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Original Article

Clinical Impact of Clinicopathological Characteristics of Undifferentiated Advanced Gastric Cancer in Elderly Patients

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ABSTRACT

Background: Little is known about the clinicopathological findings in elderly patients with undifferentiated advanced gastric cancer. The aim of this study was to clarify the clinical impact of clinicopathological characteristics of those cancers in elderly patients.

Method: A total of 42 patients aged 80 years or older with advanced gastric cancer who had undergone curative gastrectomy between 1998 and 2015 were included in this study. All patients were classified into two principal subgroups based on histology: undifferentiated group and differentiated group. The two groups were examined and compared with respect to the pathological findings and clinical outcomes.

Results: Of the 47 patients, 23 (49%) patients were in the undifferentiated group and 24 (51%) were in the differentiated group. The undifferentiated cancer was less frequently located in the upper third of the stomach than the differentiated cancer (4% vs 42%, $P < 0.01$). The frequency of the cancer with depth of T4a was higher in the undifferentiated group than in the differentiated group (48% vs. 17%, $P < 0.05$). The median number of metastatic lymph nodes in the undifferentiated group was more than that in the differentiated group (3 vs. 1, $P < 0.05$). In short- and long-term outcome after curative gastrectomy, there were no differences between the two groups.

Conclusion: In elderly patients, undifferentiated advanced gastric cancer may have more malignant potential than differentiated cancer. However, by curative gastrectomy, the elderly patients with undifferentiated advanced gastric cancer can be obtained the equivalent clinical outcome to those with differentiated cancer.

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Introduction

Recently, the number of elderly persons has been increasing worldwide [1]. Especially, the population of people over 80 years of age has risen dramatically in Japan. In line with this aging, the incidence of patients with gastric cancer has also been gradually increasing [2]. Thus, about 20% of patients over the age of 80 years in Japan have gastric cancer [3]. However, surgical treatment for elderly patients with advanced gastric cancer is still controversial, and because of their lowered immunity and increased comorbidities, they are considered at high risk for major abdominal surgery such as total gastrectomy with radical lymphadenectomy. In addition, published data and evidence on elderly

patients with advanced gastric cancer is limited. Therefore, there are still no specific therapeutic guidelines for this age group worldwide.

Presently, gastric cancer in elderly patients is considered to have pathological characteristics distinct from those in young patients [4]. Previous studies have indicated that gastric cancer in elderly patients was mainly well-differentiated adenocarcinoma, irrespectively tumor stage, and it was believed that gastric cancer in elderly patients tends to show slower tumor growth with less metastatic potential [5, 6]. However, recent studies have stressed that more aggressive pathological characteristics have been observed in elderly patients with advanced gastric cancer as compared to those at the early stage [5, 7]. These

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observations may have been made due to a trend of decreasing intestinal-type adenocarcinoma resulting from *Helicobacter pylori* eradication in elderly patients because intestinal-type and well-differentiated adenocarcinomas are well known to be closely related to gastritis caused by chronic *H. pylori* infection, and *H. pylori* eradication treatments are popular. Clinicians need to take the pathological features into consideration when treating these elderly patients with gastric cancer as pathological findings among elderly patients can indicate adenocarcinoma such as intestinal type, which is known to have good prognosis [8]. However, little is still known about the clinicopathological characteristics of undifferentiated advanced gastric cancer in elderly patients. Therefore, the aim of this study was to clarify the clinicopathological characteristics of undifferentiated advanced gastric cancer in elderly patients. We retrospectively examined patient records to compare undifferentiated with differentiated advanced gastric cancer in elderly patients aged 80 years or older after curative gastrectomy.

