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Efficacy and safety of radial incision and cutting for nonsurgical refractory benign esophageal stricture

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Conflict of Interest: The authors declare that they have no conflict of interest.

Abstract:
Background and study aims: Radial incision and cutting (RIC) was established to improve refractory esophageal anastomotic strictures but its efficacy and safety for nonsurgical refractory strictures remain unclear. To evaluate the usefulness of RIC in nonsurgical refractory strictures, we retrospectively compared outcomes between nonsurgical and surgical strictures.
Patients and methods: We retrospectively studied 54 consecutive patients who were initially treated with RIC for refractory benign esophageal stricture. The study variables included dysphasia score improvement rate, frequency of repeated RIC, cumulative patency rate, cumulative stricture improved rate, and adverse events(AEs), which were compared between nonsurgical (n = 21) and surgical (n = 33) stricture groups.
Results: Immediately after RIC, 90.5% of patients in the nonsurgical group and 84.8% of patients in the surgical group had improvement in dysphagia (P = 0.69). The frequency of intervening repeated RIC was 42.9% in the nonsurgical group and 42.4% in the surgical group (P = 0.98). During median follow-up of 22.3 months (range, 1.0-175.0), the cumulative patency rate (P = 0.23) and cumulative stricture improvement rate (P = 0.14) but there was not statistical difference between the two groups. Despite a low cumulative stricture improvement rate (9.5%) at 6 months after the first RIC in the nonsurgical group, 57.7% of patients no longer required endoscopic balloon dilatation at 2 years. The cumulative stricture improvement rate was significantly lower in patients with a history of radiation therapy. No severe AEs were observed in the nonsurgical group.
Conclusions: RIC for nonsurgical refractory benign esophageal stricture is an effective and safety treatment option.

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Introduction

Esophageal stricture causes dysphagia, significantly worsening nutritional status and quality of life. Dysphagia occurs especially after surgery, chemoradiotherapy, and widespread endoscopic resection for esophageal cancer [1–3]. Endoscopic balloon dilatation (EBD) is the standard treatment procedure for benign esophageal stricture, and many patients achieve symptomatic improvement after EBD [1, 4, 5]. However, some cases develop refractory benign esophageal stricture that does not improve with repeated EBD [1, 6, 7] .

We previously demonstrated the efficacy and safety of radial incision and cutting (RIC) as a stricture improvement procedure for surgical refractory benign esophageal stricture that does not improve after repeated EBD [8]. After the RIC procedure, 81.3% of patients were able to take solid foods, and 93.8% of patients had improved dysphagia. In addition, 63% and 62% of the patients were able to take solid foods at 6 months and 12 months, respectively. Based on these results, a phase II/III multicenter randomized controlled trial (JCOG1207, jRCTs031180177) was conducted to compare the efficacy of RIC with local steroid injection compared with EBD with local steroid injection in surgical refractory benign esophageal stricture. In the latest report of this study, RIC with steroid injection was performed safely but did not show superiority to EBD with steroid injection, thus the standard treatment is EBD, and RIC is positioned as a treatment option for surgical refractory esophageal stricture [9].

On the other hand, a non-surgical refractory benign esophageal stricture can be caused by radiotherapy, widespread endoscopic resection, photodynamic therapy, reflux

esophagitis, and corrosive esophagitis [10–12]. A case series of RIC for non-surgical refractory benign esophageal stricture showed dramatic short-term symptomatic improvement and no major complications. However, the long-term patency rate was unfavorable at 37.5% [13]. Therefore, the efficacy and safety of RIC for non-surgical refractory benign esophageal stricture, especially regarding long-term prognosis, remain unclear.

To evaluate the efficacy and safety of RIC for non-surgical refractory benign esophageal stricture, we retrospectively compared the clinical outcomes between a non-surgical stricture group and a surgical stricture group of patients who underwent RIC in our hospital.

Patients and Methods

Participants

Patients who were initially treated with RIC for refractory benign esophageal stricture from November 2007 through March 2022 were retrospectively collected in our hospital. Refractory benign esophageal stricture was defined as a benign stricture which does not relieve symptoms of dysphagia even after three or more repeated EBDs. Based on previous studies [8, 9], when there is no improvement in stricture after three or more EBD procedures, we considered refractory benign esophageal stricture and considered RIC procedures. (Reviewer #1- Major 2) We defined strictures resulting from the treatment of malignant disease as benign if there were no residual tumors. Written informed consent was obtained from all patients for the procedures of RIC and EBD.

