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DYNAMIC MANUSCRIPT

Endoscopic submucosal resection using a ligation device without injection for duodenal neuroendocrine tumors

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Abstract

Background Duodenal neuroendocrine tumors (NETs) measuring ≤ 10 mm in diameter that are confined to the submucosal layer without metastasis are suitable for endoscopic treatment. We previously reported the efficacy and safety of endoscopic submucosal resection with a ligation device (ESMR-L) for duodenal NETs. In order to make the procedure simpler, we attempted ESMR-L without submucosal injection. The aim of this study was to evaluate the efficacy of ESMR-L without injection for duodenal NETs.

Methods A total of 12 patients with small (≤ 10 mm) sporadic duodenal NETs were treated via endoscopic resection at the National Cancer Center Hospital East between December 2010 and May 2018. All patients were evaluated via endoscopy and endoscopic ultrasound, and abdominal computed tomography was performed to rule out metastatic lesions. The patients' characteristics, clinical courses, and complications, such as perforation and bleeding, were retrospectively assessed. We examined the correlation between ESMR-L with or without submucosal saline injection and clinicopathological parameters.

Results The median procedural time for ESMR-L was 13 min. All lesions invaded the submucosal layer, and the histological diagnoses were classified as NET G1 in 11 lesions and NET G2 in one lesion. *En bloc* resection and complete resection were achieved in 12 and 11 lesions, respectively. The postoperative duration of hospital stay was 4 days. At the median follow-up of 17 months, there was no incidence of local recurrence or distant metastasis. Perforation and intraoperative bleeding were not observed. However, delayed bleeding was found in one patient. ESMR-L without submucosal injection required a significantly shorter procedural time than ESMR-L with submucosal saline injection (10 min vs. 15 min, respectively; $p = 0.007$).

Conclusions ESMR-L is safe and effective. Particularly, ESMR-L without submucosal injection could be used to treat these NETs safely within a short period of time.

Keywords Duodenal neuroendocrine tumors · Endoscopic submucosal resection with a ligation device method · Endoscopic resection · Submucosal saline injection · Bipolar snare

Duodenal neuroendocrine tumors (NETs) are rare; they represent 3.8% of all gastrointestinal NETs [1]. Duodenal NETs measuring ≤ 10 mm in diameter and confined to the submucosal layer without metastasis are suitable for endoscopic treatment [2, 3]. Currently, several endoscopic resections, such as endoscopic mucosal resection (EMR) [3, 4], cap endoscopic resection (EMR-c) [4, 5], endoscopic submucosal resection with a ligation device method (ESMR-L) [3], and endoscopic submucosal dissection (ESD) [6–8] are used in the treatment of duodenal NETs. The bowel wall is thinner in the duodenum when compared to other parts of the digestive tract and deeper endoscopic resection is necessary for duodenal NETs; therefore, the incidence of perforation is high in EMR and ESD [4, 6, 7, 9].

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ESMR-L was reported to be effective for rectal NETs [10, 11]. We previously reported the efficacy and safety of ESMR-L in duodenal NETs [12]. Over several years, we encountered a few problems with ESMR-L for duodenal NETs. In the narrow duodenal space, ESMR-L for duodenal NETs is technically more difficult than that for rectal NETs and requires a relatively long procedural time. Moreover, in case of a small NET, the lesion can become indistinguishable following submucosal saline injection (Fig. 1). A previous study reported that no significant relationship was observed in terms of complication rate and procedure type between procedures with and without submucosal lifting [4]. Therefore, in order to make the procedure simpler, we attempted ESMR-L without submucosal injection. For the purpose of this study, we evaluated the efficacy of ESMR-L without submucosal saline injection for duodenal NETs.

Materials and methods

Patients and methods

A total of 12 patients with small (≤ 10 mm), sporadic duodenal NETs were treated via endoscopic resection at the National Cancer Center Hospital East between December 2010 and May 2018. The study protocol was approved by the medical ethics committee of the National Cancer Center Hospital East (2017-434). The requirement for informed consent was waived due to the retrospective design of the study. This study was performed in accordance with the ethical principles outlined in the Declaration of Helsinki.