Materials and Methods

I Patients

We retrospectively analyzed surgical and pathological data of 47 patients aged 80 years or older with advanced gastric cancer (deeper than pathological T2) who had undergone curative gastrectomy with lymph node (LN) dissection in our department between January 1998 and December 2015. We followed the methods of our previous study [9]. All patients underwent upper gastrointestinal endoscopic examination and abdominal CT examination with contrast preoperatively for the planning of curative surgery. The number of LNs and the extent of LN dissection were based on the Japanese Gastric Cancer Treatment Guidelines, 14th edition [10]. The tumors were staged according to the UICC, 7th edition. Roux-en-Y reconstruction was performed in all patients undergoing distal or total gastrectomy. Esophago-gastric tube anastomosis was performed in one patient with proximal gastrectomy. In the pathological examinations, the depth of cancer invasion into the gastric wall was examined at the longest cut section line of the tumor, and the status of LN metastasis was examined at the largest cut section of the LN. All

tissues were examined by expert pathologists. Follow-up examinations were performed at least twice a year for up to 5 years. They consisted of a clinical examination, blood tests, thoraco-abdominal CT examination, and upper gastrointestinal endoscopic examination.

All patients were classified into two principal subgroups based on histology: the undifferentiated group, including patients with poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous carcinoma, and the differentiated group, including patients with papillary and well- or moderately differentiated adenocarcinoma [9]. Patients' findings such as age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS) classification, serum levels of albumin, hemoglobin, and carcinoembryonic antigen (CEA); operative findings including procedure, approach, area of LN dissection, number of dissected LNs, operation time, and blood loss; and pathological findings including tumor location, macroscopic type, pTNM factors, tumor stage, and lymphovascular invasion were examined and compared between the undifferentiated group and the differentiated group. Postoperative complications were defined as any condition requiring conservative or surgical treatment occurring within 30 days after the operation. Postoperative surgical complications included anastomotic leakage, pancreatic fistula, intra-abdominal abscess, intra-abdominal bleeding, stasis, and surgical site infection. Postoperative general complications included respiratory, cardiovascular, and renal disorders, and enterocolitis [9]. Postoperative mortality was defined as death within 30 days of operation.

II Statistical Analysis

Quantitative data are given as the median and range. Differences between the two groups were assessed by the chi-square test, Fisher's exact test, or Mann-Whitney U test as appropriate. These analyses were carried out using EZR (version 1.33; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user EZR is a modified version of R commander (version 2.3-0) designed to add statistical functions frequently used in biostatistics. A *P*-value < 0.05 was considered statistically significant.

Table 1: Patient characteristics.

Factors	Differentiated type group (n = 24)	Undifferentiated type group (n = 23)	<i>P</i> -value
Age (years)*	83 (80-88)	83 (80-92)	0.772
Sex (M/F)	18/6	10/13	0.039
BMI (kg/m ²)*	22.1 (15.0-30.0)	22.3 (16.8-28.6)	0.792
ASA*	2 (1-3)	2 (1-3)	0.841
Comorbidity -/+	10/14	7/16	0.547
Cardiovascular	7	6	
Hypertension	5	8	
Diabetes	3	3	
Pulmonary	3	1	
Renal	1	0	
Brain infarction	2	3	
Albumin (g/dl)*	4.7 (2.7-4.5)	3.5 (2.8-4.2)	0.264
Hemoglobin (g/dl)*	12.1 (7.6-16.3)	11.4 (8.5-12.0)	0.333
CEA (ng/ml)*	2.6 (0.9-47.3)	2.3 (0.7-7.1)	0.180

*Median (range).

BMI: body mass index; ASA: American Society of Anesthesiologists; CEA: carcinoembryonic antigen.

Results

I Patients and Operative Findings

Of the 47 patients, 23 (49%) were classified into the undifferentiated group. The ratio of patients in the undifferentiated and differentiated groups was almost the same in this study. Patient characteristics and operative findings are presented in (Tables 1 & 2). Thirty patients (64%) had at least one co-morbid condition. The frequency of females was

significantly higher in the undifferentiated group than in the differentiated group (57% vs. 25%, $P < 0.05$). There were no significant differences between the two groups in age, BMI, ASA-PS classification, and comorbidities. The serum levels of hemoglobin and CEA were lower in the undifferentiated group, but not significantly so. No significant differences were observed in surgical procedures, approaches, LN dissection area, the number of dissected LNs, operative time, and intraoperative blood loss between the two groups.

Table 2: Operative findings.