This study was approved by the institutional review board in our hospital. Informed consent for this study was obtained using an opt-out method.

Study variables

To examine the efficacy and safety of RIC in the non-surgical stricture group, patients were divided into two groups according to the cause of stricture. Patients whose stricture was caused by surgery were defined as the surgical stricture group, and those whose stricture was caused by other causes were defined as the non-surgical stricture group. In patients with multiple causes of stricture, the treatment modality that developed the esophageal stricture was identified by clinical course. The following study variables were compared between the non-surgical stricture group and surgical stricture group: (1) dysphagia score (DS) improvement rate, (2) the frequency of re-RIC and duration between first RIC and re-RIC, (3) cumulative patency rate, (4) cumulative stricture improved rate, and (5) adverse events.

Evaluation of dysphagia before and after RIC and DS improvement rate

The following DS was used to evaluate the grade of swallowing ability before and after RIC: 0, able to eat a normal diet; 1, unable to swallow certain solids; 2, able to swallow semisolid foods; 3, able to swallow liquids only; and 4, unable to swallow liquid [14]. The DS was collected during an outpatient or in-treatment interview. DS improvement rates were defined as changes in DS over time after the first RIC.

RIC procedure and treatment strategy

RIC was carried out under deep sedation with a combination of midazolam, propofol, and pethidine hydrochloride. The stricture area was incised radially using an IT knife (Olympus, Tokyo, Japan) endoscopically, and the tissue between the incisions was dissected around the stricture [8]. The procedure was performed with the goal of passing a standard endoscope intraoperatively whenever possible. Endoscopic images before and after RIC are shown in Figure 1A–D. After RIC, prophylactic EBD was repeated at 1- to 2-week intervals to maintain patency until scar formation. Prophylactic EBD was gently performed during the artificial ulcer phase after RIC. Triamcinolone acetonide, one of the steroids, was injected into an ulceration after RIC and a laceration immediately after EBD.

The treatment strategy for refractory benign esophageal stricture patients is shown in Figure 1E. Repeated EBD was considered to be terminated with DS of 1 or less, and a standard diameter scope passing, which was regarded as “stricture improvement.” If the DS was greater than 2 and the standard diameter scope could not be passed, then the procedure was considered a “treatment failure”, and the attending physician considered re-RIC in light of the patient’s general condition and wishes. We considered the time to treatment failure and the time to stricter improvement to be important RIC endpoints, which we define and evaluate as described below.

Definition of treatment failure and cumulative patency rate

Treatment failure of the RIC procedure was defined as the inability to pass a standard endoscope with a diameter of 8.9 mm or larger (Q240, 1T240, H260, H260Z, H290, and H290Z; Olympus Medical Systems, Tokyo, Japan) through the stricture site after RIC,

and as the presence of dysphagia with a score of 2 or greater. The patency period, used in the analysis of cumulative patency rates, was defined as the period from the date of first RIC to the date of earliest treatment failure (Figure 1E).

Definition of stricture improvement and cumulative stricture improved rate

Because repeated EBD over time affects the patient's quality of life, achieving stricture improvement to the point where periodic EBD is no longer necessary is an important treatment endpoint. We defined the achievement of stricture improvement as DS1 or less for at least 6 months, passable by standard endoscopy, and no need for repeated EBD. Time to stricture improvement, used in the analysis of cumulative stricture improved rates, was defined as the period from the date of the first RIC to the date of the last EBD. The day that resulted in stricture improvement was used in the analysis of cumulative stricture improved rates (Figure 1E).

Evaluation of the diameter and length of the stricture

The diameter of strictures was categorized as follows: (1) an endoscope with a size of 10 mm could pass through the stricture, (2) from 2 mm to smaller than 10 mm, and (3) smaller than 2 mm. The stricture size was measured based on contrast to the tip (2.2 mm) of the IT knife. The length of stricture before RIC was categorized as follows: (1) less than 5 mm and (2) greater than 5 mm. Stricture length was calculated from the width of the notch shown fluoroscopically on the balloon at the time of the EBD.

