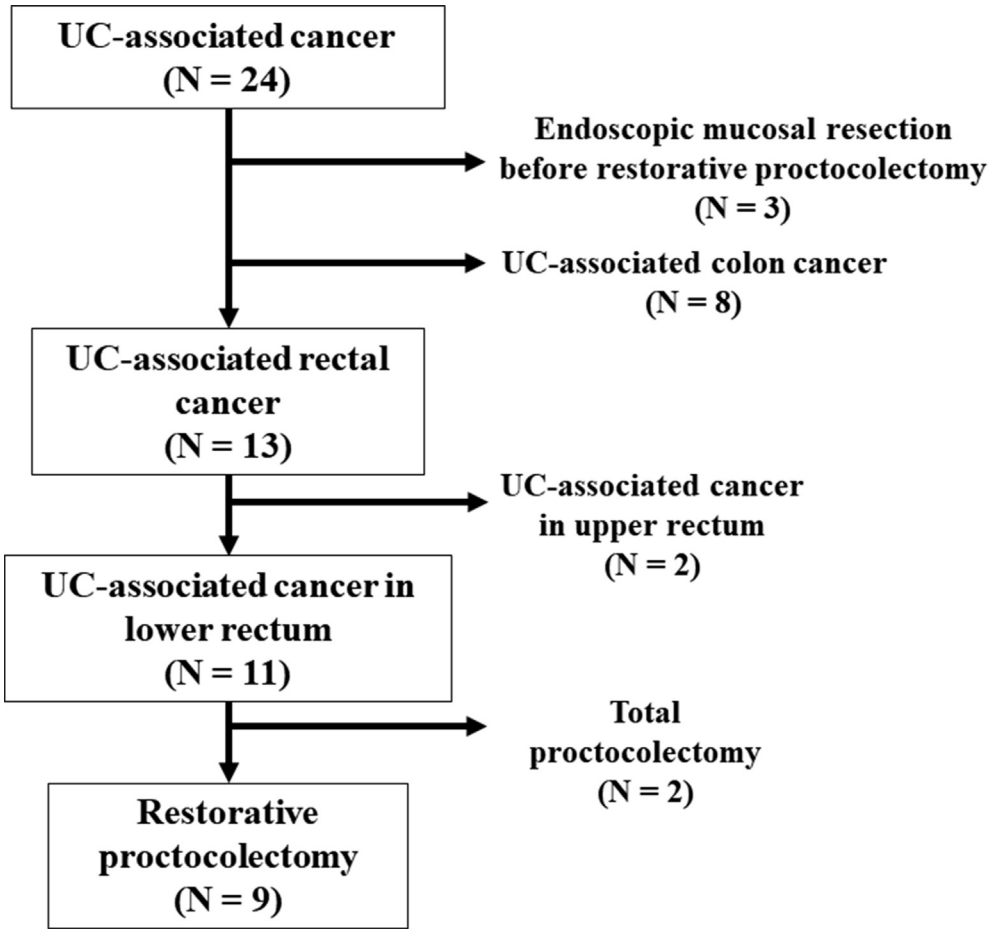

Figure 3 CONSORT diagram showing the selection of patients with ulcerative colitis-associated cancer in the study.

Table 1 Clinical features of patients who underwent restorative proctocolectomy for UC-associated lower rectal cancer.

Variable	Modality	
Age, years[a]		53 (33—76)
Sex	Male, Female	6, 3
Duration of disease prior to operation, years[a]		15 (10—41)
Extent of colitis	Pancolitis, Left-sided	8, 1
Diagnosis at surveillance colonoscopy	Yes, No	6, 3
Synchronous cancers	Yes, No	5, 4
Stage (Lower rectum)[b]	0, I, II, III, IV	5, 2, 0, 2, 0
Stage (Overall)[c]	0, I, II, III, IV	2, 4, 0, 3, 0

UC, ulcerative colitis.
[a] Data are expressed as the median (range).
[b] According to the lesion of lower rectum.
[c] When synchronous tumors were present, Stage (Overall) describes the most advanced lesion.