Factors	Differentiated type group (n = 24)	Undifferentiated type group (n = 23)	P-value
Procedure	14/9/1	17/6/0	0.441
DG/TG/PG			
Approach	14/10	19/4	0.111
Open/Lap			
Lymph node dissection area	6/4/14	10/2/11	0.388
D1/D1+/D2			
Number of dissected lymph nodes*	21.5 (7-43)	25.0 (4-51)	0.287
Operation time*	256 (143-645)	250 (145-500)	0.587
Blood loss*	195 (5-1050)	215 (5-3060)	0.595

*Median (range).

DG: distal gastrectomy; TG: total gastrectomy; PG: proximal gastrectomy; Lap: laparoscopic.

II Pathological Findings

Pathological findings are presented in (Table 3). The tumors in the undifferentiated group were less frequently located in the upper third of the stomach than those in the differentiated group (4% vs. 42%, $P < 0.01$). Six patients were observed to have Borrmann type 4 cancer only in the undifferentiated group. As for depth of cancer invasion into the gastric wall, a pathological T4a tumor was more frequently present in

the undifferentiated group than in the differentiated group (48% vs. 17%, $P < 0.05$). Although there were no significant differences in LN metastasis between the two groups, the median number of metastatic LNs in the undifferentiated group was greater than that in the differentiated group (3 vs. 1, $P < 0.05$). No significant differences were observed in macroscopic gross type, maximum diameter, tumor stage, and lymphovascular invasion between the two groups.

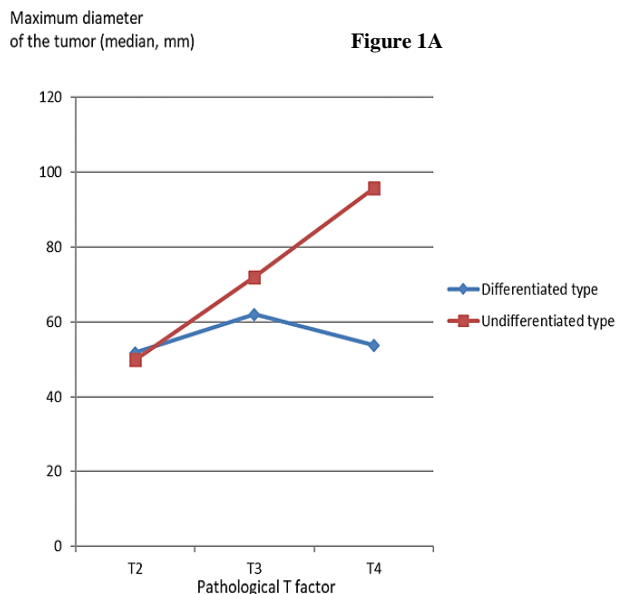
Table 3: Pathological findings.

Factors	Differentiated type group (n = 24)	Undifferentiated type group (n = 23)	P-value
Tumor location U/M/L	10/3/11	1/12/10	0.001
Macroscopic type 0/1/2/3/4	4/0/12/6/0	4/0/9/4/6	0.054
Maximum diameter (mm)*	52 (24-96)	68 (18-180)	0.139
Depth of invasion			
pT2, T3	20	12	0.031
pT4a	4	11	
pN -/+	11/13	5/18	0.125
Number of metastatic lymph nodes*	1 (0-10)	3 (0-29)	0.044
fStage			0.203
IB	9	4	
II	9	8	
III	6	11	
ly -/+	6/18	2/21	0.245
v -/+	7/17	12/11	0.142

*Median (range).

III Tumor Growth and Progression in Elderly Patients

We examined the correlation between pathological T factor and other pathological factors in each group. In the undifferentiated group, the more the pathological T factor advanced, the larger the tumor size grew



(Figure 1A). In the undifferentiated group, LN metastases were observed regardless of the cancer depth of invasion (Figure 1B). In the differentiated group, however, the more the pathological T factor advanced, the more the number of LN metastases increased.