Evaluation of the safety of RIC

Safety of RIC was evaluated in terms of procedure time, hospitalization period, and adverse events. Adverse events were evaluated by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and Grade 2 or higher was treated as a serious adverse event.

Statistical analysis

Patients' clinical characteristics, DS, timing and frequency of re-RIC and safety items were evaluated for differences between the two groups using Fisher's exact test or Wilcoxon test. The cumulative patency rates and the cumulative stricture improved rates were estimated using the Kaplan–Meier method and comparisons were made with Log-rank test. Follow-up was terminated upon death or cancer recurrence, and in the case of missed visits, follow-up was concluded on the date of the last outpatient visit. Multivariate analysis of subgroups in the non-surgical group was estimated using COX regression analysis to compare hazard ratios. All *P* values were 2-sided, and a *P* value <. 05 was considered significant. All data were analyzed using GraphPad Prism10 (GraphPad Software, Boston, MA, USA)

Results

Participants

A total of 54 patients with refractory benign esophageal stricture underwent RIC in our hospital. The demographic characteristics of the 54 patients and the characteristics of their stricture according to the cause of stricture are presented in Table 1. In the surgical stricture group (n=33), the cause of the stricture was esophagectomy in 30 patients,

proximal gastrectomy in 2 patients, and total gastrectomy in 1 patient. In the non-surgical stricture group (n=21), the causes of the stricture were chemoradiation in 10 patients, ESD or EMR in 4 patients, photodynamic therapy in 4 patients, and esophagitis in 3 patients. In the non-surgical stricture group, 15 patients (71.4%) had a history of radiotherapy to the esophagus, compared with only 1 patient (3.0%) in the surgical stricture group ($P< 0.0001$).

DS improvement over time and re-RIC intervention

Immediately after RIC, there was one case in the surgical stenosis group and one case in the non-surgical stenosis group in which the scope failed to pass; however, 90.5% of patients in the non-surgical stricture group and 84.8% of patients in the surgical stricture group showed improved dysphagia (P=0.69). Six months after RIC, 52.9% of patients in the non-surgical stricture group and 65.5% of patients in the surgical stricture group were able to maintain solid food intake without re-RIC (Figure 2).

In the non-surgical stricture group and surgical stricture group, the frequency of intervening re-RIC was 42.9% and 42.4%, respectively (P=0.98). Median duration between first RIC and re-RIC was 7.9 months (range, 0.5–14.9 months) and 2.8 months (range, 0.9–9.6 months), respectively (P=0.53). The frequency of three or more RIC was 14.3% and 24.2%, respectively (P=0.60) (Table 2).

Cumulative patency rate and cumulative stricture improved rate

During the median follow-up period of 22.3 months (range, 1.0–175.0), the cumulative patency rate, calculated as the patency period from the first RIC treatment to restenosis,

was not statistically different between the non-surgical stricture group and surgical stricture group (P=0.23) (Figure 3A). The 3-, 6-, and 12-month patency rates in the non-surgical stricture group were 56.4%, 49.4%, and 42.3%, respectively. In contrast, the 3-, 6-, and 12-month patency rates in the surgical stricture group were 66.7%, 63.3%, and 59.8%, respectively.

The cumulative stricture, calculated as the period from the first RIC treatment to achieving stricture improvement that made further EBD unnecessary, improved rate was also not statistically different between the non-surgical stricture group and surgical stricture group (P=0.14) (Figure 3B). The 6-, 12-, and 24-month stricture improved rates in the non-surgical stricture group were 9.5%, 38.3%, and 57.7%, respectively. In contrast, the 6-, 12-, and 24-month stricture improved rates in the surgical stricture group were 47.7%, 52.1%, and 72.0%, respectively. None of the patients who achieved stricture improvement came to the hospital again because of stricture symptoms during the follow-up period.

To identify poor prognostic factors in the non-surgical stricture group, further analysis was performed according to the history of radiotherapy to the esophagus (Figure 3C and 3D), stricture diameter (Figure 3E and F), and stricture length (Figure 3G and H). The cumulative stricture improved rate was significantly lower in patients with a history of radiation therapy (P=0.0018) (Figure 3D). In addition, a multivariate analysis of the subgroups in the non-surgical stricture group was performed to compare hazard ratios (Figure 3I and J). A history of radiation therapy was an independent risk factor for the resistance to stricture improvement (P=0.013) (Figure 3J).