All patients were evaluated via endoscopy and endoscopic ultrasound (EUS), and abdominal computed tomography was performed to rule out metastatic lesions. The criteria for inclusion were as follows: (1) endoscopic biopsy specimens with a positive histology, (2) lesion diameter ≤ 10 mm, (3) lesion located within the submucosal layer, and (4) no lymph node metastasis or distant metastasis detected. The exclusion criterion was patients' refusal against the use of their clinical data and tissue samples by researchers.

All 12 procedures were performed by a single endoscopist, and the operator performing the duodenal ESMR-L procedure in this study was familiar with both, the rectal ESMR-L technique and endoscopic resection (EMR and ESD). The patients' characteristics, clinical courses, and adverse events, such as perforation and bleeding, were retrospectively assessed. The resected specimens were divided into 2-mm slices after formalin fixation and were stained with hematoxylin and eosin. They were then examined microscopically for depth of invasion, lateral and vertical resection margins, and lymphovascular invasion. Histological diagnosis was performed according to the classification system devised by the World Health Organization. *En bloc* resection was defined as resection of the lesion as a single piece as opposed to piecemeal resection, in which the lesion is resected in multiple segments. *En bloc* complete resection was histopathologically defined as no lateral and vertical involvement of the margins of the resected tumor. We examined the correlation between ESMR-L with or without submucosal saline injection and clinicopathological parameters.

ESMR-L procedure

The ESMR-L procedure was performed after patients received intravenous sedation using 35 mg pethidine hydrochloride and 2–3 mg of midazolam. We used a single-channel upper gastrointestinal endoscope (GIF-Q260J, GIF-H260Z, or GIF-H290Z; Olympus Corporation, Tokyo, Japan) with an attached endoscopic variceal ligation device (MD-48709U EVL Device; Sumitomo Bakelite, Tokyo, Japan).

ESMR-L with submucosal saline injection was performed as previously described (Fig. 2) [10, 12]. We injected saline solution into the submucosal layer. Thereafter, the tumor was aspirated into the ligating barrel, and a rubber band (O-ring) was deployed, creating a pseudopolyp. Subsequently, snare

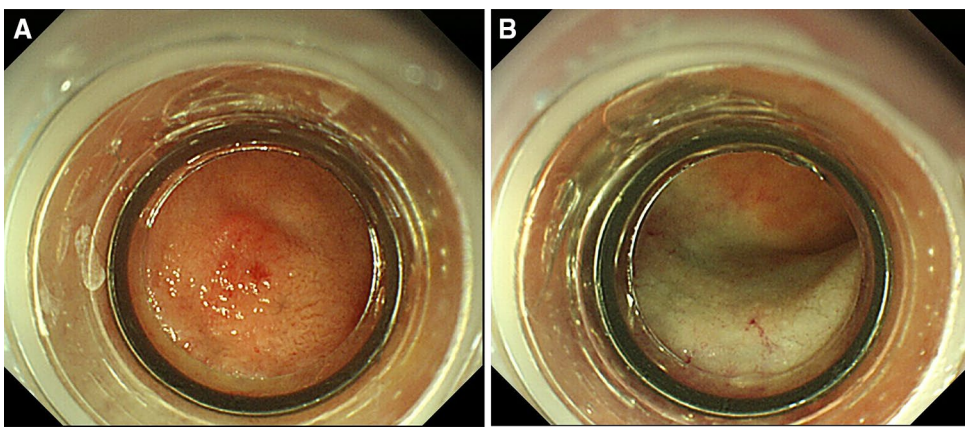

Fig. 1 **A** A neuroendocrine tumor is observed in the inferior wall of the duodenal bulb. **B** The lesion became indistinguishable following submucosal saline injection