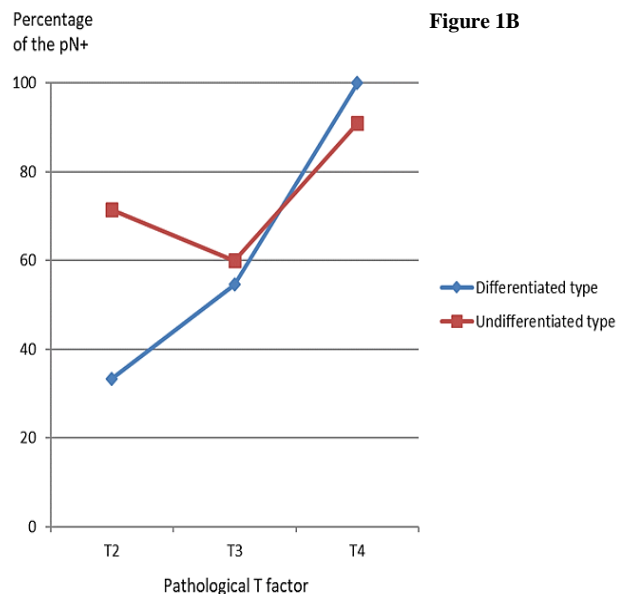


Figure 1: The correlation between pathological T factor and tumor size, and LN metastases in each group. **A)** According to tumor size, the more the pathological T factor advanced, the larger the tumor size grew in the undifferentiated group. **B)** LN metastases were observed regardless of the cancer depth of invasion in the undifferentiated group.

IV Short-Term Outcomes

Postoperative short-term outcomes are summarized in (Table 4). There were no operation-related deaths. Twenty-three postoperative complications were observed in 20 patients, and the overall morbidity rate was 43%. None of these complications were classified as grade $\geq 3b$ in the Clavien-Dindo classification, and the rate of complications of

grade 3a was 11% [12]. Postoperative complications were more frequently observed in the undifferentiated group than in the differentiated group (57% vs. 29%), but the difference was not statistically significant. There were also no significant differences in the time to tolerate a solid diet and postoperative hospital stay between the two groups.

Table 4: Postoperative short-term outcomes.

Factors	Differentiated type group (n = 24)	Undifferentiated type group (n = 23)	P-value
Postoperative complications	7 (29%)	13 (57%)	0.080
Surgical	5 (21%)	8 (35%)	0.341
Anastomotic leakage	2	2	
Pancreatic fistula	0	0	
Intra-abdominal abscess	0	1	
Intra-abdominal bleeding	0	0	
Stasis	1	4	
Surgical site infection	2	1	
General	2 (8%)	6 (26%)	0.137
Respiratory	2	4	
Cardiovascular	0	0	
Renal	0	0	
Colitis	0	2	
Hospital mortality	0	0	
Meal start (days)*	4 (4-38)	4 (4-11)	0.701
Hospital stay (days)*	19 (10-76)	20 (11-60)	0.258

*Median (range).

V Long-Term Outcomes in Elderly Patients

None of the patients in this study received adjuvant chemotherapy. Postoperative recurrences were observed in 8 patients (17%, Table 5). Postoperative recurrences were more frequently observed in the

undifferentiated group than in the differentiated group (22% vs. 13%) but not significantly so. There were also no significant differences in the rates of 3-year overall (Figure 2A) and 3-year relapse-free (Figure 2B) survival between the two groups.

Table 5: Postoperative recurrences.

Factors	Differentiated type group (n = 24)	Undifferentiated type group (n = 23)	P-value
Postoperative recurrence	3 (13%)	5 (22%)	0.461
Type of recurrence			
Local	0	1	
Lymph nodes	2	1	
Peritoneal dissemination	2	4	
Distant organ	1	1	
Liver	0	1	
Brain	1	0	