Safety evaluation for RIC

Table 3 shows details of the safety profile for RIC. The median procedure time was 22 minutes (range, 6–62) in the non-surgical stricture group and 20 minutes (range, 4–90) in the surgical stricture group (P=0.53). RIC was performed in all hospitalized cases. The median hospitalization period was 5 days (range, 4–40) and 6 days (range, 4–29), respectively (P=0.46). No CTCAE Grade 2 or higher adverse events were observed in the non-surgical stricture group. On the other hand, pinhole perforation was observed in two patients in the surgical stricture group (P=0.52). These perforations were completely closed with conservative follow-up using intravenous antibiotics and fasting. In both cases, it was difficult to determine the direction of the incision during RIC because of the high degree of stenosis.

Discussion

Benign esophageal stricture is sometimes difficult to improve even by repeated EBD [15-17]. RIC has been investigated for surgical esophageal stricture and its efficacy and safety have been clarified, and it has become one of the minimally invasive treatment options for refractory benign esophageal stricture [8, 18, 19]. Surgical strictures occur at the anastomosis site after surgery, where the narrowing is typically sutured in a robust state. In contrast, non-surgical strictures often result from radiation or inflammation, where the affected tissue is more fragile and the healing process may differ. Therefore, it is essential to investigate the safety and efficacy of RIC specifically for non-surgical strictures.

In this study, the frequency of DS improvement over time and re-RIC intervention in the non-surgical stricture group was not different from those in the surgical stricture group. There was no difference between the two groups in either the cumulative patency rate, which measures the time to restenosis, or the cumulative stenosis improvement rate, which measures the time until EBD is no longer required. No major complications were observed in the non-surgical stricture group. These results indicate that RIC for non-surgical refractory benign esophageal stricture is not inferior to surgical refractory benign esophageal stricture and then might be considered as an effective and safe treatment option.

Because repeated EBD and frequent hospital visits reduce a patient's quality of life, the ultimate goal is to achieve improvement to the point where EBD is no longer necessary. Therefore, we defined 'stricture improvement' as improvement to the point where EBD is no longer necessary as a new endpoint in this study. A recent study showed that re-RIC can be safely performed and is effective in the very short term. However, results at 3 and 6 months after re-RIC were not favorable [20]. In our study, 57.7% of patients no longer required EBD at 2 years despite a much lower cumulative stricture improved rate of 9.5% at 6 months after first RIC in the non-surgical group. This suggests that the long-term treatment strategy combining EBD and re-RIC is effective and frees about half or more of the patients from periodic EBD in the non-surgery stricture group.

Because the effects of radiotherapy and the form of stricture may be prognostic factors, an exploratory analysis was performed in the non-surgical stricture group, although the number of patients was small. A history of radiotherapy significantly lowers the cumulative stricture improved rate and was an independent poor prognostic factor in

multivariate analysis. One possibility is that tissue regeneration and wound healing processes after radiotherapy might differ from normal and limit the effectiveness of RIC and EBD. [21, 22]. This population may have to establish the usefulness of long-time combination therapy with EBD and re-RIC. Therefore, it would be important to confirm the efficacy of RIC in patients with non-surgical refractory benign esophageal stricture after radiotherapy using a nationwide real-world survey and further prospective study.

This study has some limitations. First, this was a single-center retrospective study with a small number of patients. Second, strict evaluation of the diameter of stricture and stricture length over time after each treatment was difficult. In addition to distance and length, DS improvement, cumulative patency rate, and cumulative stricture improved rate were also useful to evaluate the efficacy of RIC in this study. Third, although the patients followed a defined treatment strategy for refractory esophageal stricture, variations in the timing of re-RIC and repeat EBD may have affected the outcomes. (Reviewer #1-Major 5) Fourth, the improvement in dysphagia was the result of combination treatment with RIC, repeated EBD, and triamcinolone acetonide, and it is unclear which modality was most helpful.

In conclusion, RIC for non-surgical refractory benign esophageal stricture could be an effective and safe treatment option. Some patients in the non-surgical stricture group may have a favorable outcome if they continue to receive the combination of RIC and EBD.