RP with ISR might be a reasonable treatment option for UC-associated cancer. Inoue et al reported their experience of chemoradiotherapy followed by RP with partial ISR for advanced rectal cancer associated with ulcerative colitis.[27] In this analysis, we reported a patient who underwent RP with ISR for a clinical T1 cancer located 1 cm from dentate line in preoperative diagnosis (Table 2; Case 6). However, postoperative microscopic examination revealed a positive distal margin due to flat mucosal cancer. We consider that RP with ISR for UC-associated cancer should be carefully applied under a detailed preoperative assessment, including biopsy near the dentate line, to ensure no flat mucosal cancer extends to this line.

There is a possibility that pouch-related neoplasia occurs following RP for UC, even after RP with mucosectomy and a hand-sewn anastomosis.[28—31] While the mechanisms of pouch-related neoplasia have not been fully elucidated, two potential causes are development of neoplasia in the retained rectal mucosa and residual neoplasia remaining after RP. In our present study, the focus was on the latter possibility, so the distal margins were carefully examined. Because there is possibility of malignant change of mucosal inflamed lesion in lower rectum, we think that separate mucosectomy might not be justified for RP in UC-associated cancer. Previous studies have indicated that RP with mucosectomy does not necessarily eliminate the risk of pouch-related neoplasia, so we recommend continued surveillance of the anastomotic site and ileal pouch even if RP with mucosectomy is performed.[32,33]

Our analysis had two main limitations. First, it was a retrospective single-center design with small sample size.

Table 2 Pathologic features and outcomes in patients who underwent restorative proctocolectomy for UC-associated lower rectal cancer.

	Age (years)	Sex	Macroscopic type[a]	Flat mucosal cancer	Tumor size (mm)	Histologic grade	T category[b]	N category[b]	M category[b]	Stage (Lower rectum)[b]	Distal margin (mm)	Recurrence	Prognosis	Follow-up (months)
1	33	Male	0-IIb	Present	80	1	Tis	N0	M0	0	22	Absent	Alive	50
2	51	Male	0-IIb	Present	5	1	Tis	N0	M0	0	25	Absent	Alive	101
3	72	Female	0-IIb	Present	10	1	Tis	N0	M0	0	20	Absent	Alive	60
4	76	Female	0-IIb	Present	55	1	Tis	N0	M0	0	45	Absent	Alive	19
5	37	Male	0-IIb	Present	70	1	Tis	N0	M0	0	20	Absent	Alive	17
6	53	Male	0-Is + 0-IIb	Present	37	1	T1	N0	M0	I	0[c]	Absent	Deceased[d]	81
7	47	Female	1 + 0-IIb	Present	120	1	T2	N0	M0	I	10	Absent	Alive	65
8	71	Male	3 + 0-IIb	Present	30	3	T3	N1	M0	III	33	Absent	Alive	55
9	57	Male	2	Absent	93	2	T3	N1	M0	III	55	Absent	Alive	159

UC, ulcerative colitis.
[a] See definition of macroscopic type in the Methods section.
[b] According to the lesion of lower rectum.
[c] This patient underwent restorative proctocolectomy with intersphincteric resection for clinical T1 cancer located 1 cm from dentate line, and microscopic examination revealed a positive distal margin due to flat mucosal cancer.
[d] Patient died of primary pancreatic cancer.

However, UC-associated lower rectal cancer is rare, and previous studies of UC-associated rectal cancer reported by high-volume centers have also included small sample sizes.[16,17] In this study, we identified only nine patients with UC-associated lower rectal cancer, including invasive cancer. A second limitation was that we could not report a precise cancer location from the anal canal. This was due to flat mucosal lesions in an area of chronically inflamed mucosa, which made the border between neoplastic tissue and non-neoplastic tissue unclear. Hence, we could only detect the existence of UC-associated cancer in the lower rectum. Nevertheless, this is the first report to confirm the feasibility of RP in patients with UC-associated lower rectal cancer.

In conclusion, flat mucosal cancer is frequently observed in patients with UC-associated lower rectal cancer. However, when these patients have no invasive cancer in the anal canal, RP is feasible and not necessarily contraindicated.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.01.003.

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