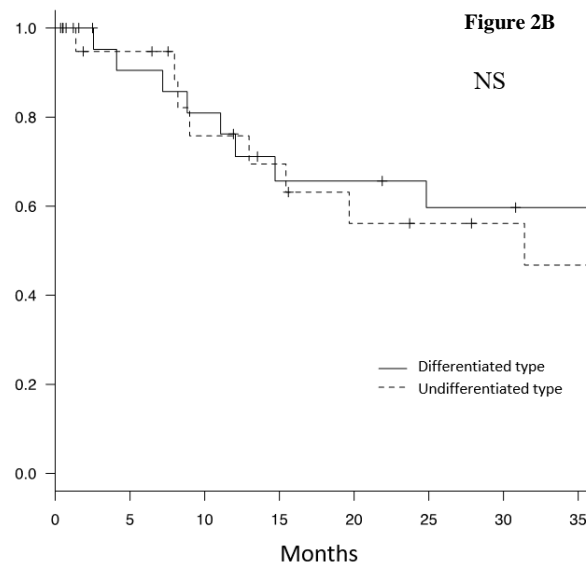
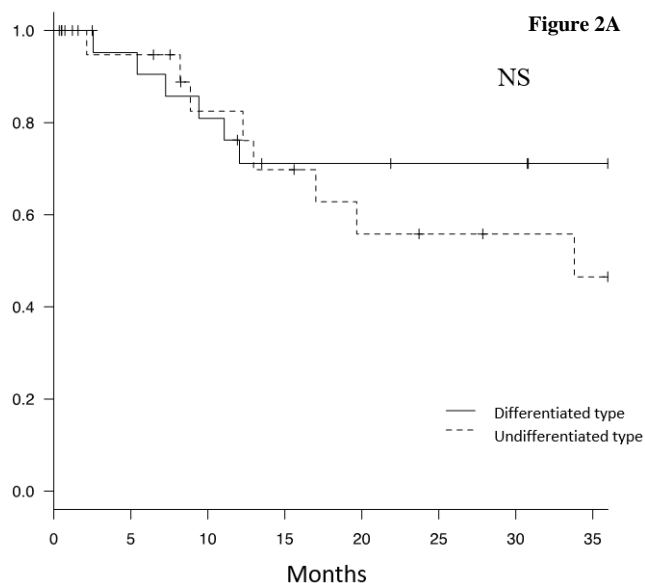


Figure 2: A) 3-year overall and B) 3-year relapse-free survival for elderly gastric cancer patients classified on the basis of tumor differentiation. There were no significant differences in the rates of 3-year overall and 3-year relapse-free survival between the two groups.

Discussion

The number of elderly patients with gastric cancer has been rapidly increasing, especially in Japan. However, there is still insufficient knowledge about the correlation between the histopathological type of cancer, such as differentiated and undifferentiated cancer, and clinical outcomes after curative gastrectomy in elderly patients with advanced gastric cancer. Therefore, this study was designed to evaluate the clinicopathological characteristics of undifferentiated cancer in elderly patients with advanced gastric cancer as compared with differentiated cancer. As a result, undifferentiated cancers were more frequently diagnosed in females and were less often located in the upper third of the stomach. The incidences of T4a cancer and LN metastasis were higher in the undifferentiated group than in the differentiated group, suggesting that undifferentiated cancer has more malignant potential than differentiated cancer. However, there were no differences in prognosis

between the undifferentiated and differentiated groups in these patients who had undergone curative gastrectomy.

Previous studies reported that differentiated gastric cancer was more common in the elderly, and many studies have noted that gastric cancer in elderly patients was predominantly localized in the lower third of the stomach [5, 13-16]. These pathological characteristics of differentiated gastric cancer in elderly patients were considered to be caused by intestinal metaplasia [17]. However, in the present study, the ratio of patients with undifferentiated and differentiated cancer was almost equal. In addition, undifferentiated cancer, which is known not to be closely related to intestinal metaplasia, was more frequently located in the middle and lower third of the stomach. Although we could not examine the ratio of patients undergoing *H. pylori* eradication treatment in our study, these results might be caused by such treatment. As the incidences of atrophic gastritis and intestinal metaplasia are gradually decreasing by *H. pylori* eradication treatment, the occurrence of

differentiated cancer might also be decreasing in elderly patients. In the upper gastrointestinal examination of elderly patients who underwent *H. pylori* eradication treatment, clinician should perform a detailed observation, especially for the occurrence of undifferentiated cancer in the lower third of the stomach and especially in female patients.

The incidence of pathological T4a cancer in the present study was greater in the undifferentiated group, and we also found that the more the pathological T factor advanced, the larger the tumor grew in this group. It is well known that differentiated gastric cancer tends to grow expansively, whereas undifferentiated cancer tends to grow in a diffuse and infiltrative manner. Kitamura *et al.* reported that one of the histopathological characteristics of gastric cancer in the elderly was an expansive growth pattern of the tumor [18]. However, some studies revealed that gastric cancer in elderly patients might principally develop as differentiated lesions that progress to undifferentiated ones [5, 16]. Usually, gastric cancer in elderly patients tends to be diagnosed at an advanced stage because of non-obvious symptoms and less frequent screening by endoscopic examination. To improve the outcome of gastric cancer in elderly patients, more aggressive screening and detailed surveillance, which may result in early diagnosis of undifferentiated gastric cancer, is needed.