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Figure legends

Figure 1. Treatment strategy for refractory benign esophageal stricture patients

A, B, C, and D: A case of refractory esophageal stricture after chemoradiotherapy for esophageal cancer. A: Severe stricture before the treatment, B: Several incisions using the IT knife, C: Dissection of the entire circumference of the stricture, D: Removal of hard necrotic tissue from the structure.

E: Schema of treatment strategy. Patency period: The period from the date of first RIC to the date of earliest treatment failure. Time to stricture improvement: The period from the date of the first RIC to the date of the last EBD.

Abbreviations: RIC, radial incision and cutting; EBD, endoscopic balloon dilatation; DS, dysphasia score; re-RIC, repeated RIC

Figure 2. Changes over time in dysphagia score in the short term after the first radial incision and cutting

re-RIC are indicated by red stars, and the number of red stars indicates the number of re-RIC within 3 and 6 months, respectively.

Abbreviations: DS, dysphasia score; re-RIC, repeated RIC

Figure 3. Cumulative patency rates and stricture improved rates after first radial incision and cutting

A, C, E, and G: Cumulative patency rates. B, D, F, and H: Cumulative stricture improved rates. A and B: Non-surgical stricture group vs. surgical stricture group, C–J:

Subgroup analysis of the non-surgical stricture group, C and D: History of radiotherapy to esophagus, E and F: Diameter of stricture, G and H: Stricture length, I and J: Relationship between the effect of the subgroups on patency and stricture improved rates.

Conflict of interest

The authors have no conflicts of interest directly relevant to the content of this article.

Table 1: Characteristics of patients with esophageal stricture undergoing radial incision and cutting

	All n=54	Non-surgical stricture n=21	Surgical stricture n=33	*P*-value
Age, median (range)	68 (33-86)	71 (47-86)	67 (33-83)	0.37
Gender （Male/ Female）	42/ 12	16/ 5	26/ 7	0.82
EBD period before RIC median (range)	6.6 months (1.2-102.4)	6.7 months (1.8-202.4)	6.6 months (1.2-61.7)	0.74
EBD count before RIC, median (range)	9 (3-41)	10 (3-41)	8 (3-20)	0.14
EBD ≥ 6 before RIC	39 (72.2%)	18 (85.7)	21 (63.6%)	0.12
Estimated diameter of stricture				0.89
2 to ≤ 10	40	16	24	
<2	14 (25.9%)	5 (23.8%)	9 (27.2%)	
Stricture length >5mm	12 (22.2%)	6 (28.6%)	6 (18.2%)	0.32
History of radiotherapy to esophagus	16 (29. 6%)	15 (71.4%)	1 (3.0%)	<0.0001
Cause of stricture		Chemoradiotherapy 10 Endoscopic resection 4 Photodynamic therapy 4 Reflux esophagitis 1 Corrosive esophagitis 2	Esophagectomy 30 Proximal gastrectomy 2 Total gastrectomy 1	

EBD: endoscopic balloon dilatation

RIC: radial incision and cutting

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Table 2: Treatment profiles of radial incision and cutting

	All n=54	Non-surgical stricture n=21	Surgical stricture n=33	*P*-value
Frequency of re-RIC	42.6% (23/54)	42.9% (9/21)	42.4% (14/33)	0.98
Median duration to re-RIC (range)	4.0 months (0.5-14.9)	7.9 months (0.5- 14.9)	2.8 months (0.9- 9.6)	0.53
Number of RIC (median, range)	1	1 (1-8)	1 (1-7)	0.6
1	31	12	19	
2	12	6	6	
3	0	0	4	
3<	7	3	4	

re-RIC: repeated radial incision and cutting

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Table 3: Safety profiles of radial incision and cutting

	All n=54	Non-surgical stricture n=21	Surgical stricture n=33	*P*-value
Procedure time, median (range)	21	22 min (6-62)	20 min (4-90)	0.53
Adverse event (CTCAE* grade1<)	2 (3.7)	0 (0%)	2 (6.1%)	0.52
Perforation of the esophagus	2	0	2	
Hospitalization period (median, range)	5 days (4-40)	5 days□4-40□	6 days□4-29□	0.46

* CTCAE: Common Terminology Criteria for Adverse Events v5.0

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