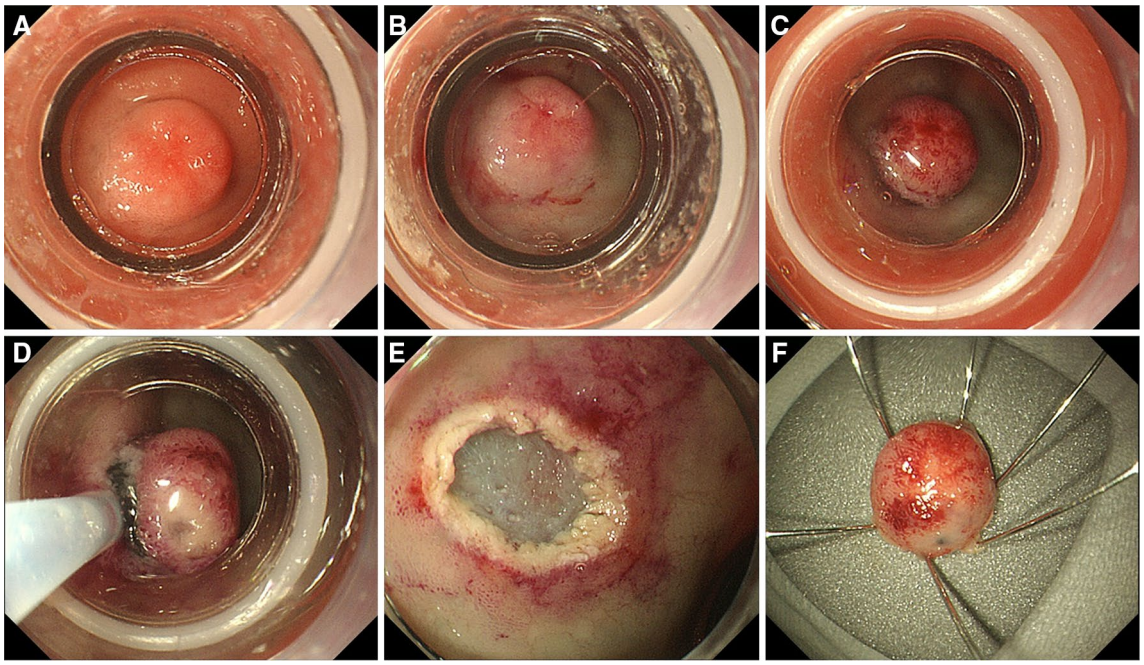

Fig. 2 The procedure of endoscopic submucosal resection using a ligation device method with submucosal saline injection. **A** A neuroendocrine tumor is observed in the anterior wall of the duodenal bulb. **B** Submucosal saline solution is injected into the submucosal layer. **C** The lesion is aspirated into the ligating barrel, and the O-ring is deployed, creating a pseudopolyp. **D** Monopolar snare resection is performed under the O-ring using blended electrosurgical current and the resection specimen is then removed by aspirating it into the cap. **E** The lesion is completely removed. **F** The surface of the resected specimen

resection of the pseudopolyp was performed under the O-ring using monopolar snare (Captivators; Boston Scientific, Boston, MA, USA) in the endo cut mode (ENDO CUT Q; Effect 3, Duration 1, Interval 3) (VIO 300D; ERBE, Germany).

ESMR-L without submucosal injection was performed as follows (Fig. 3): Without submucosal injection, the tumor was mildly aspirated into the ligating barrel, and the O-ring was deployed, creating a pseudopolyp. Subsequently, snare resection of the pseudopolyp was performed under the O-ring using a bipolar snare (Dragonare; Xemex Co. Ltd, Tokyo, Japan) in the forced coagulation mode (Effect 3, 25W) (VIO 300D; ERBE, Germany).

Finally, the resected specimen was removed by aspirating it into the cap.

Statistical analysis

The baseline characteristics of each patient were compared using χ^2 tests or Fisher's exact tests for categorical data. Mann–Whitney *U* tests were used for non-normally distributed continuous variables. Differences with *p* values of less than 0.05 (two-sided) were considered statistically significant. All analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

All 12 patients included in this study underwent ESMR-L. Seven patients (58%) were men and the median patient age was 74 years (range 55–84 years). Eleven tumors (92%) were located in the duodenal bulb, and one was in the descending portion of the duodenum. The median tumor size was 9 mm (range 4–10 mm) (Table 1).

The median procedural time was 13 min (range 5–30 min). Histological analysis revealed that all lesions invaded the submucosal layer, and the histological diagnoses were classified as NET G1 in 11 lesions (92%) and NET G2 in one lesion (8%). *En bloc* resection and complete resection were achieved in 12 (100%) and 11 lesions (92%), respectively. The mean postoperative duration of hospital stay was 4 days (range 3–11 days). At the median follow-up of 17 months (range 1–89 months) after ESMR-L, there was no incidence of local recurrence or distant metastasis (Table 2). As for complications, perforation (intraoperative or delayed) and intraoperative bleeding were not observed. However, delayed bleeding was found in one patient who was treated by endoscopic hemostasis without blood transfusion (Table 3).