In the undifferentiated cancer in this study, LN metastasis and lymphovascular invasion were observed regardless of the depth of cancer invasion into the gastric wall. We also found that the median number of metastatic LNs in the undifferentiated group was significantly greater than that in the differentiated group. Kitamura *et al.* reported that lymphovascular invasion was more frequent in the elderly than in the middle-aged patients [18]. These findings indicate that gastric cancer in elderly patients has more aggressive features in terms of LN metastasis and lymphovascular invasion, especially in undifferentiated cancer. In the present study, LN metastases were observed in more than 70% of patients with T2 gastric cancer in the undifferentiated group. Radical gastrectomy with D2 lymphadenectomy is thought to be applicable to undifferentiated gastric cancer, even if the depth of cancer invasion into the gastric wall is T2, in elderly patients without serious comorbidities and significant risk of complications.

In terms of short-term outcomes of patients with advanced cancer after gastrectomy, postoperative complications were more frequently observed in the undifferentiated group. One possible reason for this result is that open gastrectomy was performed in 83% of patients in the undifferentiated group. Thereby, respiratory complications, such as pneumonia, and colitis were more frequently observed in the undifferentiated group. As for long-term outcomes, there were no differences between the patients in the undifferentiated and differentiated groups. There is still no consensus based on previous studies of the prognosis of elderly patients with advanced gastric cancer. Some reports have shown that elderly patients had poorer survival as compared with middle-aged patients [13, 18, 19]. As reasons for this, a weakened host-defense status, delayed diagnosis, and therapeutic bias including extended radical resection and strong chemotherapy, are considered in elderly patients.

Conversely, Kim *et al.* showed that survival rates of elderly and young patients did not differ, and age itself was not an independent prognostic

factor [14]. There are a few reports on the correlation between histological differentiation of cancer and patient prognosis in elderly patients with gastric cancer. Lu *et al.* showed that well-differentiated histopathology was a factor favoring longer survival in elderly patients aged 65 years and older with advanced or metastatic gastric cancer [20]. However, Liang *et al.* reported that tumor differentiation was not an independent prognostic factor in survival analysis of elderly patients with gastric cancer [13]. Lim *et al.* showed that gastric cancer in elderly patients had less aggressive pathological features because of more lesions with microsatellite instability [21]. In the present study, we also found no correlation between the histopathologic differentiation of cancer and patient prognosis after curative gastrectomy in elderly patients with advanced gastric cancer.

There are several limitations to this study. First, this retrospective study of elderly patients with advanced gastric cancer included a small number of cases. Second, there is selection bias against the treatment of elderly patients because we excluded the patients who were diagnosed as having a systemic disease and those who were treated by endoscopic procedures. However, as far as we know, this is the first report to focus on the clinicopathological characteristics of undifferentiated advanced gastric cancer in elderly patients. For confirmation of our results, a multi-center, randomized, control study with a larger sample size would be required in the near future.

Conclusion

In this study, undifferentiated advanced gastric cancers in elderly patients were more frequently diagnosed in females and were less frequently located in the upper third of the stomach. The incidences of pathological T4a cancer and LN metastasis were higher in undifferentiated cancer than in differentiated cancer. These results suggest that undifferentiated advanced gastric cancer may have more malignant potential in elderly patients. However, with curative gastrectomy, elderly patients with undifferentiated cancer can obtain a clinical outcome equivalent to that of patients with differentiated cancer. Further studies are necessary to elucidate the clinical impact of the histopathologic differentiation of advanced gastric cancer on the survival of elderly patients with this disease.

Ethical Approval

This study was approved by the Ethical Committee of Oita University Faculty of Medicine.

Consent

All patients included in the study gave their written informed consent.

Funding

None.

Conflicts of Interest

None.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

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