Among cases involving ESMR-L procedures, 5 cases involved resection with submucosal saline injection and 7 cases involved resection without injection. Duodenal NETs

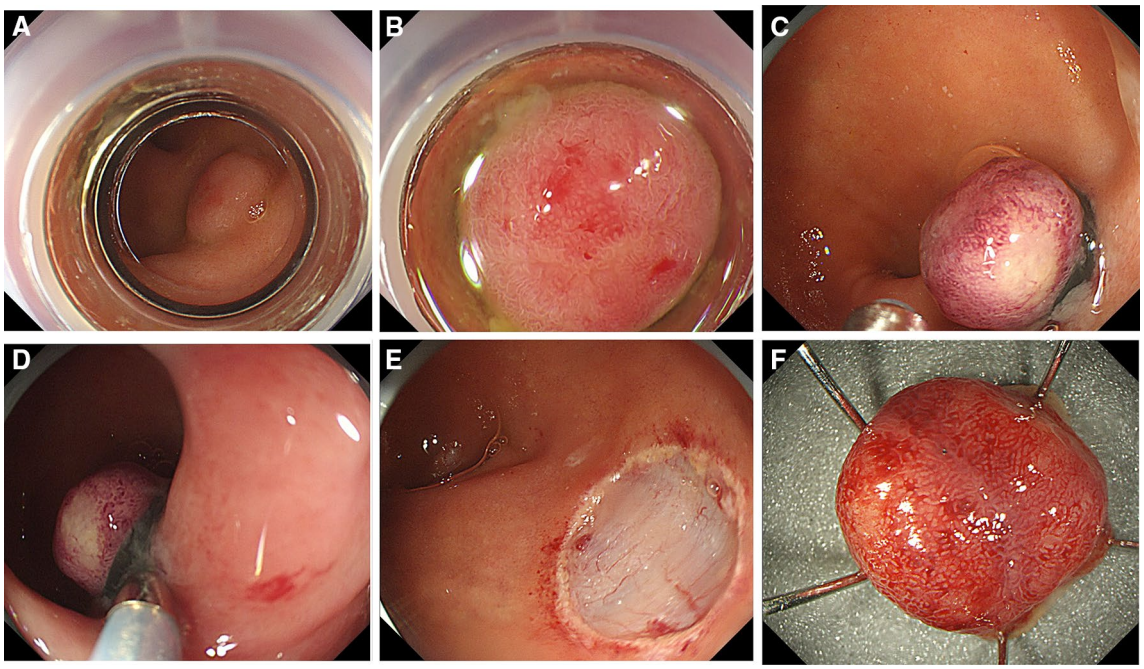

Fig. 3 The procedure of endoscopic submucosal resection using a ligation device method without submucosal saline injection. **A** A neuroendocrine tumor is observed in the inferior wall of the duodenal bulb. **B** Without submucosal injection, the lesion is mildly aspirated into the ligating barrel. **C** The O-ring is deployed, creating a pseudopolyp. **D** Bipolar snare resection is performed under the O-ring in the forced coagulation mode. **E** The muscularis propria of the resected tissue has less damage. **F** The surface of the resected specimen

Table 1 Characteristics of 12 lesions in 12 patients

Sex, *n* (%)	
Male	7 (58)
Female	5 (42)
Age, median, years, (range)	74 (55–84)
Tumor location, *n* (%)	
Bulb	11 (92)
Descending part	1 (8)
Tumor size, median, mm, (range)	9 (4–10)

after the seventh case were all resected without submucosal saline injection. Lesions resected without submucosal injection were comparable to those resected with submucosal saline injection in terms of tumor size, *en bloc* resection rate, *en bloc* complete resection rate, complications, and postoperative duration of hospital stay. However, ESMR-L without submucosal injection required a significantly shorter procedural time than ESMR-L with submucosal saline injection (10 min vs. 15 min, respectively; $p = 0.007$) (Table 4).

In one patient, the elastic band with submucosal saline injection was unclear, resulting in failure of *en bloc* complete resection.

The muscularis propria of the resected tissue obtained without submucosal injection had less burn damage than that obtained from procedures involving submucosal saline injection in terms of the snare resected surface (Figs. 2e, 3e).

Discussion

Soga et al. reported that the metastatic rate of duodenal NETs was proportional to the size of the tumor; it was 8.3% in tumors smaller than 5 mm and 10.5% in those between 5.1 and 10 mm [13]. Therefore, endoscopic resection may be considered over invasive surgical resection if a duodenal NET measuring ≤ 10 mm in diameter is diagnosed and localized within the submucosal layer by EUS examination and no metastasis are identified on computed tomography [14]. Several endoscopic resection methods, such as EMR, EMR-c, ESMR-L, and ESD, have been used in the treatment of duodenal NETs [3–8]. Previous studies have reported lower *en bloc* complete resection rates in EMR and EMR-c than in ESD [3, 4]. *En bloc* resection is recommended for duodenal NET because it enables accurate pathological assessment of the vertical and lateral margins of the resected lesions [15]. However, EMR and EMR-c are sometimes associated with margin involvement and crush injury of the resected specimens [3, 4]. Therefore, ESD rather than EMR may be preferable for endoscopic treatment of duodenal NETs. However, in the narrow space of the duodenum, ESD for

Table 2 Clinicopathological data of 12 lesions in 12 patients who underwent endoscopic submucosal resection using a ligation device

Case number	Age, years	Sex	Location in the duodenum (o'clock)	Tumor size, mm	Depth	Histology	Submucosal injection	Procedural time, min	*En bloc* resection	*En bloc* complete resection	Complication	Hospital stay after ESMR-L, d	Follow-up period, months
1	55	Male	Bulb, anterior (9)	9	SM	NET G1	+	25	Yes	Yes	-	5	90
2	68	Female	Bulb, anterior (9)	6	SM	NET G1	+	15	Yes	Yes	-	5	87
3	80	Male	Bulb, superior (12)	9	SM	NET G2	+	15	Yes	Yes	-	3	43
4	67	Male	Descending, superior (12)	10	SM	NET G1	–	10	Yes	Yes	Delayed bleeding	11	43
5	68	Male	Bulb, inferior (6)	4	SM	NET G1	+	30	Yes	Yes	-	5	41
6	84	Male	Bulb, inferior (6)	10	SM	NET G1	+	15	Yes	No	-	4	25
7	78	Female	Bulb, posterior (3)	7	SM	NET G1	–	15	Yes	Yes	-	4	11
8	77	Female	Bulb, inferior (6)	9	SM	NET G1	–	10	Yes	Yes	-	5	5
9	72	Female	Bulb, anterior (9)	9	SM	NET G1	–	10	Yes	Yes	-	4	5
10	76	Male	Bulb, anterior (9)	9	SM	NET G1	–	5	Yes	Yes	-	4	2
11	78	Female	Bulb, anterior (9)	6	SM	NET G1	–	10	Yes	Yes	-	4	2
12	65	Male	Bulb, anterior (9)	9	SM	NET G1	–	5	Yes	Yes	-	4	1

SM submucosal, *NET* neuroendocrine tumor

Table 3 Safety of endoscopic submucosal resection using a ligation device ($n = 12$, total 12 lesions)

Median procedural time, min (range)	13 (5–30)
Median hospital stay, days (range)	4 (3–11)
Complications, *n* (%)	
Intraoperative perforation	0 (0)
Delayed perforation	0 (0)
Intraoperative bleeding	0 (0)
Delayed bleeding	1 (8)

duodenal tumors is technically difficult and requires a long procedural time. Furthermore, duodenal ESD carries a high risk of complications, such as bleeding and perforation [3, 8]. In contrast, ESMR-L a significantly deeper vertical resection margin and, theoretically, a higher rate of curative resection compared with EMR [10], and we previously reported the efficacy and safety of ESMR-L for duodenal NETs [12]. In this study, ESMR-L was effective and successful in the treatment of duodenal NETs in terms of *en bloc* resection and complete resection rate. Delayed bleeding was observed in one patient, while intraoperative bleeding and perforation (intraoperative or delayed) were not observed in any of the patients. Additionally, the median procedural time was 13 min. As a result, ESMR-L is superior to ESD because it is a simpler procedure with a lower complication rate.

ESMR-L with submucosal saline injection was feasible and successful in the treatment of duodenal NETs. However, in cases of small NETs, the lesion may sometimes become indistinguishable after submucosal saline injection. In one case, the elastic band with submucosal saline injection was indistinguishable. Therefore, to avoid these problems, we evaluated ESMR-L without submucosal injection. In endoscopic resection, saline solution is injected into the submucosal layer to separate the muscularis propria from the more superficial layers to reduce the risk of perforation [3]. However, a previous report described that the frequencies of positive margin and perforation were not significantly different between snare resection with and without saline submucosal lifting [4]. In this study, ESMR-L without submucosal injection was comparable with ESMR-L with submucosal saline injection histopathologically. However, the resection time of ESMR-L without submucosal saline injection was significantly shorter than that with submucosal saline injection (10 min vs. 15 min, respectively).

In ESMR-L without submucosal injection, snare resection was performed using a bipolar snare. A previous study reported that bipolar instruments cause less damage to tissues compared to monopolar instruments [16]. With a bipolar snare, the current only passes through the tissue between the two electrodes of the instrument. It has been suggested that there is no need for a return electrode with a bipolar snare and that this confers a low risk of perforation, which is

Table 4 Correlation between endoscopic submucosal resection using a ligation device with or without submucosal injection and clinicopathological parameters ($n = 12$, total 12 lesions)

	Total	Submucosal injection (+)	Submucosal injection (−)	*p*-value
Enrolled patients, *n*	12	5	7	
Sex, *n* (%)				
Male	7 (55)	4 (80)	3 (43)	
Female	5 (42)	1 (20)	4 (57)	
Age, median, years	74	68	75	0.935
Tumor location, *n* (%)				
Bulb	11 (92)	5 (100)	6 (86)	1.000
Descending portion	1 (8)	0 (0)	1 (14)	
Tumor size, median, mm	9	9	9	0.663
Median procedural time, min (range)	13 (5–30)	15 (15–30)	10 (5–15)	0.007
En block resection, *n* (%)	12 (100)	5 (100)	7 (100)	1.000
En block complete resection, *n* (%)	11 (92)	4 (80)	7 (100)	0.417
Complications, *n* (%)	1 (8)	0 (0)	1 (14)	1.000
Median hospital stay, days (range)	4 (3–11)	5 (3–5)	4 (4–11)	0.791

advantageous, especially in the duodenum where the digestive tract is thin. This device theoretically minimizes the depth of damage and degree of tissue destruction. Bipolar snares cause less damage to the tissues than monopolar snares, especially to the muscularis propria. Therefore, we propose the use of bipolar instruments in ESMR-L without submucosal injection. In this study, delayed bleeding was observed in one patient using bipolar snare. Previous reports describe a bleeding rate of 28% (intraoperative bleeding 23% and delayed bleeding 6%) during endoscopic treatment of duodenal NET [4]. However, in this study, the bleeding rate was 8% and lower than that in the previous report. Previous reports described that the complication rates for bipolar snare with therapeutic colonoscopy appeared to be comparable with those for the monopolar snare [17]. Therefore, the delayed bleeding observed while using the bipolar snare was attributed to the small sample size.

We have several limitations in this study. First, this study was designed as a retrospective, historical, comparative study in a single institution. Second, this study had a small number of patients. Third, this study had a short follow-up period and longer follow-up periods are required to detect metastases. On account of these limitations, prospective, randomized controlled studies will be required to evaluate the effectiveness and safety of ESMR-L with or without submucosal saline injection for duodenal NETs.

Conclusions

In conclusion, ESMR-L is safe and effective for the treatment of duodenal NETs measuring ≤ 10 mm in diameter and located in the submucosal layer without metastasis. In particular, ESMR-L without submucosal injection with a bipolar snare could be used to treat these NETs safely within a short period of time.

Compliance with ethical standards

Disclosures Yasuhiro Oono, Kensuke Shinmura, Keisuke Hori, Yusuke Yoda, Genichiro Ishii, Hiroaki Ikematsu, and Tomonori Yano have no conflict of interests or financial ties to disclose.

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